New Directions for Physical Rehabilitation of Musculoskeletal Pain Conditions

Exercise-induced hypoalgesia after acute and regular exercise: experimental and clinical manifestations and possible mechanisms in individuals with and without pain
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Abstract
Exercise and physical activity is recommended treatment for a wide range of chronic pain conditions. In addition to several well-documented effects on physical and mental health, 8 to 12 weeks of exercise therapy can induce clinically relevant reductions in pain. However, exercise can also induce hypoalgesia after as little as 1 session, which is commonly referred to as exercise-induced hypoalgesia (EIH). In this review, we give a brief introduction to the methodology used in the assessment of EIH in humans followed by an overview of the findings from previous experimental studies investigating the pain response after acute and regular exercise in pain-free individuals and in individuals with different chronic pain conditions. Finally, we discuss potential mechanisms underlying the change in pain after exercise in pain-free individuals and in individuals with different chronic pain conditions, and how this may have implications for clinical exercise prescription as well as for future studies on EIH.

Keywords: Exercise, Hypoalgesia, Pain sensitivity, Mechanisms

1. Introduction
Exercise is guideline recommended treatment for a range of chronic pain conditions.\textsuperscript{49} Regular exercise and physical activity in general have well-documented positive effects on a range of physical and mental health domains including cardiovascular health, stress, mood, sleep, and sexual health.\textsuperscript{146} In addition, clinically important reductions in pain are often observed after 8 to 12 weeks of exercise therapy\textsuperscript{163}, however, as little as 1 session of exercise can induce hypoalgesia. This phenomenon is known as exercise-induced hypoalgesia (EIH).\textsuperscript{92,195} The first observation of EIH was published 40 years ago by Black et al.\textsuperscript{14} During the past few decades, the number of studies investigating the effect of exercise on pain has increased dramatically, likely reflecting the increasing burden of pain as well as the recognized role of exercise in the treatment of pain.

This article will begin with a brief introduction to the methodology used in the assessment of the manifestations and mechanisms of EIH in humans. The second part of the article will present an overview of the findings from previous experimental studies investigating changes in pain perception after acute and regular exercise in pain-free individuals and in individuals with different chronic pain conditions. Possible mechanisms underlying the response to exercise in pain-free individuals and in individuals with different chronic pain conditions will also be discussed. In the last part of the article, implications for exercise prescription and future EIH studies will be addressed.

1.1. Assessment of exercise-induced hypoalgesia—methodological considerations

The effect of a single bout of exercise on pain perception in humans has primarily been investigated experimentally in laboratory settings. The methods used in these investigations are diverse, incorporating different study designs and methods of pain assessment. Most often, EIH has been investigated using a within-group pre-post design, whereby participants’ pain is assessed at different exercising and nonexercising body sites before and during/after exercise.\textsuperscript{130} Controlled studies using similar methodology but different designs (eg, crossover trials and parallel trials) have also been conducted.\textsuperscript{80,162,195,204} The results...
of these studies, especially those where participants were randomized to exercise or control, or where the order of exercise and control were randomized and counterbalanced for crossover trials, give a less biased estimate of the effect of a single bout of exercise on pain.

1.1.1. Pain threshold, intensity, and tolerance

Pain has been quantified in a variety of ways in studies of EIH, with quantitative sensory testing used most often. Quantitative sensory testing describes a series of tests that measure the perceptual responses to systematically applied and quantifiable sensory stimuli (usually pressure, thermal, or electrical). These tests typically involve the assessment of a person’s pain threshold or pain tolerance which are, respectively, the minimum intensity of a stimulus that is perceived as painful and the maximum intensity to a noxious stimulus that the participant is willing to tolerate. Ratings of pain intensity and unpleasantness during exposure to various noxious stimuli might also be measured. As an example, pressure may be applied at an increasing intensity over the lower leg using an inflated cuff, with participants asked to rate the point at which this pressure becomes painful (threshold) and then endure it for as long as possible (tolerance) while rating its intensity or unpleasantness. Using this example, EIH could manifest as an increase in pain threshold, an increase in pain tolerance, and/or a reduction in ratings of pain intensity or unpleasantness. These measures are most commonly assessed in the immediate postexercise period (eg, 0–15 minutes), but some studies have measured pain 30 to 60 minutes after exercise cessation to investigate the persistence of EIH.

1.1.2. Pain modulatory mechanisms

Methods that assess an individual’s ability to modulate pain have been increasingly used in recent studies of EIH. These include temporal summation, spatial summation, conditioned pain modulation, and offset analgesia. Of these paradigms, temporal summation and conditioned pain modulation have been used most often. Temporal summation refers to an increase in pain after repetitive stimulation at the same intensity and is considered a behavioural correlate of wind-up—the frequency-dependent increase in C-fibre-evoked responses of dorsal horn neurons which, in turn, was associated with lower pain ratings to thermal stimuli. Ratings of pain intensity and unpleasantness during exposure to various noxious stimuli might also be measured. As an example, pressure may be applied at an increasing intensity over the lower leg using an inflated cuff, with participants asked to rate the point at which this pressure becomes painful (threshold) and then endure it for as long as possible (tolerance) while rating its intensity or unpleasantness. Using this example, EIH could manifest as an increase in pain threshold, an increase in pain tolerance, and/or a reduction in ratings of pain intensity or unpleasantness. These measures are most commonly assessed in the immediate postexercise period (eg, 0–15 minutes), but some studies have measured pain 30 to 60 minutes after exercise cessation to investigate the persistence of EIH.

The same is true of isometric exercise where the primary effect of exercise has consisted of cycling, running, and stepping of various durations (30 seconds–30 minutes) and intensities (low to high). The same is true of isometric exercise where upper-limb and lower-limb exercise of both short and long duration (<5 seconds—exhaustion) and varied intensity (10%–100% MVC) have been studied. Studies of dynamic resistance exercise have typically used whole-body training at moderate intensities. Interestingly, EIH is reproducible with each type of exercise, even when modest doses are used.

1.1.3. Nociceptive processing

Although not an assessment of pain per se, techniques that assess the function of the nociceptive pathways have sometimes been used to investigate EIH. These more complex methods, which include evoked potentials and neuroimaging, may provide greater insight into the mechanisms of EIH compared to more commonly used quantitative sensory tests. Evoked potentials are cortical responses recorded at the scalp using electroencephalography in response to brief and intense stimuli. Evoked potentials are described by their polarities (negative [N] and positive [P]), latencies, and amplitudes, and consist of early, late, and ultra-late components. When analysing pain-related evoked potentials, the peak-to-peak amplitude of the N2P2 is the component most related to nociception, whereby larger N2P2 amplitude is associated with more pain. There is evidence that both the sensory-discriminative and affective aspects of pain are captured by this late component of the evoked potential, and studies have shown exercise to reduce the amplitude of this component. Neuroimaging is widely used in the study of pain, but to the best of our knowledge, only 2 studies have used neuroimaging to investigate acute EIH. In one study, brain responses to noxious thermal stimuli before and after rest and exercise were measured using functional magnetic resonance imaging in women with fibromyalgia and healthy pain-free controls. The results suggested that, in the women with fibromyalgia, exercise-stimulated brain regions involved in descending pain inhibition which, in turn, was associated with lower pain ratings to thermal stimuli. In the second study, brain responses to noxious thermal stimuli before and after walking and running exercises were measured using functional magnetic resonance imaging in 20 athletes. The results suggested that running exercise reduced the pain-induced activation in the periaqueductal gray, a key area in descending pain inhibition which, in turn, was associated with lower pain unpleasantness ratings to thermal stimuli. Taken together, these results provide evidence that a single bout of exercise can modulate pain-related areas of the nervous system.

In addition to the different study designs and techniques used to quantify pain in investigations of EIH, the exercise protocols have also varied considerably. Aerobic and isometric exercise have been studied most often, whereas dynamic resistance exercise has not commonly been used. Within each mode of exercise, the prescription has varied too. For example, aerobic exercise has consisted of cycling, running, and stepping of various durations (30 seconds–30 minutes) and intensities (low to high). The same is true of isometric exercise where upper-limb and lower-limb exercise of both short and long duration (<5 seconds—exhaustion) and varied intensity (10%–100% MVC) have been studied. Studies of dynamic resistance exercise have typically used whole-body training at moderate intensities. Interestingly, EIH is reproducible with each type of exercise, even when modest doses are used.

This is described in more detail below.

2. Pain outcomes after acute and regular exercise in pain-free individuals

As illustrated in Table 1, a single session of exercise has repeatedly been observed to reduce pain sensitivity in pain-free individuals. Hypoalgesia after aerobic exercises (eg, bicycling or running), dynamic resistance exercises (eg, circuit training), and isometric exercises (eg, a wall squat) often produces an increase in pressure pain thresholds at exercising body areas of 15% to 20% compared with a quiet rest control condition. Increases in pain thresholds can also be observed at nonexercising body areas, although larger hypoalgesic responses are consistently observed in areas closer to the exercising muscles compared with nonexercising muscle areas. The observed EIH response is short-lasting, often with a duration lasting from 5 minutes after exercise to 30 minutes after exercise and may depend on the modality of the pain test stimulus.
Table 1

Summary of studies investigating acute exercise-induced hypoalgesia in pain-free individuals.

| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|-------------------|--------------|------------|------------|----------|------|--------|
| Aerobic       | Bicycling     | 70% HRmax | 30 min   | 10                | Chemical          | Pain intensity| Thigh      | —          | ↑ Pain intensity (hyperalgesia) | 1984 | Vecchiet et al. [225] |
| Aerobic       | Bicycling     | 50%–70% HRmax | 20 min  | 91               | Cold              | CPI          | —          | Hand      | No hypoalgesia | 1992 | Padawer and Levine [143] |
| Aerobic       | Bicycling     | 70%–75% VO2max | 6 min   | 41               | Cold              | CPT          | —          | Hand      | ↑ CPT ↑ CPTol | 2013 | Pokhrel et al. [154] |
| Aerobic       | Bicycling     | VO2max test | 8–12 min | 25               | Cold              | CPI          | —          | Arm       | ↓ CPI     | 2018 | Chretien et al. [18] |
| Aerobic       | Bicycling     | 50 W       | Max 8 min/step | 6              | Electrical        | EPT          | —          | Tooth     | ↑ EPT     | 1984 | Pertovaara et al. [149] |
| Aerobic       | Bicycling     | Increasing to 300 W | 15–30 min | 7               | Electrical        | EPT          | —          | Tooth     | ↑ EPT     | 1985 | Kemppainen et al. [87] |
| Aerobic       | Bicycling     | HR = 150/min | 20 min  | 11               | Electrical        | EPT          | —          | Tooth     | ↑ EPT     | 1986 | Olausson et al. [140] |
| Aerobic       | Bicycling     | Increasing to 300 W | Unknown | 6               | Electrical        | EPT          | —          | Tooth     | ↑ EPT     | 1986 | Kemppainen et al. [88] |
| Aerobic       | Bicycling     | Increasing to 200 W | Unknown | 6               | Electrical        | EPT          | —          | Tooth     | ↑ EPT     | 1990 | Kemppainen et al. [88] |
| Aerobic       | Bicycling     | Increasing to 250 W | Fatigue | 10              | Electrical        | EPT          | —          | Tooth     | ↑ EPT tooth ↑ EPT hand | 1991 | Droste et al. [30] |
| Aerobic       | Bicycling     | Increasing to VO2max | Unknown | 17              | Electrical        | EPTol        | —          | Hand     | ↑ EPT ↑ EPTol | 2005 | Drury et al. [33] |
| Aerobic       | Bicycling     | 1 KP       | 5 min    | 60               | Heat              | TSPh         | —          | Forearm   | ↑ HPI lower extremity (hyperalgesia of lower extremity) | 2006 | George et al. [50] |
| Aerobic       | Bicycling     | 60 W       | 10 min   | 21               | Heat              | HPI          | —          | —         | ↑ HPI     | 2014 | Ellinson et al. [26] |
| Aerobic       | Bicycling     | Increasing to 200 W | Unknown | 28              | Heat              | HPI          | —          | —         | ↑ HPI     | 2019 | St-Aubin et al. [175] |
| Aerobic       | Bicycling     | 75% VO2max | 30 min   | 16               | Pressure          | PPT          | —          | Hand     | ↑ PPT ↑ PPI | 1996 | Koltyn et al. [95] |
| Aerobic       | Bicycling     | 75% VO2max | 30 min   | 20               | Pressure          | PPT          | —          | Hand     | No hypoalgesia | 2006 | Monnier-Benoit and Groslambert [128] |
| Aerobic       | Bicycling     | 1. 75% VO2max 2. 50% VO2max | 1. 10 min 2. 20 min | 80              | Pressure          | PPT          | Thigh     | Arm  Shoulder | ↑ PPTs After 75% VO2max (10 and 20 min) | 2014 | Vaegter et al. [195] |
| Aerobic       | Bicycling     | 75% VO2max | 15 min   | 56               | Pressure          | PPT          | Thigh     | Shoulder | ↑ PPTs | 2015 | Vaegter et al. [196] |
| Aerobic       | Bicycling     | 75% VO2max | 15 min   | 56               | Pressure          | PPTol        | Lower leg | Arm       | ↑ PPTol lower leg | 2015 | Vaegter et al. [196] |
| Aerobic       | Bicycling     | 1. 75% VO2max 2. 50% VO2max | 20 min | 80              | Pressure          | PPTol        | Lower leg | Arm       | No hypoalgesia | 2015 | Vaegter et al. [196] |
| Aerobic       | Bicycling     | 1. 70% VO2max 2. 30% VO2max | 30 min | 10              | Pressure          | PPT          | Thigh     | Forearm  | ↑ PPT thigh After 70% VO2max ↑ PPT thigh and arm | 2016 | Micalos and Arendt-Nielsen [124] |

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Table 1 (continued)  
Summary of studies investigating acute exercise-induced hypoalgesia in pain-free individuals.

| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|--------------------|--------------|------------|------------|----------|------|--------|
| Aerobic       | Bicycling     | Increasing to VO$_2$max | Fatigue | 50 | Pressure | PPT | Knee | Ankle Arm Chest Head | ↓PPT chest (hyperalgesia) | 2016 | Kruger et al. | 103 |
| Aerobic       | Bicycling     | RPE = 14–15 | 20 min | 40 | Pressure | PPT | Thigh | Shin Hand | ↑PPT thigh ↑PPT hand | 2017 | Jones et al. | 81 |
| Aerobic       | Bicycling     | RPE = 17 | 5 min | 36 | Pressure | PPT | Thigh | Hand | ↑PPT thigh ↑PPT hand | 2017 | Jones et al. | 79 |
| Aerobic       | Bicycling     | RPE = 16 | 15 min | 34 | Pressure | PPT | Thigh | Shoulder | ↑PPT thigh ↑PPT shoulder | 2018 | Vaegter et al. | 193 |
| Aerobic       | Bicycling     | 1. HIIT: 90%–100% of max workload 2. MICT: 65%–75% of HR | 1 min | 10 | 3 | | | | No hypoalgesia | 2018 | Hakansson et al. | 58 |
| Aerobic       | Bicycling     | 75% VO$_2$max | 15 min | 31 | Pressure | PPT | Thigh | Back | ↑PPT thigh ↑PPT back ↑PPT hand | 2018 | Gajjar et al. | 45 |
| Aerobic       | Bicycling     | 75%–88% HRmax | 20 min | 15 | Pressure | PPT EP | Thigh | Shoulder Thoracic spine Hand Esophagus | No hypoalgesia | 2017 | van Weerdenburg et al. | 204 |
| Aerobic       | Bicycling     | 1. 70% HR max 2. 86% HR max | 24 min | 29 | Pressure | PPT HPT HPI | — | Hand | ↓HR after interval condition | 2014 | Kodesh and Weissman-Fogel | 91 |
| Aerobic       | Bicycling     | 1. 70% HRR 2. 50%–55% HRR | 20 min | 27 | Pressure | PPT PPI HPI TSPh | — | Forearm | ↑PPT after high intensity ↓HR ↓TSPh | 2014 | Naugle et al. | 132 |
| Aerobic       | Bicycling     | Intensity = pain level 3/10 | 15 min | 16 | Pressure | PPT HPT | Thigh | Hand | ↑PPT ↑HPT | 2016 | Black et al. | 11 |
| Aerobic       | Bicycling     | 1. 75% VO$_2$max 2. 50% VO$_2$max | 25 min | 43 | Pressure | PPT PPI HPI TSPh | Forearm | Forearm | ↑PPTs | 2016 | Naugle et al. | 133 |
| Aerobic       | Bicycling     | 60–70 W | 20 min | 40 | Pressure | HPT TSPh | Achilles | — | No hypoalgesia | 2016 | Stackhouse | 176 |
| Aerobic       | Bicycling     | 70% HRR | 15 min | 16 | Pressure | PPT HPT HPI | Thigh | Shin Foot | ↑PPT thigh ↑PPT shin ↑HPI foot | 2019 | Jones et al. | 78 |
| Aerobic       | Bicycling     | 200 W | 20 min | 6 | Reflex | NFR | Thigh | — | ↑NFR | 1992 | Guleu et al. | 56 |
| Aerobic       | Repeated back movements | Lifting 5 kg | 7 min | 18 | Pressure | Heat Cold TSPh | Back | Hand | ↑PPT back ↑PPT hand | 2019 | Kullat et al. | 104 |

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| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|-------------------|--------------|------------|------------|----------|-------|--------|
| Aerobic       | Running       | Near anaerobic threshold | 30 min   | 27                | Cold              | CPT          | —          | Hand       | ↑CPT     | 2011  | Wonders and Drury |
| Aerobic       | Running       | Self-selected | 40 min   | 1                 | Pressure          | PPT          | —          | Arm        | ↑PPT     | 1979  | Black et al. |
| Aerobic       | Running       | Self-selected | 1 mile   | 15                | Pressure          | PPT          | —          | Hand       | ↑PPT hand| 1981  | Haier et al. |
| Aerobic       | Running       | VO₂max test | Unknown  | 12               | Pressure          | PPI          | —          | Arm        | ↓PPI     | 2001  | Oktedalen et al. |
| Aerobic       | Running       | 1.75% VO₂max | 10 min   | 12               | Pressure          | PPI          | —          | Hand       | ↓PPI after 30 min at 75% VO₂max | 2004 | Hoffman et al. |
| Aerobic       | Running       | 65%–75% of HRR | 7 min   | 12               | Pressure          | PPT          | —          | Forearm    | ↑PPT     | 2004  | Drury et al. |
| Aerobic       | Running       | VO₂max test | Unknown  | 62               | Pressure          | PPI          | —          | Shoulder   | Hand    | 2015  | Stolzman et al. |
| Aerobic       | Running       | 110% Gas exchange threshold | 30 min   | 26               | Pressure          | PPT          | Thigh     | Forearm    | ↑PPT forearm | 2019  | Peterson et al. |
| Aerobic       | Running       | 85% VO₂max | 44 min   | 12               | Pressure          | Heat Cold    | CPT        | Hand       | ↓PPI     | 1984  | Janal et al. |
| Aerobic       | Running       | 85% HRmax | 10 min   | 63               | Heat Cold        | HPT CPI      | Hand       | Forearm    | ↓HPT (hyperalgesia) | 2001  | Stemberg et al. |
| Aerobic       | Running       | 75% VO₂max | 30 min   | 14               | Heat Cold        | HPI CPI      | —          | Hand       | No hypoalgesia | 2005  | Ruble et al. |
| Aerobic       | Step          | 63% VO₂max | 12 min   | 60               | Pressure          | PPI PTT      | —          | Hand       | ↑PPT     | 1994  | Gurevich et al. |
| Aerobic       | Step          | 50% of maximum number of steps in 1 minute | 5 min | 30               | Pressure          | PPI TSPp     | —          | Forearm    | ↓PPI     | 2019  | Naas-Heir et al. |
| Aerobic       | Walking       | 6.5 km/h | 10 min   | 5                | Pressure          | PPT          | Thigh     | Shoulder   | No hypoalgesia | 2014  | Lee |
| Aerobic       | Walking       | Fast walking | 6 min   | 35               | Pressure PPTol    | Calf         | Shoulder   | ↑PTT Calf | 2019  | Hvid et al. |
| Anaerobic     | Wingate test | "All-out" | 30 seconds | 50               | Pressure          | PPT          | —          | Shoulder   | LPPTs (hyperalgesia) | 2012  | Arroyo-Morales et al. |
| Anaerobic     | Bicycle Sprint | "All-out" | 3 × 6 seconds | 12               | Pressure          | PPT          | Thigh     | Lower leg  | LPPTs (hyperalgesia) | 2018  | Klich et al. |
| Anaerobic     | Wingate test | "All-out" | 30 seconds | 50               | Pressure          | Heat HPT PPTol TSPp TSPc   | Hand       | ↑PTT (hyperalgesia) | 2018  | Samuelly-Leichtag et al. |
| Dynamic resistance | Full-body circuit | Moderate | 20 min | 17               | Pressure          | PPT PPTol Shin  | —          | ↑PTT PPTol | 1996  | Bartholomew et al. |
| Dynamic resistance | Full-body circuit | 75% 1RM | 4 exercises 3 × 10 repetitions (45 min) | 13               | Pressure          | PPT PPTol | —          | Hand       | ↑PTT | 1998  | Koltyn and Arbogaat |
| Dynamic resistance | Full-body circuit | 75% 1RM | 4 exercises 3 × 10 repetitions (45 min) | 21               | Pressure          | PPT PPTol | —          | Hand       | ↑PTT | 2009  | Focht and Koltyn |

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### Table 1 (continued)

**Summary of studies investigating acute exercise-induced hypoalgesia in pain-free individuals.**

| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|--------------------|---------------|------------|-------------|----------|------|--------|
| Dynamic resistance | Upper-body circuit | Unknown | 10 min 40 min | 5 | Pressure | PPT | Shoulder | — | No hyperalgesia | 2014 | Lee et al.110 |
| Dynamic resistance | Full-body circuit | 60% 1RM | 3 exercises 12 repetitions | 24 | Pressure | PPT | Hand | — | ↑PPTol | 2017 | Baiamonte et al.4 |
| Dynamic resistance | Kettlebell swings | 8–12 kg | 8 × 20 seconds | 32 | Pressure | PPT | Lower back | — | ↑PPTs | 2017 | Keilman et al.84 |
| Dynamic resistance | Full-body circuit | 60% 1RM | 9 exercises 12 repetitions | 10 | Pressure | PTT | Buttock | — | ↑PTT hand | 2018 | McKean et al.119 |
| Dynamic resistance | Handgrip | 100% MVC | 30 contractions in 1 minute | 12 | Pressure | PPT | Forearm | — | ↑PPT | 2004 | Drury et al.119 |
| Dynamic resistance | Handgrip | Medium | Maximum of 40 contractions in 1 minute | 48 | Heat | HPI | Hand | — | ↑HPI | 2008 | Weissman-Fogel et al.207 |
| Dynamic resistance | Back extensions | Bodyweight | 3 × 15 repetitions | 20 | Heat | HPI | Foot | — | ↑HPI (lower extremity) | 2006 | George et al.50 |
| Dynamic resistance | Cervical flexions | Head weight | 3 × 10 repetitions | 30 | Pressure | HPI | Foot | — | ↑HPI | 2011 | Bishop et al.10 |
| Eccentric | Wrist extension | 30% MVC | 5 × 10 repetitions | 13 | Pressure | PPT | Forearm | — | ↑PPT | 2010 | Slater et al.171 |
| Eccentric | Elbow flexion | Max | 10 × 6 repetitions | 10 | Pressure | EPT | Arm | — | ↑EPT (hyperalgesia) | 2015 | Lau et al.108 |
| Eccentric | Heel-raise | Bodyweight | 4 × 15 contractions | 40 | Pressure | Heat | HPI | — | ↓HPI and ↓PPT | 2016 | Stackhouse et al.176 |
| Isometric | 1. Knee extension 2. Elbow flexion | 1. 30% MVC 2. 60% MVC | 1. 90 seconds 2. 1,180 seconds 2. 90 seconds 2. 1,180 seconds | 80 | Pressure | PPT | Thigh (knee extension) | Arm (elbow flexion) | ↑PPTs (after low and high intensity exercises) | 2014 | Vaegter et al.195 |
| Isometric | 1. Knee extension 2. Elbow flexion | 1. 30% MVC 2. 60% MVC | 3 min | 80 | Pressure | PPTol | Lower leg | Arm | ↑PPTol (after both elbow and knee exercises) | 2015 | Vaegter et al.195 |
| Isometric | 1. Knee extension 2. Elbow flexion | 20% of MVC | Fatigue | 64 | Pressure | PPT | — | Hand | ↑PPT after elbow flexion (women only) | 2016 | Lemley et al.113 |
| Isometric | 1. Knee extension 2. Shoulder rotation | 1. 1 kg 2. 0.5 kg | Fatigue | 24 | Pressure | PPT | — | — | ↑PPT thigh + shoulder both conditions | 2003 | Kosek and Lundberg151 |
| Isometric | Back extension | — | 2 min | 29 | Pressure | PPT | Back | Thigh | ↑PPT thigh | 2017 | Gajsar et al.46 |

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| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|--------------------|--------------|------------|------------|----------|-------|--------|
| Isometric     | Elbow flexion | 4. 80% MVC | 4. Fatigue | 40                | Pressure           | PPI          | —          | Hand       | ↑PPT and ↓PPI after max and after 25% MVC until fatigue | 2008 | Hoeger Bement et al. |
| Isometric     | Elbow flexion | 25% MVC    | Fatigue   | 20                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT LPI | 2009 | Hoeger Bement et al. |
| Isometric     | Elbow flexion | 25% MVC    | Fatigue   | 26                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT LPI (men only) | 2014 | Bement et al. |
| Isometric     | Elbow flexion | 1. Max contractions 1. 3 reps | 3. 25% MVC | 24                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT LPI (women only) | 2014 | Lemley et al. |
| Isometric     | Elbow flexion | 25% MVC    | Fatigue   | 39                | Pressure           | PPT          | PPI Hand   | —          | ↓PPI | 2014 | Lemley et al. |
| Isometric     | Elbow flexion | 40% MVC    | 3 min     | 26                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT | 2016 | Jones et al. |
| Isometric     | Arm abduction | 1 kg       | Fatigue   | 25                | Pressure           | PPT          | Shoulder   | Shoulder   | ↑PPTs | 2000 | Persson et al. |
| Isometric     | Handgrip      | 25% MVC    | 2 min     | 134               | Cold               | CPT          | CPI        | —          | ↑CPT hand | 2017 | Foxen-Craft and Dahlquist |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 34                | Electrical         | EPI          | —          | Lower leg  | ↓LEPI | 2016 | Umeda et al. |
| Isometric     | Handgrip      | 1. 40% MVC  | 2. 25% MVC | 88                | Heat               | TSPh         | Hand       | —          | ↓TSPh for both conditions | 2013 | Koltyn et al. |
| Isometric     | Handgrip      | 1. Maximal 2. 40%–50% MVC | 2 min     | 31                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT LPI | 2001 | Koltyn et al. |
| Isometric     | Handgrip      | 40%–50% MVC | 2 min     | 40                | Pressure           | PPT          | PPI Hand   | Hand       | ↑PPT both sites LPP both sites | 2007 | Koltyn and Umeda |
| Isometric     | Handgrip      | 33% MVC    | 3 min     | 79                | Pressure           | PPTol        | Hand       | —          | ↑PPTol | 2009 | Alghamdi and Al-Sheikh |
| Isometric     | Handgrip      | 1. 25% MVC 2. 25% MVC | 1. 1 minute 2. 3 min | 23                | Pressure           | PPT          | PPI Hand   | —          | No hypoalgesia | 2009 | Umeda et al. |
| Isometric     | Handgrip      | 25% MVC    | 1. 1 minute 2. 3 min 3. 5 min | 50                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT and ↑PPI after all durations | 2010 | Umeda et al. |
| Isometric     | Handgrip      | 50% MVC    | Fatigue   | 50                | Pressure           | PPT          | Forearm    | Forearm    | ↑PPT | 2017 | Black et al. |
| Isometric     | Handgrip      | 50% MVC    | Fatigue   | 26                | Pressure           | PPT          | Forearm    | Thigh      | ↑PPT forearm ↑PPT thigh | 2019 | Peterson et al. |
| Isometric     | Handgrip      | 25% MVC    | 1. 1% MVC 2. 15% MVC 3. 25% MVC | Unknown | 2008               | Electrical   | Reflex     | —          | ↓LEPI after 15% and 25% MVC | 2008 | Ring et al. |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 27                | Pressure           | PPT          | PPI Hand   | TSPh Forearm | ↑PPT LPI (women) | 2014 | Naugle et al. |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 58                | Pressure           | PPT          | PPI Hand   | —          | ↑PPT | 2014 | Koltyn et al. |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 43                | Pressure           | PPT          | PPI TSPh   | Forearm    | ↑PPT | 2016 | Naugle et al. |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 58                | Pressure           | PPT          | PPI TSPh   | Hand       | ↑PPT | 2017 | Brellenthin et al. |
| Isometric     | Handgrip      | 25% MVC    | 3 min     | 58                | Pressure           | PPI          | Hand       | —          | ↓PPI hand | 2018 | Crombie et al. |
Table 1 (continued)

| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|--------------------|--------------|------------|-------------|----------|------|--------|
| Isometric     | Handgrip      | 25% MVC   | 3 min    | 52                | Pressure           | Thigh        | Forearm    | PPT (hyperalgesia) | 2018    | Ohnman et al.¹³³  |
| Isometric     | Knee extension| 21% MVC   | Fatigue  | 14                | Pressure           | PPT          | —          | Thigh       | ↑PPT    | 1995 | Kosek and Ekholm⁹⁹ |
| Isometric     | Knee extension| 30% MVC   | Fatigue  | 134               | Pressure           | PPT          | —          | Shoulder    | ↑PPT    | 2017 | Tour et al.¹⁵⁶    |
| Isometric     | Knee extension| 0.75 kg   | 12 min   | 15                | Pressure           | Thigh        | Thigh      | Larter leg | ↑PPTol  | 2017 | van Weerenburg et al.³⁴⁴ |
| Isometric     | Knee extension| 30% MVC   | 3 min    | 20                | Pressure           | Shin         | Neck       | ↑PPT shrin  | 2018    | Harris et al.⁵¹    |
| Isometric     | Pinch grip    | 25% MVC   | 5 min    | 38                | Heat               | HPI          | Hand       | Hand        | No hypoalgesia   | 2013  | Paris et al.¹⁴⁴  |
| Isometric     | Pinch grip    | 1. 5% MVC | 15 seconds| 38              | Heat               | HPI          | Hand       | Hand        | ↑HPI with larger effects for higher intensity | 2014  | Misra et al.¹²⁷    |
| Isometric     | Teeth-clenching| —         | Fatigue  | 33                | Pressure           | Jaw          | Forearm    | ↑PPT jaw    | 2019    | Laneffet et al.¹⁰⁸  |
| Isometric     | Trunk flexion | —         | Fatigue  | 70                | Pressure           | Abdomen     | Naileded   | ↑PPT Abdomen | 2019    | Deering et al.²⁷    |
| Isometric     | Wall squat    | —         | 3 min    | 35                | Pressure           | Thigh       | Shoulder   | ↑PPT thigh   | 2019    | Vaeger et al.²⁰⁰   |

The table is organized according to exercise type, exercise form, pain test modality, and year of publication.

CPI, cold pain intensity; CPT, cold pain threshold; CPI, electrical pain intensity; EPT, electrical pain threshold; EPTol, electrical pain tolerance; HPI, heat pain intensity; HPI with larger effects for higher intensity; HPT, heat pain threshold; HPTol, pressure pain tolerance; RM, repetition maximum; RPE, rating of perceived exertion; TSP, temporal summation of pain; TSPH, temporal summation of heat pain; TSPo, temporal summation of pressure pain; VO₂max, maximal aerobic capacity.

2.1. Exercise intensity and duration

The hypoalgesic responses seem to be similar between exercise types,¹³³,¹⁵⁶ although EIH differences have been observed,³⁵² but exercise intensity and duration quite consistently affect the EIH response. Exercise intensity affects the EIH response after aerobic exercise.¹⁰⁹,¹²⁴,¹³²,¹⁵⁶ For example, in 80 pain-free individuals, it was observed that a moderate-to-high intensity bicycling exercise produced significantly larger EIH responses at the exercising quadriceps muscle, as well as at the nonexercising biceps and trapezius muscles, compared with a low-intensity bicycling exercise.¹⁵⁶ Findings on the influence of aerobic exercise intensity are more equivocal, with one study observing a dose-response with larger effects after bicycling for 30 minutes compared with 10 minutes,⁹⁹ and one study observing no difference between bicycling for 10 minutes compared with 20 minutes.¹⁵⁶ Moreover, the fact that very short-duration aerobic exercise can elicit EIH¹²⁵,¹⁶² implies that intensity, or the combination of intensity and duration, may be more important for determining the size of EIH after aerobic exercise than either variable alone.

Exercise intensity and duration may also affect the EIH response after isometric exercises,⁶⁴,¹²⁷,¹⁵⁷ although the results are more inconsistent. In 40 individuals, pressure pain thresholds at the hand were increased and pressure pain intensity was decreased after low-intensity (25% of maximal voluntary contraction [MVC]) isometric elbow flexion until exhaustion. However, no hypoalgesia was observed when the contraction was held for only 2 minutes.⁶⁴ By contrast, hypoalgesia was found after 90 and 180 seconds isometric knee extensions and elbow flexion exercises at 30% MVC and 60%, respectively, in 80 healthy individuals; however, the hypoalgesic responses were not different in magnitude between low-intensity and high-intensity contractions nor between shorter or longer durations.¹⁶⁰ The fact that very low doses of isometric exercise (eg, three maximal contractions of 5-second duration, totaling 15 seconds of exercise) can produce EIH⁶⁴ lends further support to the lack of clear dose-response, which is further evidenced by a study of 50 individuals where elevations in pain threshold were not different between isometric handgrip exercises at 25% MVC for 1, 3, or 5 minutes.¹⁸⁹

2.2. Effects on pain modulatory mechanisms

As described, robust increases in pressure pain thresholds are observed after exercise, but exercise can also affect spinal and supraspinal mechanisms of pain. Temporal summation of pressure and heat pain was reduced after submaximal isometric exercises at 25% to 40% of MVC for 3 minutes,⁹⁴,⁹⁶,¹³¹,¹⁵⁶ and 20 minutes of aerobic exercise at 55% to 70% of heart rate reserve reduced temporal summation of heat pain¹³²; however,
temporal summation of pressure pain was not affected by 15 to 20 minutes of aerobic exercise at 50% to 75% of VO₂max. However, not all studies have shown exercise to have positive effects on pain mechanisms. For example, Alsouhibi et al. observed a decrease in the CPM response after exercise. By contrast, other studies have found exercise to have no effect on CPM or offset analgesia, suggesting that exercise can, but does not always, influence spinal and supraspinal mechanisms of pain. Exercise can also influence the ability to cope with pain. The perceived pain intensity of a supra-threshold stimulus is consistently reduced by aerobic, isometric, and dynamic resistance exercises, and acute exercise can reduce ratings of pain unpleasantness even in the absence of a change in pain intensity. In addition, low-intensity non-aerobic and isometric exercises also increase the tolerance to a painful stimulus. A 20% increase in pain tolerance was observed by Vaegter et al. after a 3-minute submaximal isometric knee extension exercise, and after a 6-minute walking exercise compared with rest in 35 pain-free individuals.

2.3. Factors influencing exercise-induced hypoalgesia

Exercise that produces acute hypoalgesia is often perceived as moderately painful with peak pain intensity ratings around 5 or 6 on a 0 to 10 numerical rating scale, and painful exercises seem to have larger hypoalgesic effects than nonpainful exercises, at least in pain-free individuals, but perhaps not in individuals with chronic pain. Treatment expectations are a well-recognized factor known to modulate treatment outcomes and the information about the effect of exercise given to individuals before exercise influences the magnitude of the EIH response. First, a randomized controlled trial by Jones et al. observed that the hypoalgesic effect after bicycling was slightly increased if positive information about EIH was given before the exercise compared to when no EIH information was given before exercise. Second, a randomized controlled trial by Vaegter et al. comparing positive vs negative pre-exercise information observed a 22% increase in pain thresholds in the positive information group, whereas the negative information group had a 4% decrease (hyperalgesia) in pain threshold at the exercising muscle (Vaegter et al., in review). Both studies observed a positive correlation between expectancies and hypoalgesia after exercise.

Despite robust hypoalgesia after exercise on a group level, the response to exercise is not identical across individuals and across days. Several studies have investigated the stability of the EIH response in pain-free individuals across different days using a number of aerobic and isometric exercise protocols. Across protocols, some individuals consistently show hypoalgesia after exercise, some individuals consistently showed hyperalgesia after exercise, and some individuals had a change in their response from hypoalgesic to hyperalgesic or vice versa between days. Interestingly, the majority of individuals showed hypoalgesia at some point.

2.4. Regular exercise and pain

The effect of regular exercise and physical activity on pain sensitivity has been investigated, albeit less than the effect of a single session of exercise. In pain-free individuals, there have been relatively few studies investigating whether those who are more physically active experience greater EIH. The results of these studies show that EIH is usually similar between inactive and active pain-free individuals irrespective of the type of exercise they regularly perform (ie, aerobic or strength training) and the methods used to assess physical activity (ie, self-report or objectively measured using accelerometry). However, Ellingson et al. observed lower pain intensity ratings and lower pain unpleasantness ratings to suprathreshold heat pain stimulations in pain-free women who were physically active as defined by the current public health recommendations compared with women who were less physically active than recommended. There is also some evidence that individuals who are more physically fit experience greater EIH.

Regarding the effect of a longer period of exercise training in pain-free individuals, Hakansson et al. observed changes in PPT in the legs after 6 weeks of moderate bicycling exercises (3 times/week) but not after high-intensity interval exercise. In addition, Jones et al. observed increases in pressure pain tolerance but not pain threshold after bicycling 30 minutes at 75% of VO₂ max 3 times/week for 6 weeks compared with a control condition. These findings suggest that regular exercise in pain-free individuals specifically influences the ability to cope with pain (ie, pain perception above the pain threshold) rather than the level at which pain is first perceived (pain threshold). Similar observations have been found in athletes compared with less active individuals. A systematic review by Tesarz et al. showed consistently higher pain tolerance across different pain modalities (ie, pressure, heat, cold, electrical, and ischemic) in athletes; however, for pain thresholds, the conclusion was less consistent.

In addition to the effect on pain tolerance, regular exercise may also affect the ability to inhibit pain as assessed by the CPM paradigm. Naugle et al. observed that pain-free individuals reporting more regular physical activity also had a larger CPM response compared with individuals reporting less regular physical activity. Although previous investigations on CPM in athletes have been equivocal because increased CPM has been observed, the potential effect of regular exercise on CPM may be a potential mechanism underlying the preventive effect of exercise on pain because better CPM capacity has been associated with a reduced risk of chronic pain. The preventive effect of regular exercise is supported by a recent systematic review with meta-analysis concluding that regular exercise performed 2 to 3 times/week reduces the risk of low back pain by 33%. This is true even in those who are at an increased risk of developing chronic pain.

3. Pain outcomes after acute and regular exercise in individuals with chronic pain

In individuals with different chronic pain conditions, the response to a single session of exercise is less consistent as hypoalgesia, reduced hypoalgesia, or even hyperalgesia (ie, increased sensitivity to pain) has been observed. As illustrated in Table 2, hypoalgesia after exercise has, eg, been observed in individuals with chronic musculoskeletal pain, patella femoral pain, knee osteoarthritis, menstrual pain, and rheumatoid arthritis. However, reduced EIH responses or even hyperalgesia after exercise has often been demonstrated in individuals with whiplash-associated disorder, fibromyalgia, painful diabetic neuropathy, chronic musculoskeletal pain, and in a delayed-onset muscular soreness pain model. Hyperalgesia after exercise is often observed in individuals with more widespread chronic pain conditions. This was first observed by in 5 individuals with fibromyalgia who showed
| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain condition | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|----------------|-------------------|--------------|------------|------------|----------|------|--------|
| Aerobic       | Bicycling     | Increasing to 75% HRmax | Unknown | 20 | ME/CFS | Clinical | Pain intensity | — | — | No hypoalgesia | 2017 | Oosterwijck et al.141 |
| Aerobic       | Bicycling     | VO₂max test | 8–12 min | 25 | Chronic pain | Cold | CPI | — | Arm | No hypoalgesia | 2018 | Chretien et al.18 |
| Aerobic       | Bicycling     | 1 KPa | 5 min | 12 | Chronic Low back pain | Heat | HPI | TSPh | — | Forearm Lower leg | ↓ TSPh forearm | 2009 | Bialosky et al.9 |
| Aerobic       | Bicycling     | 80% VO₂max | 30 min | 23 | DOMS MODEL | Pressure | PPT | — | Arm | No hypoalgesia | 2002 | Darnacker et al.25 |
| Aerobic       | Bicycling     | 70% VO₂max | 20 min | 8 | Chronic low back pain | Pressure | PPI | — | Hand | ↓ PPI | 2005 | Hoffman et al.68 |
| Aerobic       | Bicycling     | Increasing to 130 W | 37 min | 26 | Chronic fatigue syndrome | Pressure | PPT | Lower leg | Hand Lower back | tPPTs (hyperalgesia) | 2010 | Meeus et al.123 |
| Aerobic       | Bicycling     | Increasing to 130 W | 37 min | 21 | Chronic low back pain | Pressure | PPT | Lower leg | Hand Lower back | tPPTs (hyperalgesia) | 2010 | Meeus et al.123 |
| Aerobic       | Bicycling     | 1. 75% HRmax 2. Self-paced | Unknown | 22 | Chronic fatigue syndrome | Pressure | PPT | Lower leg | Hand Lower back | No hypoalgesia/ some hyperalgesia | 2010 | Van Oosterwijck et al.202 |
| Aerobic       | Bicycling     | 1. Increasing to 75% HRmax 2. Self-paced 1. Unknown 2. Individual | 20 | ME/CFS | Pressure | PPT | Lower leg | Hand Lower back | tPPT and PPTtol (both conditions) | ↓ PPI (both conditions) | 2011 | Newcomb et al.136 |
| Aerobic       | Bicycling     | 1. 62% HRmax 2. Self-paced | 20 min | 21 | Fibromyalgia | Pressure | PPT | — | Hand | ↑ PPT lower back (after self-paced) | ↓ PPI (both conditions) | ↑ PPTs (both conditions) | 2012 | Van Oosterwijck et al.203 |
| Aerobic       | Bicycling     | Increasing to 75% HRmax | Maximum of 15 min | 19 | Fibromyalgia with chronic fatigue | Pressure | TSPp | — | Shoulder Hand | No hypoalgesia | 2015 | Meeus et al.122 |
| Aerobic       | Bicycling     | Increasing to 75% HRmax | Maximum of 15 min | 16 | RA | Pressure | TSPp | — | Shoulder Hand | No hypoalgesia | 2015 | Meeus et al.122 |
| Aerobic       | Bicycling     | 75% of VO₂max | 15 min | 61 | Chronic MSK pain | Pressure | PPT | PPTtol | Thigh | Arm Shoulder Lower leg | tPPTs | 2016 | Vaegter et al.197 |
| Aerobic       | Bicycling     | 1. 70% HRmax 1. Continuous 20 min | 15 | Chronic fatigue syndrome | Pressure | PPT | Thigh | Shoulder Hand | tPPT thigh after interval | 2016 | Sandler et al.164 |

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| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain condition | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|----------------|-------------------|--------------|------------|------------|----------|-------|--------|
| Aerobic       | Bicycling     | 2. 75%–85% HRmax | 2. Interval 5 × 4 min 15 min | 14 | Knee OA | Pressure | PTTol | Thigh | Arm Shoulder Lower leg | ↑PPTs | 2017 | Vaeger et al. 
|               |               | 75% of VO₂max |                      |              |                |               |            |          |            |         |       | 194    |
| Aerobic       | Bicycling     | 75% of HRmax | 30 min | 21 | WAD | Pressure | PPT | — | Neck Shin | No hypoalgesia | 2017 | Smith et al. |
| Aerobic       | Bicycling     | Increasing to 75% HRmax | Unknown | 40 | Knee OA | Pressure | PPT | Thigh Knee | Forearm | ↑PPTs (if normal CPM) ↓PPTs (if abnormal CPM) No hyperalgesia | 2017 | Fingleton et al. | 40
|               |               |                  |          |      |         |               |               |          |            |          |       | 118    |
| Aerobic       | Bicycling     | 50 W | 12 min | 20 | Chronic fatigue syndrome | Pressure | TSPp | Thigh | Shoulder | ↑PPTs (if normal CPM) ↓PPTs (if abnormal CPM) No hyperalgesia | 2018 | Malflief et al. |
| Aerobic       | Bicycling     | 70% VO₂max | 30 min | 27 | Gulf veterans | Pressure | Heat | PPT | HPI | Hand | ↑HPI (if pain) (hyperalgesia) | 2010 | Cook et al. |
| Aerobic       | Running       | Bruce test | Fatigue | 10 | Fibromyalgia | Heat | TSPh | — | Hands | ↓PPTs (hyperalgesia) | 2001 | Vierck et al. |
| Aerobic       | Running       | 5 km/hour | 3 × 5min | 5 | Chronic fatigue syndrome | Pressure | PPT | — | Hands | ↓PPTs (hyperalgesia) | 2004 | Whiteside et al. |
| Aerobic       | Walking       | Self-selected | | | | | | | | | | | |
|               | Walking       | 4 min | 20 | Plantar fasciopathy | Clinical pain PPT | Pain intensity during test | Heel | — | No hypoalgesia | 2018 | Riel et al. |
|                |               | 1. Continuous 1.3 m/second |                    |              |                |               |            |          |            |         |       | 156    |
| Aerobic       | Walking       | 6 min | 24 | Knee OA | Clinical pain | Pressure | PPT | — | Forearm | ↓TSPp | 2019 | da Cunha Ribeiro et al. |
| Dynamic resistance | Leg exercises | 1. 60% 1RM | 2 exercises | 32 | Fibromyalgia | Clinical | Pain intensity | — | — | Hyperalgesia | 2018 | da Cunha Ribeiro et al. |
| Dynamic resistance | Knee extensions | 1RM | 6 × 10 repetitions | 20 | Knee OA | Clinical | Pain intensity | DOMS | Knee | — | No change in pain intensity More DOMS than controls | 2013 | Germanou et al. |
| Dynamic resistance | Knee extensions | 8RM | 1 exercise 3 × 8 repetitions | 21 | Patellar tendinopathy | Clinical pressure | Pain intensity during SLS PPT | Knee shin | Forearm | ↓Pain intensity ↑PPT shin | 2019 | Holden et al. |
| Dynamic resistance | Arm-raises | Fast | 6 min | 24 | Knee OA | Pressure | PPT | Shoulder Thigh | ↑PPT shoulder | 2020 | Hansen et al. |
| Dynamic resistance | 1. Hip abductions 2. Knee extensions | Load = 12RM | 3 exercises | 30 | PFP | Pressure | PPT PTTol TSPp | Knee Lower leg Elbow (PPT) | ↑PPT (lower leg) ↑PPTol (after knee exercises) | 2019 | Straszek et al. |

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Table 2 (continued)

Summary of studies investigating acute exercise-induced hypoalgesia in individuals with different pain conditions.

| Exercise type | Exercise form | Intensity | Duration | # of participants | Pain condition | Pain test modality | Pain outcome | Local site | Remote site | Findings | Year | Author |
|---------------|---------------|-----------|----------|-------------------|----------------|--------------------|--------------|------------|------------|----------|-------|---------|
| Dynamic resistance | Lower-body circuit | 60% 1RM | 3 exercises 10 repetitions | 11 | Knee OA | Pressure | PPT | Shoulder Knee Shin | Arm Forearm Hand | No hypoalgesia | 2014 | Burrows et al.17 |
| Dynamic resistance | Upper-body circuit | 60% 1RM | 3 exercises 10 repetitions | 11 | Knee OA | Pressure | PPT | Shoulder Arm Forearm Hand | Thigh Knee Shin | ↑PPTs (across sites) | 2014 | Burrows et al.17 |
| Dynamic resistance | Back extensions | Bodyweight | 3 × 15 repetitions | 12 | Chronic low back pain | Heat | HPI TSPb | — | Forearm Lower | Thigh Knee Shin | ↓TSPb forearm | 2009 | Bialosky et al.9 |
| Dynamic resistance | Repeated back movements | Lifting 5 kg | 7 min | 18 | Chronic low back pain | Heat | Pressure Cold | PPT | Back Leg | Hand | ↑TPT hand | 2019 | Kilanthen et al.104 |
| Dynamic resistance | Cervical flexion | Head weight | 10 × 10 seconds | 13 | Chronic neck pain | Clinical pain | Pressure | Pain intensity PPT | Neck Shoulder | ↑Pain intensity ↑PPTs | 2018 | Galindez-Ibarbengoetxea et al.47 |
| Isometric | Elbow flexion | 1. 25% MVC 2. 25% MVC 3. 100% MVC | 1. 2 min 2. Fatigue 3. 3 reps | 15 | Fibromyalgia | Pressure | PPT | — | Hand | No hypoalgesia | 2011 | Hoeger Bement et al.66 |
| Isometric | Handgrip | 25% MVC | 3 min | 18 | Diabetic neuropathy | Heat | HPI TSPb | Hand Forearm | — | Thigh Forearm | ↑PPTs (if no pain) No changes (if pain) | 2014 | Knauf and Koltyn90 |
| Isometric | Handgrip | 25% MVC | 3 min | 64 | Menstrual pain | Pressure | PPT | Forearm Shin | ↑PPTs | 2018 | Travers et al.186 |
| Isometric | Handgrip | 30% MVC | 90 seconds | 12 | Fibromyalgia | Pressure | PPT | Forearm Forearm | — | PPTs | 2005 | Staud et al.177 |
| Isometric | Knee extension | 20%–25% MVC | Fatigue | 14 | Fibromyalgia | Pressure | PPT | Thigh | — | PPT (hyperalgesia) | 1996 | Kosek et al.100 |
| Isometric | Knee extension | 10%–15% MVC | Fatigue | 17 | Fibromyalgia | Pressure | PPT | Thigh | Shoulder | ↑PPT (hyperalgesia) | 2007 | Kadetoff and Kosek101 |
| Isometric | Knee extension | 50% MVC | Fatigue | 66 | Knee OA | Pressure | PPT | Thigh | Shoulder | ↑PPTs | 2013 | Kosek et al.102 |
| Isometric | Knee extension | 50% MVC | Fatigue | 47 | Hip OA | Pressure | PPT | Thigh | Shoulder | ↑PPTs | 2013 | Kosek et al.102 |
| Isometric | Knee extension | 30% MVC | 90 seconds | 61 | Chronic MSK pain | Pressure | PPT | Arm Shoulder Lower leg | ↑PPTs | 2016 | Vaegter et al.197 |
| Isometric | Knee extension | 30% MVC | 90 seconds | 14 | Knee OA | Pressure | PPT | Thigh | Arm | ↑PPTs (if normal CPM) ↑PPTs (if abnormal CPM) | 2017 | Vaegter et al.194 |
| Isometric | Knee extension | 10% MVC | 5 min | 40 | Knee OA | Pressure | PPT | Thigh Knee | Forearm | ↑PPTs | 2017 | Fingleton et al.40 |
| Isometric | Knee extension | 30% MVC | Fatigue | 130 | Fibromyalgia | Pressure | PPT | — | Shoulder | ↑PPT | 2017 | Tour et al.185 |
| Isometric | Knee extension | 30% MVC | 5 min | 46 | RA | Pressure | PPT | Thigh | Shoulder | ↑PPTs | 2018 | Lofgren et al.117 |

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a decrease in pain thresholds during and after an isometric knee extension exercise. The observation of hypoalgesia after exercise in some groups with chronic pain conditions and the observation of hyperalgesia after exercise in other groups with chronic pain may be influenced by whether the exercise is performed using a painful or nonpainful body area. Lannersten and Kosek\textsuperscript{107} observed hypoalgesia after a 5-minute submaximal (25\% of MVC) isometric exercise in individuals with shoulder myalgia when the exercise was performed by a nonpainful leg muscle but when the exercise was performed by the painful shoulder muscle, no hypoalgesic response was observed. Similarly, Burrows et al.\textsuperscript{17} observed increases in pressure pain threshold after upper-body but not lower-body resistance exercise in people with knee osteoarthritis. These findings suggest that hypoalgesia can be induced by exercising nonpainful muscles in subjects with chronic pain,\textsuperscript{101} which may have important implications for exercise prescription in the clinical setting.

### 3.1. Factors related to lack of exercise-induced hypoalgesia

Individuals with facilitated central pain mechanisms, which are commonly observed in several chronic musculoskeletal pain conditions,\textsuperscript{121,127} often report reduced hypoalgesia after exercise. Vaegter et al.\textsuperscript{187} observed reduced EIH after submaximal isometric exercise and after bicycling exercise in chronic pain patients with high widespread pain sensitivity compared with patients with low pain sensitivity. In addition, in high pain-sensitive patients, an increase in temporal summation of pain was observed after aerobic exercise\textsuperscript{177,197} possibly mimicking the pain flare-up after exercise reported in clinical practice by some individuals with widespread chronic pain.\textsuperscript{24} Also, Fingleton et al.\textsuperscript{106} observed reduced pressure pain thresholds (hyperalgesia) after both aerobic and isometric exercises in individuals with knee osteoarthritis who demonstrated an impaired CPM response. By contrast, pain thresholds increased in knee osteoarthritis individuals with a normal CPM response suggesting that patients with impaired CPM, which is also a common finding in individuals with chronic pain,\textsuperscript{114,121} may have less acute hypoalgesic effect from exercise.

Another possible explanation for the lack of hypoalgesia after exercise often observed in individuals with chronic pain is that the exercise dose–response relationship is different in individuals with chronic pain compared with pain-free subjects. Newcomb et al.\textsuperscript{106} observed a larger EIH response in individuals with fibromyalgia after 20 minutes of aerobic exercise at a preferred intensity (45\% of maximal heart rate) compared with a prescribed and higher-intensity aerobic exercise (60\%–75\% of maximal heart rate). Similarly, Coombes et al.\textsuperscript{20} showed that isometric exercise above but not below an individual’s pain threshold increased pain responses to exercise in people with lateral epicondylalgia. These results could indicate that lower-intensity exercise creates less input to facilitated central pain mechanisms resulting in a net balance of pain inhibition and a reduction in the pain sensitivity after exercise. This may be different for chronic exercise, however, where a small benefit of painful over nonpainful exercise has been observed, albeit for clinical pain at
baseline as opposed to experimental pain in the immediate post-exercise period.174 Other possible explanations for reduced EIH include use of opioids and negative expectations about the effect of exercise. Interactions between EIH mechanisms and the use of analgesics may affect the response to exercise. Individuals treated with opioids report less CPM,150 and reduced effects of opioids have been reported in animals after long-term exercise.174 As observed in pain-free individuals, negative expectations are associated with the hypoalgesic response after exercise. Interestingly, most patients with chronic pain referred to multidisciplinary pain treatment do not expect exercises to cause less pain; on the contrary, the majority expects more pain after exercise (Fig. 1).

3.2. Regular exercise and pain

Regular exercise is guideline-recommended treatment for a wide range of chronic pain conditions.49,146 Regular exercise is safe and generally well accepted by individuals with mild to moderate chronic pain; however, the effects on pain and pain sensitivity are somewhat conflicting, and the level of evidence for a positive effect is generally low.49 Clinically relevant reductions in pain and pain sensitivity are often observed after 8 to 12 weeks of exercise therapy in individuals with knee or hip osteoarthritis,170 but randomized controlled trials often observe smaller effects with pain reductions of less than 10 on a 100-point numerical rating scale62 or even no change in pain after exercise therapy compared with passive sham therapy.8

To the best of our knowledge, only 2 studies have investigated whether habitual physical activity levels predict pain responses to acute exercise in individuals with chronic pain. Coriolano et al.21 found that people with knee osteoarthritis who self-reported more physical activity experienced less exacerbation in pain after completing performance-based tests and a physiological test (submaximal arm ergometer test). In people with fibromyalgia, Umeda et al.187 showed that participants who were more physically active reported a smaller increase in ratings of muscle pain intensity during isometric handgrip exercise. Taken together, these results suggest that being more physically active is associated with reduced pain responses to acute exercise in individuals with chronic pain. These results are consistent with cross-sectional data showing negative associations between fitness and pain (ie, more fitness, less pain) in people with fibromyalgia177 and knee osteoarthritis (Jones et al., in review) as well as longitudinal data showing benefit of longer periods of regular exercise training on reducing pain in individuals with chronic pain.49

4. Underlying mechanisms of exercise-induced hypoalgesia in humans

There are numerous biological and cognitive factors that contribute to pain, so changes in any one or more of these by acute exercise could account for EIH. It is not clear, however, what these mechanisms are or whether the mechanisms are similar or distinct between healthy individuals and individuals with chronic pain. The contrasting magnitude of EIH between pain-free individuals and individuals with chronic pain150 suggests that the mechanisms of EIH are disrupted in individuals with chronic pain. That is, some aspect of chronic pain (eg, inflammation, sensitization, and fear of movement) interferes with the normal hypoalgesic effect of acute exercise. These potential mechanisms will be described in more detail hereafter.

4.1. Opioid and cannabinoid systems

The most commonly proposed mechanism of EIH is enhanced descending inhibition by activation of the opioid and cannabinoid systems. The contraction of skeletal muscle increases the discharge of mechanosensitive afferents (ie, A-delta and C-fibres) which, in turn, activates central descending opioid pain pathways.29,164 Exercise also increases the release of endogenous cannabinoids. These opioid and cannabinoid pathways have receptors throughout the peripheral and central nervous systems that can produce analgesia when stimulated.29,184

Human studies investigating the role of opioids and cannabinoids in EIH have yielded equivocal findings. For example, opioid antagonists such as naloxone and naltrexone have been shown to increase, decrease, or have no effect on EIH.90,31,74,94,140 Moreover, correlations between EIH and exercise-induced changes in plasma concentrations of beta-endorphins and endocannabinoids are not always observed.94,139,165 A limitation of these human investigations is that they are more constrained than rodent studies in their ability to investigate whether opioids and cannabinoids are acting through peripheral and/or central actions to influence pain after exercise; however, there is some evidence that blocking blood flow to a limb during exercise attenuates EIH in pain-free individuals, suggesting that peripheral factors are important.79

4.2. Stress-induced hypoalgesia

Exercise-induced hypoalgesia might also be a form of stress-induced analgesia, related to the release of various stress hormones during exercise. However, evidence to support this in humans is mixed. For example, EIH is related to increases in growth hormone during exercise,149 but another study found that the suppression of exercise-induced growth hormone release by cyproheptadine had no effect on EIH.96 Dexamethasone, a steroid medication, has been shown to attenuate EIH by reducing secretion of adrenocorticotropin86; however, other studies have found no effect of dexamethasone on pain in healthy individuals.209 A small pilot study of 7 healthy individuals showed that exercise-induced changes in neuropeptide Y, allopregnanolone, pregnenolone, and dehydroepiandrosterone were related to EIH.167 However, because concentrations of these substances were only measured in the plasma, it is not clear whether they were acting through peripheral or central mechanisms to influence pain. Moreover, because this was only a small pilot study, more studies are needed to confirm the findings.

4.3. Cardiovascular systems

Exercise-induced changes in the cardiovascular system have also been proposed as a mechanism of EIH. That is, elevations in blood pressure by exercise are thought to attenuate pain through baroreceptor-related mechanisms (ie, the activation of arterial baroreceptors by exercise subsequently activates pain-related brain areas involved in pain modulation). Although it is true that people with high blood pressure are less sensitive to pain (ie, hypertension-associated hypoalgesia),161 there is currently little evidence that acute changes in blood pressure by exercise are related to EIH.28,157,188,190 Moreover, acute increases in blood pressure by exercise could not account for the persistence of EIH after exercise (eg, 15 minutes after exercise cessation213 because blood pressure would have presumably returned to baseline, or indeed be lower, by this time).

4.4. Central pain modulatory systems

The influence of exercise on reducing the sensitivity of the central nervous system has also been explored as a mechanism of EIH.
These studies show that acute exercise can reduce temporal summation\(^\text{96,131,196,206}\) and increase thresholds to elicit the nociceptive withdrawal reflex,\(^\text{55}\) although there is some evidence contrary to the latter observation.\(^\text{125}\) These results imply that exercise can reduce pain through reductions in central nervous system sensitivity at spinal and supraspinal levels, but exactly where in the nociceptive pathway these changes occur is not known. Improved efficacy of descending inhibitory pathways by exercise has been studied as a mechanism of EIH as well, but there is little direct evidence to support this. For example, Alsouhibani et al.\(^\text{2}\) observed a decrease in the CPM response after exercise, Meeus et al.\(^\text{122}\) found no effect of aerobic exercise on CPM in healthy individuals,\(^\text{122}\) and Ellingson et al.\(^\text{36}\) showed that EIH was comparable for nonpainful and painful exercise, although the latter should have evoked a larger “pain inhibits pain” effect. A few studies have found small positive correlations between conditioned pain modulation and EIH\(^\text{13,112,198}\) suggesting that the 2 may share similar mechanisms; however, EIH is usually somewhat smaller in magnitude but more enduring than conditioned pain modulation so the 2 are likely distinct.\(^\text{112,195}\)

### 4.5. Psychological contributing factors

Changes in pain cognition might also account for some of the effect of acute exercise on pain. It has been shown that exercise can reduce ratings of pain unpleasantness in the absence of a change in ratings of pain intensity,\(^\text{80}\) suggesting that alterations in the appraisal of noxious stimuli contribute to EIH. Cognitive and psychosocial factors including pain self-efficacy, coping strategies, fear of pain, and stress are known to underlie some of the difference in pain between athletes and nonathletes,\(^\text{53,75,142}\) but their relation to EIH is less clear. For example, several studies have shown that individuals with higher levels of catastrophizing experience less EIH,\(^\text{16,131,207}\) although this is not always observed and correlations between EIH and other psychosocial factors (eg, fear of pain, pain attitudes, and anxiety) seem negligible.\(^\text{112,201}\) Therefore, the contribution of cognitive factors to EIH remains poorly understood but seems limited. More studies are needed to investigate whether these cognitive factors are related to EIH and, more importantly, whether they can be manipulated to augment it.\(^\text{81}\)

### 4.6. Impaired EIH: disrupted or distinct mechanisms

The mechanisms of EIH in individuals with chronic pain are equally if not more unclear. Because exercise has such varying effects on pain within and between individuals with chronic pain, it is difficult to determine whether there is a consistent mechanism that contributes to changes in pain with acute exercise. Moreover, it is not clear if the mechanisms of EIH in individuals
with chronic pain are the same as pain-free individuals and are just disrupted, or whether separate mechanisms related to the presence of chronic pain are involved as well.

The fact that EIH can occur at exercised and remote sites in individuals with chronic pain shows that EIH is not always disrupted in these individuals. However, there are also several demonstrations that exercise with a painful joint or muscle can either diminish EIH compared to when a nonpainful body part is exercised (ie, exercise of the upper limb in people with knee osteoarthritis, but pain measurement in the lower limb) or, worse, can increase pain. These results are both opposite to what is normally seen in pain-free individuals where EIH is usually greatest for the exercised body part. Therefore, the results of the above studies provide some evidence that compared to healthy individuals, the mechanisms of EIH in individuals with chronic pain are both similar and distinct. However, because the mechanisms of EIH are still poorly understood in both groups, there is little direct evidence to support this.

Regarding mechanisms of EIH that may be similar, but disrupted, in individuals with chronic pain compared to pain-free individuals, altered excitability of the central nervous system after exercise is perhaps the most obvious. In pain-free individuals, acute exercise reliably reduces temporal summation, whereas the opposite effect has been observed in individuals with chronic pain. By contrast, one of the few studies to combine acute exercise with analgesic medication showed that paracetamol and placebo had comparable effects on temporal summation and conditioned pain modulation after exercise in pain-free individuals and individuals with chronic pain. Because paracetamol is a predominantly central acting drug with less ubiquitous effects would be useful to further investigate how different substances are involved in EIH in humans and whether these differ between pain-free individuals and individuals with chronic pain.

As for mechanisms of EIH that might be distinct between pain-free individuals and individuals with chronic pain, reductions in inflammation by acute exercise are one such possibility. Inflammation plays a key role in the pathogenesis of several chronic pain states, so it is possible that reductions in inflammation by exercise may reduce pain in these individuals. However, the results of studies examining the effect of acute exercise on inflammation in individuals with chronic pain are mixed and the relation between the changes in inflammatory markers and pain has seldom been explored. Moreover, differences in the exercise-induced changes in inflammatory markers between individuals with chronic pain and pain-free individuals were only sometimes, but not always, observed. Therefore, it remains unclear to what extent EIH is related to acute changes in inflammation by exercise in individuals with chronic pain or whether this is a distinct mechanism of EIH in these populations. Another possibility is opioid-induced hyperalgesia. As already mentioned, interactions between EIH mechanisms and the use of analgesics may affect the response to exercise. Individuals treated with opioids report less CPM, and reduced effects of opioids have been reported in animals after long-term exercise. This may be explained by opioid-induced hyperalgesia which, paradoxically, leads to a reduction in central opioid receptor availability and hence less potential to modulate pain through opioidergic mechanisms (as shown in pain-free individuals).

Psychosocial and cognitive factors are heavily implicated in the development and persistence of chronic pain. These same cognitive factors influence responses to experimental noxious stimuli in pain-free individuals as well, but their relation to EIH has seldom been examined, particularly in individuals with chronic pain. Accordingly, it is still not known whether cognitive factors are directly involved in EIH, or, perhaps more importantly, whether they can be manipulated to influence pain responses to exercise. Although there is some evidence to support this in pain-free individuals, it remains to be determined whether preceding exercise with education can also influence EIH in individuals with chronic pain in whom negative expectations about pain and exercise are more prevalent and therefore likely harder to change. It may be that, because of their more entrenched negative beliefs about pain and exercise, more intensive education is required in individuals with chronic pain to produce the same effect. Some combination of pain neuroscience education and EIH education might also be required. Nonetheless, if the effect can be replicated in individuals with chronic pain, it could have important applications for exercise prescription in clinical practice.

Regarding regular exercise, despite the large number of studies that have shown exercise training to reduce pain in people with chronic pain, the mechanisms by which it does this is poorly understood. This is largely because many of the studies did not analyze which changes occurring with exercise (biological and/or psychological changes) were associated with the observed improvements in pain. Moreover, few of the studies investigated where in the nociceptive pathways (ie, peripheral, spinal, and/or supraspinal pathways) changes might be occurring due to exercise, which could account for the observed reductions in pain. As a result, the precise mechanisms of pain attenuation by exercise training are not known, but several possibilities exist that are likely common to individuals with chronic pain.

Improved structure and function of the musculoskeletal system is one such possibility. In people with knee osteoarthritis, chronic exercise can improve several musculoskeletal factors important in the development and progression of the disease including body mass, joint alignment, proprioception, cartilage structure and function, inflammation, and muscle strength. Of these possible mediators, improvements in muscle strength are the strongest contributor to the positive effect of physical exercise on improved osteoarthritis symptoms. Desensitization of the nervous system is another possibility. In humans, exercise-induced changes in biomarkers associated with nociceptive pathways have been reported (eg, inflammatory factors and neurotransmitters), but again it is not clear whether these changes reduce pain due to the peripheral or central actions of these factors. Preliminary evidence shows that exercise can normalise aberrant brain activity in people with fibromyalgia. This finding is in agreement with the results of a few cross-sectional studies showing that people with fibromyalgia who are more physically active have more typical brain responses to pain compared to less active individuals. However, not all studies have shown chronic exercise to attenuate aberrant brain responses in individuals with chronic pain, so the role of changes in brain activity as a mechanism of pain relief by regular exercise remains unclear.

Finally, exercise-induced improvements in mood could be another shared mediator of the positive effect of exercise on pain in individuals with chronic pain. The role of both general (eg, depression and anxiety) and pain-specific (eg, catastrophizing and self-efficacy) psychosocial processes in the development
and maintenance of chronic pain is clear.\textsuperscript{34} Many of these psychosocial factors are positively influenced by exercise,\textsuperscript{85,183} so it is plausible that this could result in improvements in pain either directly or indirectly through changes in both the sensory and emotional aspects of pain.

5. Implications and future perspectives

5.1. Clinical implications

Most types of exercise can reduce pain sensitivity at exercising and nonexercising muscles in pain-free individuals, with a larger hypoalgesic response at the exercising muscles. In individuals with chronic pain, the hypoalgesic response after exercise is less consistent; however, in addition to other well-documented physical and mental health benefits related to exercise, exercise can sometimes induce hypoalgesia in individuals with chronic pain. Regarding exercise prescription in clinical settings, it may be worth considering: (1) that exercising nonpainful body areas if possible as well as using low-intensity exercises such as walking may be useful as a first step, (2) that individuals’ beliefs, expectations, and exercise preference should be assessed before exercise prescription to minimize the risk of a poor outcome, and (3) that these beliefs and expectations could be modified through education or other interventions to improve pain responses to exercise in people with chronic pain. There is some evidence that combining exercise training and education has superior effects compared to exercise alone in individuals with chronic pain,\textsuperscript{15,183} but this is yet to be properly explored in the context of pain responses to a single bout of acute exercise in individuals with chronic pain.

5.2. Implications for future exercise-induced hypoalgesia studies

In addition to the above-mentioned implications, we also propose several methodological recommendations for future studies of EIH. First, studies should use a randomized controlled design (parallel or crossover), or at the very least include a control group/condition. This is because the causal effects of exercise on pain are best inferred from randomized controlled trials. As shown in Tables 1 and 2, there have been well over 150 studies of EIH in pain-free individuals and individuals with chronic pain. However, the minority of these used a randomized controlled design or a nonrandomized controlled design. Instead, EIH was often investigated using a single-arm pre-post design. A major limitation of this type of study design is that the effects of habituation to noxious stimuli, as well as statistical phenomena such as regression to the mean, are not accounted for. To truly determine whether a single bout of exercise causes a reduction in pain, randomized controlled trials are needed. Second, it is important that these randomized controlled trials use large(r) sample sizes. The majority of EIH studies are small (n ≤ 50), and it is well documented that small studies are inherently biased to find larger effects.\textsuperscript{26} Hence, most studies of EIH probably overestimate the effect of exercise on pain. Consequently, despite the enormous amount of EIH studies to date, the true effect of a single bout of exercise on pain is still unknown. Larger randomized controlled trials, of which there are currently very few, are clearly needed to determine this.

As evident in Tables 1 and 2, there is substantial heterogeneity in methodology used in EIH studies, making it difficult to synthesise the results of this vast literature. Therefore, we also recommend that future EIH studies share a somewhat common methodology so that the results between studies can be more easily compared. To this end, it may be useful for future studies to share a common method of pain assessment. Pressure pain thresholds at local and remote sites may be the most appropriate because these have been studied most often and do not require expensive equipment (although they may be more prone to experimenter bias if using handheld algometry). It would also be of benefit to include assessment of both experimental and clinical pain in individuals with chronic pain to better understand the effects of exercise on “real life” pain. Moreover, it may be useful to prescribe and report exercise using a common index so that the amount of work performed can be quantified. This would help clarify the dose–response effect of exercise on pain, a result that may have important clinical implications such as determining the minimal effective dose with respect to hypoalgesia for each mode of exercise as well as identifying volumes and/or intensities of exercise that may be more likely to exacerbate pain in individuals with chronic pain. Finally, Lee et al.\textsuperscript{109} recently outlined several issues in clinical pain research including transparency, underpowered studies, and researcher degrees of freedom. The use of preregistration and registered reports, data sharing, and greater adherence to reporting guidelines were suggested as areas for improvement and we believe that EIH studies would benefit from adopting these recommendations.

Disclosures

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