Preprint version 2024/12/19, submitted for peer review

Unravelling the pain trajectory in chronic low back pain patients during a physical exercise training program

Maxime, Bergevin[a,b], Anna Bendas[b], Florian Bobeuf[b], Erika Gentile[c], Arthur Woznowski-Vu[d], Timothy H. Wideman[e], Nicolas Berryman[b,f,g], Louis Bherer[b,h,i], Mathieu Roy*[b,c,j] and Benjamin Pageaux*[a,b,k]

* both authors equally contributed to this work

[a] École de kinésiologie et des sciences de l'activité physique (EKSAP), Faculté de médecine, Montreal, Canada

[b] Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM), Montreal, Canada

[c] Department of Psychology, McGill University, Montreal, Canada

[d] School of Physical and Occupational Therapy, McGill University, Montreal, Canada

[e] Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada

[f] Institut national du sport du Québec

[g] Département des sciences de l'activité physique, Faculté des Sciences, Université du Québec à Montréal (UQAM), Montreal, Canada

[h] Département de médecine, Université de Montréal

[i] Montreal Heart Institute

[j] Alan Edwards Centre for Research on Pain, McGill University, Montreal, Canada

[k] Centre interdisciplinaire de recherche sur le cerveau et l'apprentissage (CIRCA), Montreal, QC, Canada

Author's contributions: All listed authors have contributed substantially to this work. MR, LB, TW, NB, BP and MB designed the study. AB, FB, AWV, EG and MB collected the data. MB performed the statistical analyses and drafted the first version of the manuscript. All authors revised and agreed on the final version of the manuscript.

Manuscript: 3565 words
Tables: 2
Figures: 4

Corresponding authors:
Mathieu Roy
Address: Department of Psychology, 2001 McGill College, 7th floor, Montreal, Qc, Canada, H3A 1G1. Tel.: 514-398-4232, email-address: mathieu.roy3@mcgill.ca

ORCID :
Maxime Bergevin: https://orcid.org/ 0000-0002-0343-8900
Nicolas Berryman: https://orcid.org/0000-0002-4868-7986
Mathieu Roy: https://orcid.org/0000-0002-3335-445X
Benjamin Pageaux : https://orcid.org/0000-0001-9302-5183

Please cite as: Maxime, B., Bendas, A., Bobeuf, F., Gentile, E., Woznowski-Vu, A., Wideman, T. H., Berryman, N., Bherer, L., Roy, M., & Pageaux, B. (2024). Unravelling the pain trajectory in chronic low back pain patients during a physical exercise training program. SportRχiv. https://doi.org/10.XXXXXX

Abstract

Objective

Physical exercise can transiently decrease pain intensity within a single session and improve physical capacities while reducing pain over a training program. However, pain trajectory throughout a concurrent physical training program remains unknown. This study aimed to model pain trajectory during a training program including both aerobic and resistance exercises, considering both acute (within-session) and chronic (across-program) effects of physical exercise.

Design

Prospective observational study

Method

Participants completed a 14-week training program (42 sessions; n = 28) or were assigned to a waiting list (n = 29). In the exercise group, low back pain intensity was measured before and after each training session. Pain intensity averaged over the last week was measured before and after the 14-week period in both groups. Linear mixed-effects modelling was performed to describe the pain trajectory.

Results

Pain intensity averaged over the last week decreased only in the exercise group (exercise: 4.9 ± 0.3 vs 2.5 ± 0.3; control: 5.6 ± 0.3 vs 5.3 ± 0.3). Pain trajectory was characterized by a linear and a quadratic term (p's < 0.001), suggesting pain reduction decelerated as the program progressed. Pain intensity decreased after each training session ($p < 0.001$) with this effect remaining constant throughout the program (non-significant interactions, p's > 0.585).

Conclusions

Pain decreases more markedly during the initial weeks of the program. Acute exercise-induced hypoalgesia persisted throughout the program, suggesting patients may use physical exercise to manage pain flare-ups even after several weeks of training.

242/250 words

Keywords: chronic pain, exercise therapy, resistance training, high-intensity interval training, exercise-induced hypoalgesia, concurrent training

1 Introduction

Chronic low back pain (CLBP) is a leading cause of disability worldwide [1] and is associated with increase prevalence of other physical and mental comorbidities, including cardiorespiratory disease, metabolic conditions, and mood disorders [2]. Additionally, CLBP patients show signs of physical deconditioning [3], contributing to functional decline.

Various treatment strategies have shown comparable effectiveness, ranging from small to moderate [4]. While pharmacotherapy can be helpful in pain management, it often comes with serious side effects such as addiction, overdose, and increase mortality risk [5]. Therefore, non-pharmacological approaches are generally preferable. Physical exercise, a key non-pharmacological approach, is safe even at high intensities [6] and alleviates CLBP symptoms, including pain and disability [4] while enhancing physical and mental health [7]. Concurrent training combining both aerobic and resistance exercises can promote cardiorespiratory and neuromuscular adaptations, potentially addressing the deconditioning often observed in CLBP patients.

Physical exercise is now recommended as a first-line treatment in the management of CLBP [8]. Acutely, exercise sessions, including both aerobic and resistance exercises, can transiently decrease pain sensitivity [9], a phenomenon known as acute exercise-induced hypoalgesia. Chronically, training programs consistently decrease pain intensities in the lower back [4]. However, the relationship between these acute and chronic pain responses remains unclear. Recent research in exercise physiology suggests that acute stress responses to exercise are crucial for long-term adaptations [10]. Applying this principle to pain management, we might hypothesize that as the body adapts to a physical exercise program, the acute physiological stress to each session could change over time, potentially influencing both the immediate exercise-induced hypoalgesia and the trajectory of chronic pain reduction. However, current research focuses on pre- and post-intervention pain differences, leaving the dynamics of within-session pain response and their relationship to long-term outcomes unexplored. Moreover, meta-analyses have shown that effect

sizes of physical exercise interventions for CLBP are typically small to moderate [4]. This limitation suggests that current training programs either are too short to realize the full potential of physical exercise, or that there is an inherent limit to its effectiveness. If the latter is true, we might expect a non-linear pain reduction trajectory, where pain decreases more rapidly initially, then gradually slows down until reaching a plateau.

The primary aim of this study was to explore the trajectory of low back pain intensity during a physical training program including both aerobic and resistance exercises. A second aim was to test whether acute exercise-induced hypoalgesia was maintained throughout the training program.

2 Methods

This study examined the trajectory of low back pain throughout a training program at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM). All procedures were approved by the institutional ethics committee (CER VN 16-17-11). All participants provided written informed consent prior to the study. This investigation is part of a larger research project examining the effects of physical exercise training on changes in brain connectivity and gene expression [11]. However, the present study was specifically designed as an ancillary project to address distinct objectives, including disentangling the short- and long-term effects of physical exercise on pain and identifying pain predictors of chronic pain trajectories during the training program. The aims and data presented here are independent and minimally overlap with other analyses from the broader project, ensuring that the findings are substantially and uniquely valuable.

2.1 Study design

Participants with CLBP were randomly assigned to a 14-week training program (exercise group) or a waiting period (control group; with access to an online version of the training program afterwards). Both groups underwent identical tests before and after the protocol, except for maximal aerobic power and one-repetition maximum (1RM). We used these tests to individualize the load during the training sessions. As the control group was on a waiting list not performing any training sessions, we decided not to perform these tests in this group to avoid additional laboratory visits as well as to minimize unnecessary negative affective responses elicited by maximal exercise performed until exhaustion. Physical and psychosocial outcomes were measured one week before and after the intervention period. Detailed methodology is available in **supplementary material S1**.

2.2 Participants

While our planned sample size was 100 participants (50 per group), the project was performed during the COVID lockdown in Quebec. Therefore, we had to comply with sanitary measures, which delayed data collection and limited our sample size to 57 participants. Consequently, and in line with funding duration,

we were able to recruit 28 and 29 participants in the exercise and control groups, respectively (**table 1**). Inclusion criteria followed the Canadian minimum dataset for CLBP research [12]: back pain persisting >3 months or pain for at least half of the days in the past 6 months. Exclusion criteria included recent analgesic injections, cancer therapy, self-reported pain <4/10 when asked to rate their average pain over the past week, severe neurological or psychiatric disorders, or significant health issues preventing physical training participation.

2.3 Physical training program

The program consisted of a concurrent aerobic and resistance exercise training. Participants were familiarized with low-intensity exercises during the first 4 sessions. Maximal aerobic power and 1RM (leg press, chest press and lateral pulldown) were assessed during session 5 and 6. Testing results were used to calibrate workloads for session 7-40. Maximal aerobic power was measured using an incremental protocol on a recumbent cycle ergometer (Corival Recumbent, Lode B.V., Groningen, The Netherlands). The initial power output was set at 50W for males and 35W for females, with increments of 15W per minute until participants reached volitional exhaustion. For 1RM testing, three exercises were performed on resistance machines: leg press, chest press and lateral pulldown (Atlantis Inc, Laval, Canada). For each exercise, the initial load was set by the kinesiologist to 90% of the estimated 1RM. Then, the load increased by 2.5-5% after each successful repetition. The procedure was repeated with 3 min of recovery between each trial until the participant was unable to lift the weight.

Three 1-hour sessions were conducted weekly (Monday, Wednesday, Friday; **figure 1**), each including a warm-up, resistance exercises, followed by aerobic exercises. On Mondays and Fridays, participants completed two circuits of resistance exercises. The first circuit combined elastic bands, free weights and body mass. It included 5 exercises, each performed for 1 set of 10-15 repetitions, The second circuit included resistance machines and consisted of 4 exercises, performed for 3 sets of 10-15 repetitions each. Following completion of these two circuits of resistance exercises, participants completed a high-intensity interval training exercise. The high-intensity interval exercise consisted of alternating between 60% maximal

aerobic power for 1 minute and 80-85% maximal aerobic power for 2 minutes. Following this, participants completed an additional two sets of 6-minute intervals, alternating every 15 seconds between 60% maximal aerobic power and 100% maximal aerobic power. In total, participants completed 14 min of high-intensity interval exercise per training session. On Wednesdays, participants completed a circuit of resistance exercise with elastic bands, free weights and body mass exercises. Following completion of this circuit of resistance exercises, participants completed an aerobic exercise consisting of a 25-min incremental protocol on the recumbent cycle ergometer. The exercise started at 65% maximal aerobic power for the first 5 min. Then the workload increased by 5% every 5 min until reaching 85% of the maximal aerobic power. A home training protocols were provided for missed sessions, which included body mass exercises and a 15-minute cardiovascular walk. A detailed overview of the physical exercise program and testing procedures can be found in **supplementary material S1**.

**** insert figure 1 here ****

2.4 Outcomes

Physical and functional outcomes were measured in a single visit and administered as per the American College of Sports Medicine's guidelines [13] In both groups, measures of muscular capacities included maximal handgrip strength and a 30-second (s) sit-to-stand test. Measures of cardiorespiratory capacities included a 6-minute (min) walk test and an incremental ergocycle protocol terminating at 85% of the estimated maximal heart rate using Tanaka's formula (HR_{max} = [208 – 0.7 × age]) [14]. Mobility was assessed via the Timed Up-and-Go and 10-m Walk Test. Both tests were performed three times at comfortable and maximal paces. For the exercise group only, additional measures were taken as described previously: maximal aerobic power was assessed using a maximal incremental ergocycle test, and one-repetition maximum (1RM) was determined for leg press, chest press and lateral pulldown exercises.

Psychosocial and pain outcomes. Both groups reported their pain averaged in the past week (7-day pain) using an 11-point numerical rating scale (NRS; 0=no pain, 10=extreme pain). Physical and functional test-evoked pain (*i.e.*, pain following each physical test) was also measured during the physical assessment using

the same NRS. Averaged test-evoked pain was then computed pre- and post-training program. The Tampa Scale of Kinesiophobia [15], Pain Catastrophizing Scale [16] and Oswestry Disability Index [17] were administered to the participants. Participants in the exercise group were asked to rate their pain in the lower back during quiet standing using the 11-point NRS before and after each training session to monitor the pain trajectory.

2.4 Statistical Analyses

Analyses were performed using R version 4.2.1. Baseline measures were analyzed with t (continuous variables) or χ^2 (categorical variables) tests. We used linear mixed-effects models (LMM) to test the effect of the physical training program on the outcomes measured in both groups. Pain trajectory was fitted using LMM taking into consideration change in pain scores due to the training program (i.e., over several training sessions) and due to the training sessions (i.e., pre-/post-session). To account for the possibility of non-linear change in pain over time, the effect of the program was modeled using an orthogonal quadratic trend. This approach avoids the issue of collinearity between the linear (pain relief) and quadratic terms (limitation in pain relief), thus allowing independent moderation analysis on both terms. Given that previous research on moderators of physical exercise effectiveness has been limited to pre- and post-intervention data [18], we conducted exploratory analyses to investigate potential moderators of pain trajectories. This approach allows for the identification of different pain response patterns that may be associated with individual characteristics, which could be missed in traditional pre-post designs. To assess potential moderators of training session effects and overall program effects, the following continuous variables were centered around their respective means to reduce the risk of multicollinearity: baseline 7-day pain, maximal aerobic power, muscle strength and age. Muscle strength was computed as a composite score by averaging the individual z-scores of the 1RM. Sex and pain duration were also included as categorical moderators. Due to COVID-19 lockdown restrictions, our final sample size (N=28) was lower than initially planned. To mitigate the risk of overfitting in our cross-level interaction analyses, we constructed separate models for each potential moderator. We therefore tested 6 additional models, adjusted with the Bonferroni correction for

multiple testing. A justification for each moderator is available in **supplementary material S1**. Alpha level was set at $\alpha = 0.05$. All results are reported as β-coefficients with 95% confidence intervals and associated p-values.

**** insert figure 2 here ****

3 Results

Fifty-seven consented to participate (**figure 2**). None of the baseline demographic characteristics differed between the groups ($p > 0.113$, **table 1**). Both groups also did not differ at baseline for any outcomes except for disability ($\beta = -3.76$ [-0.29, -7.23], $p = 0.034$) for which the exercise group scored lower. The exercise group also tended to have less pain-related fear ($\beta = -1.76$ [-3.54, 0.02], $p = 0.053$).

**** insert table 1 here ****

3.1 Effect of the training program on outcomes

As we were interested in whether the exercise group changed differently than the control group, only the interaction effects are reported. Main effects are available in **supplementary material S2**. Participants completed, on average, 40 ± 2 sessions of the training program. Estimated marginal means with 95% confidence intervals are shown in **table 2** for all outcomes.

Physical and functional outcomes. The exercise group improved in maximal aerobic power and 1RM for all exercise tested. The interaction effect on the 6-min walk test and submaximal ergocycle test revealed that the exercise, but not the control group, improved following the program. Both groups improved similarly at the short walking tests and the 30-s sit-to-stand (main effect of time: p's < 0.021; group × time interaction: p's > 0.104).

**** insert table 2 here ****

Psychosocial and pain outcomes. Following the protocol, 7-day pain decreased solely in the exercise group ($p < 0.001$). After the training program, participants in the exercise group reported less pain evoked by the physical and functional tests ($p < 0.001$). Similarly, the exercise group, but not the control group, reported less disability, pain-related fear and pain catastrophizing at the end of the training program (p's < 0.017).

**** insert figure 3 here ****

3.4 Pain trajectory

As expected, pain decreased throughout the training program (β = -0.03 [-0.03, -0.02], p < 0.001). Adding a quadratic term to our LMM significantly improved the fit (BIC: 6742.6 vs 6737.9, p < 0.001). This indicates that pain reduction followed a non-linear pattern over the 42 training sessions (**figure 4A**). This pattern was characterized by a rapid initial decline in pain (linear term: β = -14.57 [-17.52, -11.62], p < 0.001). While our model suggests that pain continues to decrease throughout the program, the positive coefficient of the quadratic term (β = 4.17 [1.22, 7.12], p = 0.006) indicates a diminishing rate of pain reduction as the number of sessions increases, consistent with the possibility of a floor effect. In addition, participants reported significant pain relief after each training session (β = -0.62 [-0.71, -0.53], p < 0.001; **figure 4B**) and this acute exercise-induced hypoalgesia was not altered across sessions (session × program interaction: p's > 0.585 on both linear and quadratic terms; **figure 4C**).

To explore potential moderators of pain trajectories, we constructed separate models for each moderator (**figure 4D-I**). Orthogonal polynomials were used to model the effect of the 42 training sessions, eliminating the dependence between the linear and quadratic terms, at the cost of reduced interpretability of the coefficients. The complete table of the coefficients can be found in the **supplementary material S2**. Initial pain decline was steeper for participants with higher baseline 7-day pain, shorter pain duration and younger age (p's < 0.001). The rate of pain reduction attenuated more rapidly for those with higher baseline pain (p < 0.001) and older age (p = 0.008). Acute pain relief was greater for participants with higher baseline pain, shorter pain duration and for males (p's < 0.001). There was also a tendency for greater acute pain relief in participating with higher maximal aerobic power (p = 0.071) and muscle strength (p = 0.058).

**** insert figure 4 here ****

4 Discussion

This study aimed to model pain trajectory during a concurrent training program. Pain initially decreased rapidly, but the rate of reduction gradually slowed down, revealing a non-linear pattern. We also investigated potential changes in acute exercise-induced hypoalgesia by measuring pain before and after each session. While we reproduced the acute exercise-induced hypoalgesia [9], our findings suggest the training program did not alter the magnitude of pain relief experienced by participants following each training session.

Training program effect. In line with current literature [4, 7], our data shows that moderate-to-high intensity physical training can reduce chronic low back pain. Importantly, we observed a non-linear pattern of pain reduction over the course of the training program. Pain intensity decreased more rapidly during the initial weeks of the training, with the rate of improvement gradually slowing over time. This non-linear trajectory suggests that the greatest benefits of exercise intervention may be realized early in the program. However, continued engagement in physical training program appears to maintain these pain reductions [4], even as the rate of improvement plateaus. This pattern aligns with the principle of diminishing returns often observed in exercise adaptations [19]. Understanding this non-linear trajectory may be crucial for patient education and expectation management. For instance, patients might become discouraged if they perceive a slowdown as a lack of ongoing benefit, which may in turn decrease adherence to physical exercise [20]. Our exploratory analyses revealed that baseline pain intensity and age moderated chronic pain trajectory. These were associated with steeper initial declines in pain intensity, but also quicker attenuation in the rate of pain reduction. This suggest that these individuals may converge towards similar overall outcomes despite taking different trajectories. This convergence aligns with a recent meta-analysis that found limited effects of various moderators in pre- and post-intervention designs [18]. However, short-standing pain (<5 years) predicted greater pain relief throughout the program, underscoring the importance of early intervention.

Training session effect. Our findings further support the acute exercise-induced hypoalgesia effect in CLBP [9]. Moderate-to-high intensity exercise, as performed in our training program, is known to induce

muscle pain [21]. This exercise-induced muscle pain can in turn enhance acute exercise-induced hypoalgesia via descending pain mechanisms, such as diffuse noxious inhibitory control [22]. Moreover, allowing patients to engage in painful exercise might serve as a form of exposure therapy [22]. Given that fear of reinjury is often linked to avoidance behaviours and disability [23], some patients may actively avoid physical activity. This increase in sedentary behaviour may exacerbate pain intensity [24] and contribute to deconditioning [3], in turn accelerating the functional decline observed in CLBP patients. In chronic pain conditions like CLPB, the central nervous system often associates certain movements with perceived threats, triggering the experience of pain [25]. Exposing patients to painful sensations in a controlled and safe environment may help break this association [22]. Additionally, exercise-induced hypoalgesia itself may further weaken this movement-threat link, as exercise not only involves movement, but also brings acute pain relief [9]. Interestingly, patients exercising at higher intensities have reported greater pain reduction after an exercise program [6]. This may be due to the physiological adaptations to the training, but also because of the dose-response relationship between exercise intensity and exercise-induced hypoalgesia, where more intense exercise leads to greater acute post-exercise pain relief [26]. Our exploratory analyses revealed that higher baseline pain intensity predicted greater acute pain relief, suggesting that despite potential apprehension toward physical exercise [25], patients experiencing more severe pain may benefit significantly from exercising at higher intensities.

The lack of interaction between long- and short-term effects of exercise suggests that these two phenomena may have distinct mechanisms. Chronic pain is increasingly recognized as a disease state, driven by maladaptive changes in the central nervous system. While the exact mechanisms remain unclear, neuroinflammation, possibly linked to a dysregulated immune system [27], may play a role. Given exercise's anti-inflammatory effects [10], chronic exercise could reverse these maladaptive changes, reducing chronic pain. Conversely, acute exercise-induced hypoalgesia has been attributed to various systems, including opioids, serotonin and endocannabinoids [28]. An active lifestyle may increase serotonin

and opioids in pain control areas of the brain [29]. One important nuance is that studies usually investigate acute exercise-induced hypoalgesia using pain sensitivity [28], which may capture changes in pain modulation systems. In contrast, we measured pain experienced during quiet standing, which may better reflect the overall daily pain experience of CLBP patients. As such, it is unclear whether the acute exercise-induced hypoalgesia we observed is underpinned by the same mechanisms as those identified in traditional pain sensitivity tests.

4.1 Limitations

Focusing on pain during quiet standing yielded low pain ratings. Future studies should consider monitoring pain intensity evoked during the completion of physical exercises to more closely reflect the everyday pain experiences of CLBP patients. Additionally, our study did not include longitudinal pain ratings for the control group, preventing us from modelling pain trajectory over time for this group. This limitation makes it challenging to determine whether the observed pain reduction in the exercise group was due to regression to the mean or a true effect of physical exercise. However, it should be noted that if this were merely an effect of regression to the mean, we would expect to observe an increase in pain for participants with the lowest pain ratings, which is not the case (**figure 4A**). Furthermore, our pre-post analysis revealed that participants in the exercise group experienced significant pain relief, whereas those in the control group did not. Given the consistent findings in the literature supporting the effectiveness of physical exercise [4], we are confident that the pain relief observed in our study is not merely due to regression to the mean.

4.2 Research & clinical implications

The non-linear pattern in pain reduction observed in this study may be due to diminishing returns, similar to those seen in other health outcomes [19]. However, it is also likely that this residual pain arises from distinct mechanisms not directly targeted by exercise. For instance, intervertebral disc degeneration is a frequent cause of low back pain [30]. Future research should therefore focus on confirming whether exercise primarily reduces pain stemming from central sensitization (i.e., nociplastic pain). Remaining pain post-

intervention could potentially be attributed to disc degeneration or other structural abnormalities. This distinction between nociplastic and nociceptive pain could inform the development of more targeted interventions. Physical exercise could be used to address nociplastic pain, while complementary strategies could be explored to manage residual nociceptive pain.

Clinically, high-intensity exercise may yield better outcomes for CLBP than lower intensities [6]. As no consistent moderators of individual response have been identified [18], patients should generally be encouraged to engage in a physical training program unless contraindicated. Our findings indicate that initial pain reduction is most pronounced within the first few weeks, but sustained physical activity is necessary to maintain these benefits [4, 24] and potentially reduce the risk of developing comorbidities [2]. Finally, the consistent acute pain relief we observed across the training program reinforces the importance for CLPB patients of maintaining engagement in moderate-to-high intensity exercise to manage pain flare-ups, regardless of their baseline activity level or stage in the training program.

Practical implication

- Pain relief was most rapid in the beginning stages of the training program, then slowed down over the 14-week period.
- Participants felt less pain right after each session, with pain levels dropping by around 0.6 on a 10-point scale every time they exercised.
- The pain relief experienced right after exercise seems to work differently than the gradual, long-term pain relief. While immediate pain relief continued steadily, the overall pain reduction slowed down overtime.

Acknowledgments

Acknowledgments: The authors warmly thank the CRIUGM senior statistician Ali Filali-Mouhim for his help with statistical analyses.

Funding: This work was supported by the Canadian Institutes of Health Research [grant number CIHR-390119]. MB was supported by the Canadian Institutes of Health Research through the Canada Graduate Scholarships – Master's Frederick Banting and Charles Best grant, the "Formation de maîtrise" scholarship from the Fonds de recherche du Québec – Santé (FRQS) and an MSc scholarship from the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM). BP's research is supported by the Natural Sciences and Engineering Research Council of Canada—Discovery Grants Program and the Chercheur Boursier Junior 1 award from the FRQS. MR's research is supported by the Canadian Institutes of Health Research (CIHR). LB is supported by the Mirella and Lino Saputo Research Chair in Cardiovascular Health and the prevention of cognitive decline at Université de Montréal

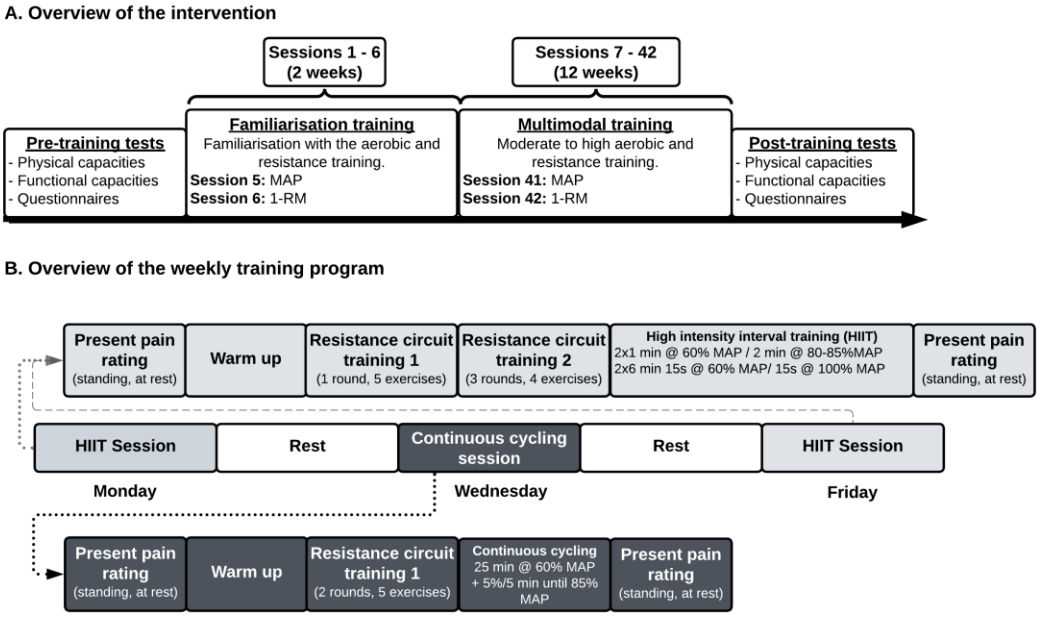
Conflicts of interest: All authors declare having no conflict of interest that are directly relevant to the content of this article.

References

1. Collaborators, G.B.D.R.F., *Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet (London, England), 2018. **392**(10159): p. 1923-1994 DOI: 10.1016/S0140-6736(18)32225-6.
2. Xu, Y., et al., *The comorbidity of mental and physical disorders with self-reported chronic back or neck pain: Results from the China Mental Health Survey.* Journal of affective disorders, 2020. **260**: p. 334-341.
3. Steele, J., S. Bruce-Low, and D. Smith, *A reappraisal of the deconditioning hypothesis in low back pain: review of evidence from a triumvirate of research methods on specific lumbar extensor deconditioning.* Current Medical Research and Opinion, 2014. **30**(5): p. 865-911 DOI: 10.1185/03007995.2013.875465.
4. Hayden, J.A., et al., *Exercise therapy for chronic low back pain.* Cochrane Database of Systematic Reviews, 2021. **2021**(10) DOI: 10.1002/14651858.CD009790.pub2.
5. Tucker, H.-R., et al., *Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: a systematic review.* British Journal of Sports Medicine, 2020. **54**(11): p. 664-664 DOI: 10.1136/bjsports-2018-099805.
6. Verbrugghe, J., et al., *Exercise Intensity Matters in Chronic Nonspecific Low Back Pain Rehabilitation.* Medicine & Science in Sports & Exercise, 2019. **51**(12): p. 2434-2442 DOI: 10.1249/MSS.0000000000002078.
7. Owen, P.J., et al., *Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis.* British Journal of Sports Medicine, 2020. **54**(21): p. 1279-1287 DOI: 10.1136/bjsports-2019-100886.
8. Qaseem, A., et al., *Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians.* Annals of Internal Medicine, 2017. **166**(7): p. 514 DOI: 10.7326/M16-2367.
9. Naugle, K.M., R.B. Fillingim, and J.L. Riley, *A Meta-Analytic Review of the Hypoalgesic Effects of Exercise.* The Journal of Pain, 2012. **13**(12): p. 1139-1150 DOI: 10.1016/j.jpain.2012.09.006.
10. Langston, P.K. and D. Mathis, *Immunological regulation of skeletal muscle adaptation to exercise.* Cell Metabolism, 2024: p. S1550413124001219 DOI: 10.1016/j.cmet.2024.04.001.
11. Thompson, S.J., et al., *Effects of Physical Exercise Training on Chronic Low Back Pain are Mediated by Changes in Frontostriatal Connectivity and Gene Expression.* 2024 DOI: https://doi.org/10.31219/osf.io/9jhcq.
12. Lacasse, A., et al., *The Canadian minimum dataset for chronic low back pain research: a cross-cultural adaptation of the National Institutes of Health Task Force Research Standards.* CMAJ open, 2017. **5**(1): p. E237 DOI: 10.9778/cmajo.20160117.
13. ACSM, *ACSM's exercise testing and prescription*. 2017: Lippincott williams & wilkins.
14. Tanaka, H., K.D. Monahan, and D.R. Seals, *Age-predicted maximal heart rate revisited.* J Am Coll Cardiol, 2001. **37**(1): p. 153-6 DOI: 10.1016/s0735-1097(00)01054-8.
15. Roelofs, J., et al., *The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia.* European Journal of Pain, 2004. **8**(5): p. 495-502 DOI: 10.1016/j.ejpain.2003.11.016.

16. Franchignoni, F., et al., *Measurement precision of the Pain Catastrophizing Scale and its short forms in chronic low back pain.* Scientific Reports, 2022. **12**(1): p. 12042 DOI: 10.1038/s41598-022-15522-x.
17. Chiarotto, A., et al., *Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis.* Physical Therapy, 2016. **96**(10): p. 1620-1637 DOI: 10.2522/ptj.20150420.
18. Hayden, J.A., et al., *Exercise treatment effect modifiers in persistent low back pain: an individual participant data meta-analysis of 3514 participants from 27 randomised controlled trials.* British Journal of Sports Medicine, 2020. **54**(21): p. 1277-1278 DOI: 10.1136/bjsports-2019-101205.
19. Powell, K.E., A.E. Paluch, and S.N. Blair, *Physical activity for health: What kind? How much? How intense? On top of what?* Annual review of public health, 2011. **32**: p. 349-365.
20. Friedrich, M., et al., *Combined exercise and motivation program: Effect on the compliance and level of disability of patients with chronic low back pain: A randomized controlled trial.* Archives of Physical Medicine and Rehabilitation, 1998. **79**(5): p. 475-487 DOI: 10.1016/S0003-9993(98)90059-4.
21. Cook, D.B., et al., *Naturally occurring muscle pain during exercise: assessment and experimental evidence.* Medicine & Science in Sports & Exercise, 1997. **29**(8): p. 999.
22. Smith, B.E., et al., *Musculoskeletal pain and exercise—challenging existing paradigms and introducing new*. British Journal of Sports Medicine, 2019. **53**(14): p. 907-912 DOI: 10.1136/bjsports-2017-098983.
23. Verbunt, J.A., et al., *Fear of injury and physical deconditioning in patients with chronic low back pain.* Archives of Physical Medicine and Rehabilitation, 2003. **84**(8): p. 1227-1232 DOI: 10.1016/S0003-9993(03)00132-1.
24. Årnes, A.P., et al., *Longitudinal relationships between habitual physical activity and pain tolerance in the general population.* PLOS ONE, 2023. **18**(5): p. e0285041 DOI: 10.1371/journal.pone.0285041.
25. Meulders, A., *From fear of movement-related pain and avoidance to chronic pain disability: a state-of-the-art review.* Current Opinion in Behavioral Sciences, 2019. **26**: p. 130-136.
26. Naugle, K.M., et al., *Intensity Thresholds for Aerobic Exercise-Induced Hypoalgesia.* Medicine & Science in Sports & Exercise, 2014. **46**(4): p. 817-825 DOI: 10.1249/MSS.0000000000000143.
27. Ji, R.-R., et al., *Neuroinflammation and Central Sensitization in Chronic and Widespread Pain.* Anesthesiology, 2018. **129**(2): p. 343-366 DOI: 10.1097/ALN.0000000000002130.
28. Rice, D., et al., *Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions.* J Pain, 2019. **20**(11): p. 1249-1266 DOI: 10.1016/j.jpain.2019.03.005.
29. Sluka, K.A., L. Frey-Law, and M. Hoeger Bement, *Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation.* PAIN, 2018. **159**: p. S91-S97 DOI: 10.1097/j.pain.0000000000001235.
30. Novais, E.J., et al., *A new perspective on intervertebral disc calcification—from bench to bedside.* Bone Research, 2024. **12**(1): p. 1-12 DOI: 10.1038/s41413-023-00307-3.

457



458

459 **Figure 1** Overview of the weekly physical training program (A). Two resistance training circuits
460 (approximately 25 min) and one HIIT circuit (approximately 20 min) were performed on Mondays and
461 Fridays (B). One resistance training circuit (approximately 15 min) and one incremental continuous cycling
462 (approximately 50 min) bout were performed on Wednesdays. Approximately 10 min of stretching exercises
463 for the main muscle groups involved was completed at the end of each training session. Current pain in the
464 lower back, while standing still, was measured before and after each training session. HIIT: high-intensity
465 interval training; MAP: maximal aerobic power.

466

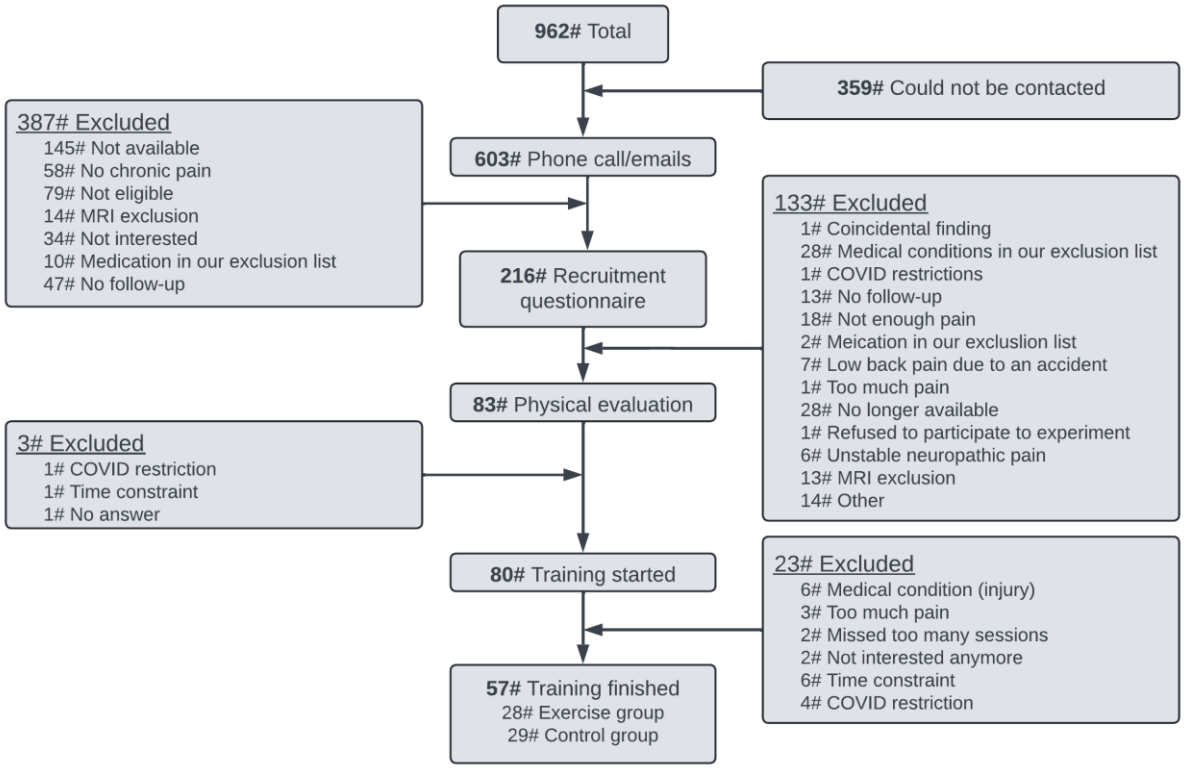


Figure 2 Consort flow diagram depicting patients' progression throughout the protocol.

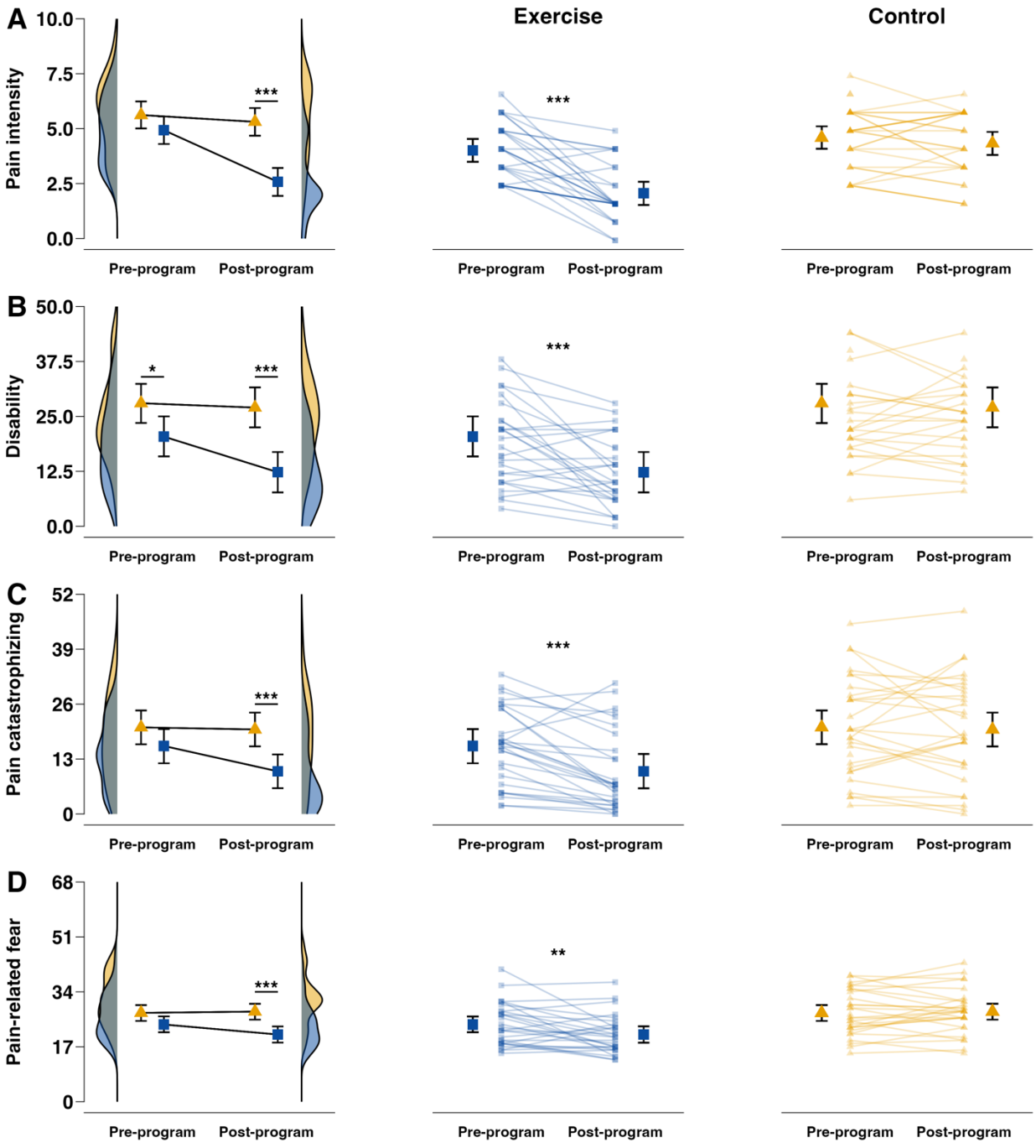


Figure 3. Change in psychosocial outcomes in the exercise (blue squares) and control (yellow triangles) groups. The exercise group, but not the control group, improved in 7-day averaged pain (A), disability as measured with the Oswestry Disability Index (B), pain catastrophizing (C) and pain-related fear (D). Estimated marginal means shown with 95% confidence intervals. Data distribution shown by vertical

density curves. Individual data for the exercise group (blue) and the waiting list (yellow) shown by colored lines. One symbol represents $p < .05$, two symbols $p < .01$, and three symbols $p < .001$.

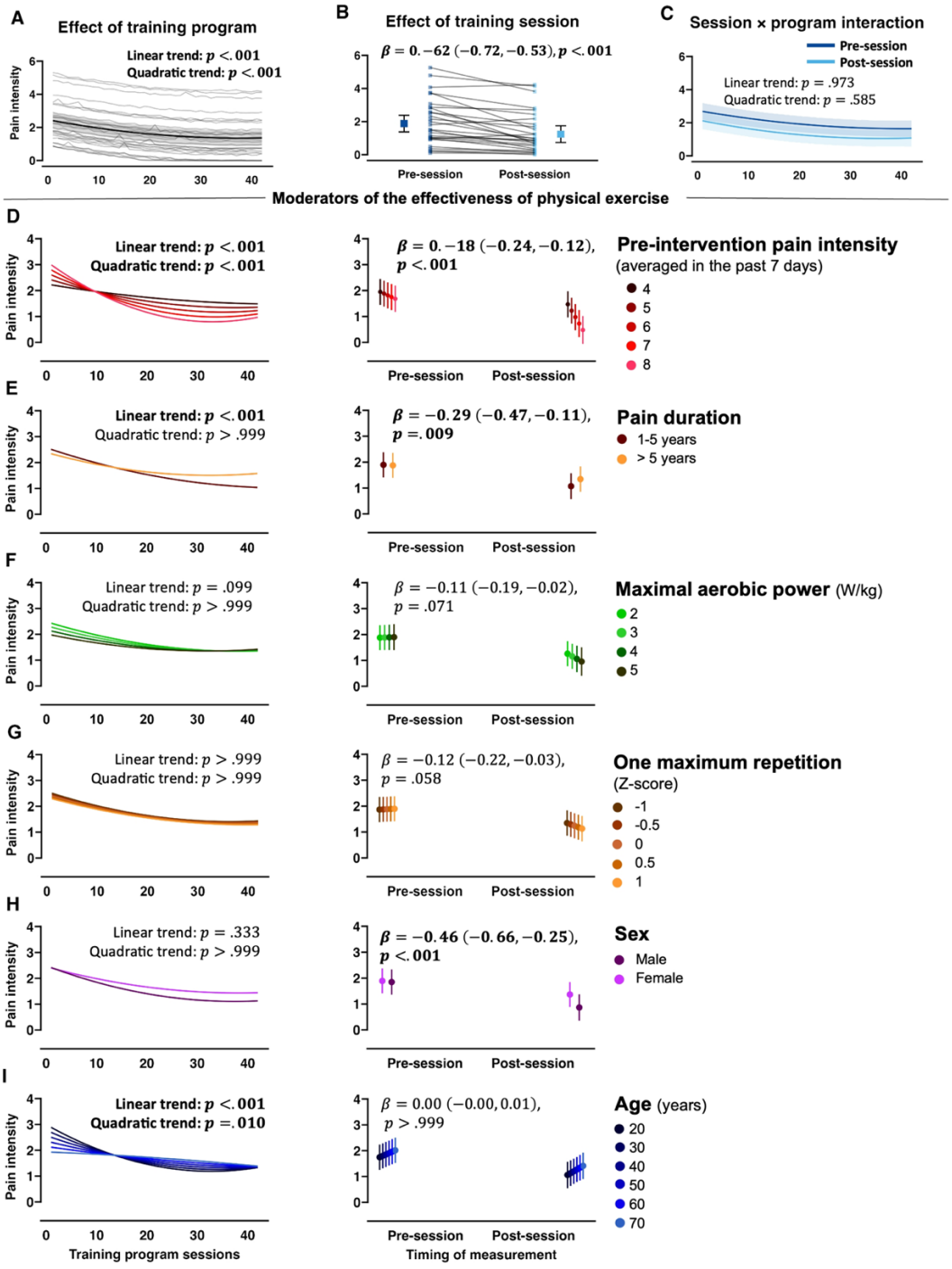


Figure 4 Pain trajectory of low back pain throughout the exercise regimen. Pain intensity decreased following chronic (A) and acute (B) exercise. Short-term hypoalgesia induced by a single training session (i.e., acute exercise) remains present during the entire physical training program (C). Pain decreased non-linearly over time, slowing down as participants went through the physical training program. On average,

each training session reduced participants' low back pain by ~0.6/10. Panels D through I show cross-level interactions with 2nd-level moderators. All range displayed for moderators are consistent with observed values in our samples.

Table 1 Comparison of baseline characteristics.

	Exercise (n=28)	**Control** (n=29)	***p***
Sex			0.302
Male	7	12	
Female	21	17	
Age	45.25 (15.14)	45.86 (12.8)	0.870
Height	1.66 (0.09)	1.68 (0.09)	0.438
Weight	72.7 (13.13)	78.20 (16.56)	0.171
BMI	26.3 (4.43)	27.60 (4.90)	0.300
Pain intensity	4.93 (1.54)	5.62 (1.70)	0.113
Pain duration			
> 5 years	17	15	0.125
1 -5 years	11	10	
< 1 years	0	4	

Table 2 Linear mixed-effects model on the physical and psychosocial outcomes. Estimates are shown with their 95% confidence intervals.

	Exercise group		**Control group**		**Interaction**
	Pre	**Post**	**Pre**	**Post**	***β***
Cardiorespiratory fitness					
Submaximal exercise testing	131 (115, 146)	**145 (140, 152)** $^{\$\$\$}$	128(113, 143)	128 (122, 135)	**-4.38 (-6.52, -2.23)**
6-min walk test (m)	573 (536, 610)	**618 (581, 655)** $^{\$\$}$	535 (499, 571)	539 (503, 576)	**-10.06 (-17.9, -2.21)**
Muscular strength					
Handgrip (kg)	72.6 (63.8, 81.4)	67.6 (59.0, 76.3)	71.6 (62.8,	64.2 (55.6,	-0.61 (-1.68, 0.46)
Chairstand (nbr of repetitions)	10.9 (9.9, 12.0)	9.7 (8.7, 10.7)	12.2 (11.1,	9.9 (8.9, 11.0)	-0.24 (-0.
Short walking tests					
Timed Up-and-go (usual gait;	8.6 (7.6, 9.5)	8.0 (7.1, 8.9)	9.6 (8.6, 10.5)	9.0 (8.1, 9.4)	0.01 (-0.16, 0.19)
Timed Up-and-go (fast gait; s)	6.3 (5.6, 7.0)	6.0 (5.3, 6.7)	7.0 (6.23, 7.7)	6.7 (6.1, 7.4)	0.03 (-0.07, 0.13)
10m-walk test (usual gait; m/s)	1.3 (1.2, 1.4)	1.4 (1.3, 1.5)	1.3 (1.1, 1.4)	1.3 (1.2, 1.4)	-0.04 (-0.14, 0.05)
10m-walk test (fast gait; m/s)	1.9 (1.8, 2.0)	2.0 (1.9, 2.1)	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)	-0.06 (-0.16, 0.04)
Psychosocial and pain outcomes					
Average pain (past week; /10)	4.9 (4.3, 5.6)	**2.6 (1.9, 3.2)** $^{\$\$\$}$	5.6 (5.0, 6.2)	5.3 (4.7, 5.9)	**0.51 (0.29, 0.73)** ⁂
Average test-evoked pain (/10)	3.11 (2.3, 3.9)	**1.6 (0.8, 2.4)** $^{\$\$\$}$	4.1 (3.4, 4.9)	4.5 (3.6, 5.3)	**0.47 (0.23, 0.71)** ⁂
Oswestry Disability Index	**20.4 (15.9, 25.0)**	**12.3 (7.7, 16.9)** $^{\$\$\$}$	28.0 (23.5,	27.0 (22.5,	**1.81 (0.36, 3.25)** ⁂
Tampa Scale of Kinesiophobia	**23.9 (21.5, 26.4)**	**20.8 (18.3, 23.3)**	27.5 (25.0,	27.9 (25.4,	**0.89 (0.18, 1.61)** ⁂
Pain catastrophizing Scale	16.1 (12.0, 20.1)	**10.1 (6.1, 14.2)** $^{\$\$}$	20.5 (16.5,	20.0 (16.0,	**1.36 (0.37, 2.36)** ⁂

* denotes a significant group x time interaction. $^{\$}$ denotes a significant difference between the two groups at the same time point. One, two and three symbols represent $p<.05$, $p<.01$, $p<.001$ respectively.

489

490