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A meta-analytic review of the hypoalgesic effects of exercise

Kelly M. Naugle, **Roger B. Fillingim**, and **Joseph L. Riley III**
Comprehensive Center for Pain Research, University of Florida

Abstract

The purpose of this article was to examine the effects of acute exercise on pain perception in healthy adults and adults with chronic pain using meta-analytic techniques. Specifically, studies using a repeated measures design to examine the effect of acute isometric, aerobic, or dynamic resistance exercise on pain threshold and pain intensity measures were included in this metaanalysis. The results suggest that all three types of exercise reduce perception of experimentally induced pain in healthy participants, with effects ranging from small to large depending on pain induction method and exercise protocol. In healthy participants, the mean effect size for aerobic exercise was moderate (d_{thr} =0.41, d_{int} =0.59), while the mean effect sizes for isometric exercise (d_{thr} =1.02, d_{int} =0.72) and dynamic resistance exercise (d_{thr} =0.83, d_{int} =0.75) were large. In chronic pain populations, the magnitude and direction of the effect sizes were highly variable for aerobic and isometric exercise and appeared to depend on the chronic pain condition being studied as well as the intensity of the exercise. While trends could be identified, the optimal dose of exercise that is needed to produce hypoalgesia could not be systematically determined with the amount of data available.

Index words

hypoalgesia; analgesia; aerobic exercise; isometric exercise; resistance exercise; pain

Introduction

Physical exercise is an important component in the treatment and rehabilitation of many patients with chronic pain, as well as vital to the overall health and wellbeing of any individual. Importantly, laboratory studies report that acute exercise reduces sensitivity to painful stimuli in healthy individuals, indicative of a hypoalgesic response. This phenomenon has been termed exercise-induced analgesia or exercise-induced hypoalgesia (EIH).[36,37] However, the methodology of studies investigating exercise-induced hypoalgesia is diverse and the results are not always consistent. A comprehensive understanding of how exercise influences pain perception is necessary to optimize the clinical utility of exercise as a method of pain management.

Corresponding Author: Kelly M. Naugle, Comprehensive Center for Pain Research, College of Dentistry, University of Florida, Phone: 352-273-5975, Fax: 352-273-5985, knaugle@dental.ufl.edu.

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Numerous experimental studies have examined the effect of acute exercise on responses to experimentally induced noxious stimulation. These studies have included a variety of exercise modalities, as well as a variety of pain induction techniques and measurement procedures. For example, exercise modalities have included aerobic exercise, isometric exercise, and dynamic resistance exercises. Aerobic exercises have typically included stationary cycling, running, or step exercise. Isometric and dynamic resistance exercises are both a form of strength training. Isometric exercise involves a static contraction in which the joint angle does not change, whereas dynamic resistance exercise involves muscle contractions that do produce joint movement. These exercise modes have differed across many dimensions including the type, intensity, and duration of exercise. Furthermore, techniques of pain induction have included electrical, pressure, thermal, and other forms of noxious stimulation. These stimuli also differ across many dimensions, including site of bodily application and temporal parameters of the stimulation. Pain measures have most commonly included pain thresholds (i.e., the point at which noxious stimulation is first perceived as painful) and/or suprathreshold pain intensity ratings during and following exercise. EIH has also been investigated in healthy and clinical populations, including fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS), chronic low back pain (CLB), chronic musculoskeletal pain (CMP), and shoulder myalgia. These collective differences between studies have made direct comparisons across studies difficult.

While several narrative reviews have elegantly summarized the exercise-induced hypoalgesia literature[36,37], to our knowledge no quantitative review of the acute exercise literature has been published. Meta-analytic methods offer an alternative method to study the impact of acute exercise on pain in terms of the magnitude and direction of effect. Therefore, to extend and update the work in the previous reviews, the present study used meta-analysis methodology to answer the following questions: 1) Is there a hypoalgesic effect of acute bouts of exercise using measures of pain intensity and/or threshold 2) If there is a hypoalgesic effect, what is its magnitude using the effect size metric? 3) Does the magnitude of the effect vary by exercise mode (aerobic, isometric, dynamic resistance)? 4) Is a hypoalgesic effect of exercise on experimental pain observed in healthy and chronic pain populations?

Methods

Sample of Studies

Acute exercise studies that used an outcome measure involving pain were located on computer based searches conducted on PubMED, Medline, PsychINFO, and Academic Search Premier databases from 1900 to May 2012. The key words included ‘pain’, ‘exercise’, ‘contraction’, ‘hypoalgesia’, ‘analgesia’, and ‘isometric’. These searches were extended by examining reference sections from published articles identified from the databases. We believe that these studies represent a comprehensive selection of empirical studies. Only published research was included in the analysis, which may have biased the results as non-significant results are less likely to be published than those with significant findings. When studies did not provide adequate statistical information for the calculation of effect sizes, means and standard deviations were estimated from figures and authors were contacted via electronic mail. Studies were included if they met the following criteria: 1) study was performed on healthy adults or a chronic pain population, 2) a repeated measures, with-in subject design was used, 3) pain threshold and/or intensity measures were used, 4) exercise protocol was standardized, 5) pain induction protocol was standardized. The literature search located 50 total studies. Eleven studies did not provide adequate information for the calculation of effect sizes[6,7,16,32,33,34,43,44,52,53,56], three studies did not include pain threshold or intensity measures[2,10,31], two studies did not implement standardized exercise[1,66], two studies did not standardize the method of pain induction[18,54], two studies combined exercise with another manipulation[25,70], and one study did not use a repeated measures, within subjects design[4]. Thus, a total of 25 studies met criteria to be included in the analysis, consisting of 622 participants (437 healthy, 185 chronic pain) and 118 effects (88 healthy, 28 chronic pain).

Statistical Analysis

The effect size (ES) for each study was calculated using Cohen's d, defined as the mean for the control condition minus the mean for the exercise condition, divided by the pooled within group standard deviation ($\underline{d}=[X_{\text{control}} - X_{\text{exercise}}]$/pooled standard deviation). Thus, $\underline{d}$ is a standardized mean difference that can be interpreted in the same manner as any standard score. If data were reported separately for men and women, the effects were averaged into one[13]. Effect sizes were calculated so that reductions in pain sensitivity resulted in positive effect sizes. Due to the within subjects designs of the studies, the effect sizes were adjusted as recommended by Portney and Watkins.[58]

The mean effect size of $\underline{d}$ was calculated using the pooled effect sizes within each exercise mode for measures of threshold and intensity ratings (across pain stimuli). Due to the variation in sample sizes, it has been argued that not all studies in meta-analyses should be given equal weight. Hedges[19,20], noting the bias in estimates of $\underline{d}$ when weighting for sample size, developed a weighted estimator of effect size (d) which is asymptotically efficient and appropriate for group sizes greater than 10:

$$d = \Sigma wd/\Sigma w \text{ where } w=2N/8+d^2$$

In sum, we report the mean of the raw effect size $\underline{d}$, standard deviation of $\underline{d}$, and weighted mean effect size (d). The effect sizes of healthy adults and those with chronic pain were analyzed separately, and thus are presented separately.

Results

Division of Studies

The studies were first divided by type of exercise, with 12 studies implementing isometric exercise (healthy: N=267, 59 effects; chronic pain: N= 84; 21 effects), 11 studies using aerobic exercise (healthy: N= 136 participants, 23 effects; chronic pain: N=101, 10 effects), and 2 studies using dynamic resistance training (healthy: N=34, 8 effects). They were further subdivided by threshold and intensity pain measures. Of the 12 isometric studies, ten measured threshold (healthy: 42 effects; chronic pain: 18 effects) and seven measured intensity (healthy: 17 effects; chronic pain: 2 effects). Ten studies used pressure stimuli as the method of pain induction, one study used thermal heat, and one used electric stimulation. Of the eleven aerobic studies, six used threshold (healthy: 8 effects; chronic pain: 6 effects) and nine used intensity (healthy: 15 effects; chronic pain: 4 effects) measures. Six studies used pressure stimuli as the pain induction method, three used thermal heat stimuli, and three used cold stimuli. The two dynamic resistance exercise studies measured threshold (4 effects) and intensity (4 effects) of pain induced by pressure stimuli.

Healthy Adults

Aerobic Exercise

Table 1 presents the results for the eight studies involving aerobic exercise and measuring pain threshold and/or intensity. This table shows that aerobic exercise reduced pain sensitivity across all types of pain stimuli and exercise type, with the largest effects found for studies using pressure stimuli and the smallest effects on average for those using cold and heat stimuli. The summary results (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, and weighted mean effect size (d) averaged within each exercise type and stimuli) for pain threshold and intensity are shown in Table 2 and Table 3, respectively. When averaged across pain stimuli, the effect size for pain threshold was positive and moderate at 0.48 and when adjusted for sample size and bias, 0.43. Two studies, Meeus et al.[48] and Koltyn et al.[39], used pressure pain thresholds to test for EIH and reported moderate effect sizes, d =0.58. Koltyn et al. found that pain threshold continued to be reduced 15 minutes post exercise, with an effect size of 0.79. One study, Ruble et al.[62], tested pain thresholds using hot and cold thermal stimuli and found trivial effects, $\underline{d}$'s= 0.04. Ruble et al. also found no effect of thermal stimuli 30 minutes post exercise, $\underline{d}$'s=0.21–0.25. However, Kemppainen et al. reported a moderate and positive effect of 0.48 using cold stimuli.[31]

Averaged across stimuli, the average effect size for pain intensity was positive and slightly greater in magnitude than for pain threshold at 0.68, and 0.64 when adjusted for sample size. Once again, the effect size pooled within pressure stimuli was greater at 0.69 (3 studies - 5 effects) than those for heat stimuli, d=0.59 (2 studies – 2 effects), and cold stimuli d=0.61 (3 studies – 3 effects). Two studies took follow-up pain intensity measures 30 minutes post exercise, with an average effect size of 0.33 (SD= 0.12).[26,67]

The pre-post exercise measurement design involving repeated tests before and after exercise is commonly used in the EIH literature. This study design without the inclusion of a resting control condition for comparison is flawed by the possibility that post-exercise pain ratings are influenced by pre-exercise pain tests. Two studies, Koltyn et al.[39] and Vierck et al.[72], compared pain measures assessed during an exercise condition to a resting control condition. Importantly, these studies actually found positive and larger effect sizes ($\underline{d}$'s = 0.83–1.18) than studies employing pre-post designs without a resting control comparison condition, with the exception of Gurevich et al.[17] Two studies, Gurevich et al.[17] and Ruble et al.[62], conducted reliability testing in which pain measures were assessed pre and post quiet rest. These studies found no significant changes in pain ratings from pre to post, with effect sizes ranging from −0.14 to 0.16.

Isometric Exercise

Table 4 presents the results for the 11 studies assessing pain threshold and/or intensity immediately following or during isometric exercise. This table shows that isometric exercise reduced pain perception across all pain stimuli and exercise protocols, with the exception of the pain intensity measure in Umeda et al. 2009.[69] The summary results for threshold and intensity measures (the mean of effect size $\underline{d}$, standard deviation of $\underline{d}$, and weighted mean effect size (d) averaged within each exercise type and stimuli) are shown in Table 2 and Table 3, respectively. The average effect size for pain threshold (9 studies – 43 effects, all studies used pressure stimuli) was positive and large at 1.27, with the weighted mean value of 1.05. Three studies measured pain threshold during the contraction and reported large positive effect sizes (14 effects: $\underline{d}$=1.76, d=1.69)[30,45,46], while six studies measured pain threshold immediately after exercise reporting moderate to large effects (14 effects: $\underline{d}$=0.70, d=0.69).[22,40,42,68,69] Three studies also measured pain threshold 15 minutes post contraction (14 effects)[30,45,46], with values of 0.58 and 0.43 for $\underline{d}$ and d, respectively.

The effect size for pain intensity measures averaged across stimuli was also positive and large at 0.83, while the unbiased effect size was 0.72 (7 studies – 17 effects). Five studies used pressure stimuli to test for EIH, with an unbiased effect size of 0.73. One study, Staud et al.[65], tested pain sensitivity using thermal heat stimuli and found a mean effect size of 1.35 (2 effects). The study using electrical stimulation, Ring et al.[61], reported a medium mean effect size of 0.40 (2 effects). Two studies measured pain intensity during the contraction with an average effect of 0.87 and an unbiased effect of 0.67 (4 effects).[61,65] The average effect size for the studies measuring pain intensity immediately following the contraction was similar at 0.81, with an unbiased effect of 0.72 (12 effects). [22,40,42,68,69] No studies conducted follow-up (i.e., 15–30 minutes post exercise) pain intensity tests.

Five studies assessed pain measures on the contracting body area, as well as on a remote body area (often contralateral to contracting body part) following isometric exercise.[30,42,45,46,65] The average effect size for pain threshold (6 effects) assessed on the contracting body area was 1.74 (SD= 0.53), and almost identical on the remote body area at 1.73 (SD=0.82). The average effect size for pain intensity (2 effects) assessed on the contracting body area was 2.02 (SD=1.13), and slightly lower on the remote body area at 1.54 (SD=0.08). Thus, isometric exercise appears to exert a generalized pain inhibitory response.

The magnitude of the effect of isometric exercise on pain threshold and intensity generally increased for contractions of longer duration. Contractions of 1 minute or less had an average effect size of 0.51 (SD=0.27, 2 effects) for threshold and 0.87 (SD=0.72, 4 effects) for intensity. Contractions of 2–3 minutes had an average effect size of 0.96 (SD=0.36, 6 effects) for threshold and 0.83 (SD=1.00, 6 effects) for intensity, while contractions 5 minutes or greater were even larger at 1.74 (SD=0.75, 15 effects) and 1.70 (SD=0.13; 2 effects) for threshold and intensity, respectively. Examination of contraction intensity reveals the largest positive effects at moderate intensity contractions. Those at 40–50% MVC had an average effect size of 1.75 (SD=0.99, 3 effects) for intensity and 1.12 (SD= 0.14, 3 effects) for threshold, while those for the 10–25% MVC contractions were 0.67 (SD= 0.51, 11 effects) and 1.13 (SD=0.72, 16 effects) for intensity and threshold, respectively. Contractions at 80%–100% MVC had the smallest effect on pain intensity (M=0.50, SD=0.29, 3 effects) and threshold (M=0.57, SD=0.33, 3 effects) measures.

Few isometric exercise studies included a resting control condition in the experimental design. Umeda et al. applied a pressure stimulus to the forefinger for 2 minutes following isometric exercise and quiet rest.[69] Interestingly, the effect sizes were generally smaller in magnitude compared to the other isometric studies, ranging from −0.16 to 0.54. Ring et al. compared pain intensity measures during 15 and 25% MVC contractions to a 1% MVC control condition and reported moderate effect sizes (0.31–0.41).[61] Hoeger Bement et al. found trivial changes in the pain measures during reliability testing consisting of 30 minutes of quiet rest (threshold = −0.03, intensity= 0.04).[22]

Dynamic Resistance Exercise

Two studies measured pain threshold and intensity immediately following dynamic resistance exercise (See Table 5).[9,38] The mean effect size for pain threshold was 0.99 (SD=0.18) and the weighted mean effect size was 0.83. The mean effect size for pain intensity was 0.83 (SD=0.37) and the weighted mean effect size was 0.75. Both studies took follow-up measures at 15 minutes post exercise, with the unbiased average effect size of 0.21 for threshold and 0.18 for intensity. Koltyn & Arbogast included a quiet rest condition, which showed no significant changes from pre to post immediately following exercise, d= −0.118, or 15 minutes post exercise, d=0.04.[38]

Chronic pain populations

Aerobic Exercise

As a reminder, the effect size data presented for chronic pain populations represent subjects' responses to experimental pain and not subjects' assessments of their pre-existing chronic pain. Table 6 presents the results for the five studies involving chronic pain subjects and aerobic exercise. As shown in the table, the effects sizes were highly variable, ranging from - 1.13 to 1.50. When averaged across chronic pain syndromes, the effect for pain threshold was positive and small at 0.19 (SD=0.52) and when adjusted for sample size and bias, 0.15. The effect sizes for pain intensity were highly variable with an average effect size of 0.42 (SD=1.53) and the adjusted effect size similar at 0.43. The two studies investigated FMS reported contrasting effect sizes which were likely due to differing aerobic and pain testing protocols.[51,72] Newcomb et al. found that cycle ergometry at a self-selected intensity increased PPTs, $\underline{d}$=1.11, and decreased pressure pain intensity ratings, $\underline{d}$=0.64.[51] Cycle ergometry at a prescribed intensity of 60–75% of HRmax had no effect on pressure pain threshold, $\underline{d}$=0.01, and a moderate pain reducing effect on pain intensity, $\underline{d}$=0.55. In contrast, Vierck et al. reported that temporal summation of pain was increased following maximal treadmill exercise, with an effect size of - 1.59.[72] One study investigated CFS and found reduced PPTs following submaximal aerobic exercise, $\underline{d}$=−0.45.[48] Two studies examining CLB found pain reducing effects of submaximal cycle ergometry.[27,48] Meeus et al. reported a small hypoalgesic effect on PPTs, $\underline{d}$= 0.11, while Hoffman and colleagues reported a large hypoalgesic effect on pressure pain intensity ratings 2 and 32 minutes following exercise, $\underline{d}$=1.50 and 1.14, respectively. One study investigating CMP reported small to minimal effects of submaximal cycle ergometry on pressure and heat pain thresholds, with values of 0.07 and 0.31, respectively.[3]

Isometric Exercise

Table 7 presents the results for the four studies assessing EIH in chronic pain populations using isometric exercise. This table primarily shows that isometric exercise reduces pain perception for individuals with shoulder myalgia, but increases pain perception for individuals with FMS. Across chronic pain conditions, the average effect size for pain threshold was 0.40 (SD=1.43), while the unbiased effect size was 0.17. The average effect size for pain intensity was −1.94 (SD=0.36), with the unbiased effect size −1.92. Three studies assessed PPTs in individuals with FMS following[24] or during[30,46] isometric contractions, with an unbiased effect size of −0.20 (11 effects). Two of these studies also took threshold measures 10–15 minutes post isometric exercise, with values of 0.37 and 0.18 (8 effects) for $\underline{d}$ and *d*, respectively. One study of FMS patients measured pain intensity using thermal stimuli during isometric exercise and found large hyperalgesic effects on the contracting and contralateral forearms, with values of −1.68, and −2.2, respectively.[65] One study assessed EIH in individuals with should myalgia using pressure pain thresholds.[46] When subjects contracted the affected shoulder, PPTs assessed on that shoulder were lower indicating a hyperalgesic effect, $\underline{d}$=−0.94. However, a hypoalgesic effect (average effect size of 1.25) was found 1) when PPTs were assessed on resting muscles during contraction of the affected shoulder and 2) during contractions of the knee when PPTs were assessed at the contracting knee, resting knee, and affected shoulder.

Discussion

The impact of acute exercise on experimentally induced noxious stimulation was evaluated with meta-analytic techniques. Effect sizes were derived from studies that measured pain perception following or during aerobic, isometric, and dynamic resistance exercise. The results suggest that all three types of acute exercise reduce perception of experimentally induced pain in healthy participants, with the largest effect sizes found following isometric exercise. In addition, pain response measures of threshold and intensity ratings were similar in healthy adults, with threshold differences somewhat larger for isometric and dynamic resistance exercise and intensity differences larger for aerobic exercise. The size and direction of the effects for chronic pain conditions depended on the type of medical condition being studied.

Aerobic Exercise in Healthy Adults

The overall effect for aerobic EIH for pain threshold was moderate at 0.43 and somewhat larger for pain intensity ratings at 0.64. The magnitude of the effect was variable, ranging from 0.11 to 1.18 for intensity and from 0.04 to 1.47 for threshold. This broad range was likely a function of several factors including pain induction techniques and intensity and duration of exercise. Additionally, alterations in pain perception after exercise appeared to last up to 15 minutes post exercise[39], with trivial to small effects at 30 minutes post exercise.[29,62]

The average effect size for the four studies assessing pain threshold and/or intensity using pressure pain was moderate, with the results suggesting a dose response relationship between the intensity and duration of exercise and its hypoalgesic effect. The largest effect sizes were found when exercise was performed at a high intensity (i.e., 75% of VO_{2max}) and relatively longer duration (> 10 minutes). Thirty minutes of exercise performed at 50% $VO_{2\ max}$ produced a comparatively smaller effect, but still in the moderate range, while 10 minutes of high intensity exercise produced a small effect.[62] Given that this dose-response hypothesis is based on only a small number of effects, more work is needed to confirm this relationship and determine whether it applies to other pain stimuli.

The four studies using thermal stimulation showed considerable variability in the magnitude of the effect of exercise on pain perception, ranging from 0.04 – 1.17. Ruble et al. found small and trivial effects (0.04–0.20) of 30 minutes of aerobic exercise performed at 75% VO_{2max} when hot and cold thermal stimuli were delivered using a thermode placed on the thenar eminence of the hand.[62] In contrast, Sternberg et al. reported a moderate effect of 10 minutes of treadmill running at 85% VO_{2max} on intensity of cold pressor ratings.[67] However, this effect separated by gender revealed a large effect for women (0.88) and no effect for men (0.01). Additionally, Kemppainen et al. found moderate to large effects of 24–32 minutes of incremental cycling exercise using a cold pressor task in male fighter pilots without neck pain.[31] In contrast to Ruble's thermal heat results, Vierck et al. revealed a large effect of treadmill running to exhaustion on temporal summation of late pain responses to heated thermal stimulation.[72] Temporal summation of second pain is related to C-fiber mediated processes, whereas suprathreshold first pain measures are mediated by A-delta fibers.[71] Research has shown that exercise activates endogenous opioid mechanisms, and A-delta mediated pain is less susceptible to opioid inhibition.[64,71] As such, the source of nociceptive input may be a potentially important factor to consider when testing the effect of exercise on thermal pain responses. Furthermore, it has been suggested that the mixed results for thermal stimulation could be attributed to changes in skin and body temperature during exercise, causing hot and cold thresholds to be obtained at higher stimulation temperatures following exercise.[35,36,53] However, evidence has also shown that heat pain thresholds are not impacted by skin or body temperature.[35] Nevertheless, future research is needed to determine the magnitude of aerobic EIH with thermal stimulation techniques and whether the effect differs depending on the type of measure (i.e., first pain responses vs. second pain responses).

It should be noted that a substantial number of studies using aerobic exercise had to be excluded from this meta-analysis because of either of a lack of information to calculate effect size, not using intensity or threshold measures, or not standardizing exercise. All eight of the studies excluded for a lack of information to calculate effect sizes found a hypoalgesic effect of exercise (N=63) in healthy adults, with either an increase in pain thresholds or a decrease in pain ratings following cycling exercise. Seven out of eight of these studies found a reduction in pain using electrical dental pulp stimulation techniques. Thus, inclusion of these studies in this metaanalysis would likely have confirmed or even strengthened the hypoalgesic effect of aerobic exercise, while also extending it to an additional pain induction technique. Additionally, three of the excluded studies showed attenuation of pain responses to heat and cold pressor pain following exercise.[10,66,67] For example, Sternberg and colleagues found reduced pain responses on a cold pressor test after participants competed in basketball, track, and fencing competitions.[66,67] Additionally, Robinson and Fuller found lower discriminability measures on a heat pain perception task following the completion of a 6 mile outdoor road course.[9] However, these studies did not control for the intensity and duration of exercise and the competition within the exercise bouts provided a potential confounding variable when determining the interaction between exercise and thermal pain perception.

In sum, aerobic exercise has shown to be an effective means to reduce pain perception in healthy adults among a variety of pain induction techniques. EIH appeared to be the strongest when exercise was performed at a moderate to high intensity pace. Additionally, hypoalgesia following exercise was found more consistently in studies that used pressure stimuli to produce pain compared to studies that used thermal stimulation. Due to the small number of studies, conclusions regarding differences in the magnitude of aerobic EIH among pain induction techniques remain tenable.

Isometric Exercise in Healthy Adults

The magnitude of EIH for isometric exercise was generally moderate to large for both threshold and intensity measures taken immediately after or during exercise, regardless of the contraction location, intensity or duration, as well as the pain induction stimulus and location. However, within the moderate to large effect size range, subtle patterns did emerge with the hypoalgesic effect tending to be larger for contractions at a low to moderate intensity held for longer durations. This finding was supported by Hoeger Bement et al. who investigated the dose response of isometric contractions on pain perception and found the greatest changes in pain threshold and intensity following long duration (i.e., until task failure, ~ 5–9 minutes), low intensity contractions compared to low intensity contractions held for a relatively shorter duration (2 minutes) and high intensity contractions held for 3–5 seconds.[22] During a longduration static muscle contraction, active motor units eventually become fatigued and higher threshold motor units become increasingly recruited to maintain the required force.[8,11] Thus, the authors explained their findings by suggesting that high-threshold motor units need to be recruited during isometric contractions to elicit a significant hypoalgesic response. However, this is likely not a complete explanation because other studies have found moderate to large hypoalgesic effects following contractions of shorter duration (i.e., 2 minutes or less).[40,65,68]

In regards to pain induction technique, only two studies have investigated changes in pain perception following isometric contractions using pain induction techniques other than pressure stimuli. The study employing electrical stimulation of the sural nerve found a moderate effect of low-intensity handgrip contractions held for 4–5 minutes in men.[61] Staud et al. found very large effects of low intensity handgrip contractions on pain ratings of 5 s supra-threshold heat stimuli applied to the forearm in women.[65] While the results of these two studies are promising, additional evidence is needed to confirm the efficacy of isometric contractions in producing hypoalgesia with experimental pain induction techniques other than pressure.

Several studies assessed the effect of isometric exercise on the contracting body part, as well as on the contralateral and a distant body part to the contracting one.[30,45,46,65] Importantly, the hypoalgesic effect of isometric exercise was multisegmental and not isolated to the contracting muscle. Moreover, the pain reducing effects of isometric exercise on the contralateral and distant body parts were similar in magnitude to the local body part. These results suggest that a central widespread inhibitory mechanism is activated by static muscle contractions. As discussed by Kosek and Lundenburg, these central mechanisms may include increased secretion of β-endorphins, attention mechanisms, activation of diffuse noxious inhibitory controls, or an interaction of the cardiovascular and pain regulatory systems.[45]

Duration of the hypoalgesic effect of exercise has important implications for the use of exercise as a method to manage clinical pain symptoms. The data suggest that isometric contractions produce moderate to large pain reducing effects during the contraction and immediately following the contraction, with the effects attenuating over time. For example, Lannersten and Kosek assessed pain thresholds 10 minutes post contraction and EIH had almost completely dissipated in the non-contracting body areas, but moderate effects still existed in the contracting muscle.[46] Kosek and Lundenburg revealed small effects of isometric contractions in the contracting muscle 30 minutes post contraction and no effect in the non-contracting body areas.[45] This result is similar to the aerobic and dynamic resistance exercise literature showing no EIH 30 minutes after the cessation of exercise.[9,26,38,62]

Dynamic Resistance Exercise in Healthy Adults

Only two dynamic resistance exercise studies measuring threshold and/or intensity were included in the analysis.[9,38] Both measures showed large effect sizes when assessed one to five minutes after the dynamic resistance exercise session and small effects when assessed 15 minutes post exercise. Dynamic resistance exercise sessions were identical in each study, including 10 repetitions of four different exercises performed at 75% 1RM. As such, the threshold of dynamic resistance exercise required to produce EIH still needs to be determined. For example, would completion of only one of the exercises produce the same effect? Additionally, both studies used pressure stimuli to induce pain; therefore, whether EIH elicited by dynamic resistance exercise generalizes to other types of pain stimuli remains unknown. Importantly though, these studies showed that intermittent exercise, and not just continuous exercise, is capable of producing medium to large EIH effects.

EIH in Chronic Pain Populations

The effect sizes for pain threshold and intensity measures from studies examining EIH in chronic pain populations were highly variable for both aerobic and isometric exercise. The type of chronic pain condition partially explained this variability. For example, studies examining CLB found EIH effects similar to healthy individuals.[27,48] Meeus et al. even found that incremental cycle ergometry had pain reducing effects on PPTs at multiple body sites, including the back. Furthermore, Hoffman et al. demonstrated that this effect is still large 30 minutes post exercise.[27] In individuals with shoulder myalgia, isometric contractions of the quadriceps muscle elicited large hypoalgesic effects.[46] Indeed, PPTs assessed at the chronically painful shoulder even increased, with a large effect. However, during contractions of the shoulder with myalgia, PPTs were lower at that shoulder. These studies suggest that exercise of nonpainful muscles for individuals with regional chronic pain conditions produce a hypoalgesic effect and may be an effective method to temporarily relieve pain in painful muscles. Importantly, future research needs to determine the effects of acute exercise on pre-existing clinical pain.

Several studies indicated that moderate submaximal isometric exercise and vigorous aerobic exercise have a moderate to large hyperalgesic effect on experimental pain in FMS.[46,65,72] However, aerobic exercise performed at a preferred intensity or a prescribed moderate intensity elicited EIH in individuals with FM, with large to moderate effects.[51] Furthermore, submaximal isometric contractions performed at a low intensity (~10%) increased PPTs of the deltoid muscle in FM patients, also with a large effect.[30] These results suggest that EIH in FM patients may only be elicited in response to low to moderate intensity exercise, which is in contrast to the results for healthy adults. However, additional studies are needed to confirm this hypothesis. Moderate to vigorous intensity aerobic exercise also had a moderate hyperalgesic effect on PPTs in individuals with CFS with chronic widespread pain[48] and minimal effects on heat and pressure thresholds in Gulf War veterans with CMP.[3] The mechanisms underlying exercise-induced hyperalgesia in response to moderate or vigorous exercise in these chronic widespread conditions remain unknown, but have been suggested to be caused by abnormal descending inhibition or excessive activation of muscle nociceptive afferents.[65,72]

Conclusions

The analysis from this study provides quantitative evidence to address the question of the magnitude of exercise-induced hypoalgesia in response to experimentally induced pain. We found the average effect size to range from moderate to large in healthy adults depending on pain induction method and exercise protocol. Importantly, all three types of exercise were capable of producing large effects in healthy adults, although the effects were generally transient. Also, while trends could be identified, the optimal dose of exercise that is needed to produce hypoalgesia could not be systematically determined with the amount of data available. We also found small to large EIH effects in individuals with regional chronic pain conditions at the painful muscle when a distant muscle was being exercised and in individuals with FMS when exercising at a low to moderate intensity. However, EIH was nonexistent in individuals with chronic widespread pain when exercising at a moderate to high intensity, with exercise often exacerbating experimental pain.

Although the exact mechanisms remain unknown, several have been proposed to explain exercise-induced hypoalgesia. Perhaps the most widely considered mechanism is that the activation of the endogenous opioid system during exercise reduces pain perception following exercise. Exercise of sufficient intensity and duration results in the release of peripheral and central beta-endorphins which have been associated with changes in pain sensitivity.[15,55,57,64] However, animal research has provided the most consistent support for this hypothesis[23,64], while the human data has been mixed.[6,18,31,52] Animal data also shows that non-opioid systems exist (e.g., endocannabinoid, neurotransmitters such as serotonin and norephinephrine) and that parameters of the exercise (i.e., duration of session, continuous vs. intermittent, and varying water temperature for swim protocols) may determine which system is activated.[5,28,50]

Another potential mechanism involves an interaction between pain modulatory and cardiovascular systems (See Koltyn & Umeda for a review).[40] For example, pain regulation and blood pressure control involve the same brain stem nuclei[47,74], neurotransmitters (e.g., monoamines) and neuropeptides (e.g., opioids).[12,60] Additionally, blood pressure and heart rate increase significantly during aerobic and isometric exercise and these elevations have been reported in conjunction with alterations in sensitivity to painful stimuli.[12,13,63] However, only a few studies have systematically tested the relationship between blood pressure and exerciseinduced hypoalgesia producing equivocal results.[61,68,69] Other potential mechanisms with mixed support include activation of ascending (e.g., activation of muscle afferent A delta and C fibers)[49] and descending (e.g., exercise acting as a distraction and altering attention away from the pain stimulus)[73] pain inhibition pathways by exercise. The conflicting evidence for the causal mechanisms of EIH illustrates the complexity of this phenomenon and suggests that EIH is likely caused by a combination of factors.

Experimental rigor is an important factor which can influence the magnitude of effect sizes, with poorly designed studies having the potential to inflate or yield smaller effects. An important study design characteristic includes the inclusion of a control condition. Few studies in this meta-analysis compared pain perception during an exercise condition to a control condition. The aerobic exercise studies that included a control condition found greater effect sizes than those without a control condition, suggesting that this factor likely did not lead to the overestimation of the overall effect of aerobic exercise on pain perception. The two isometric exercise studies with a control comparison condition reported considerably smaller effects than the overall average effect size for isometric exercise. As such, it is essential that future studies include a resting control condition so that valid estimations of EIH elicited by isometric exercise can be estimated. Importantly, several studies did perform reliability testing and found small and trivial effects of repeated pain testing on the pain measures, indicating that the hypoalgesic effect was produced by exercise and not pain pre-testing.

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Disclosures

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Perspective: This article presents a quantitative review of the exercise-induced hypoalgesia literature. This review raises several important questions that need to be addressed while also demonstrating that acute exercise has a hypoalgesic effect on experimentally-induced pain in healthy adults, and both a hypoalgesic and hyperalgesic effect in adults with chronic pain.

Table 1

Studies examining pain perception following acute bouts of aerobic exercise in healthy participants

Author, year	**Sample Size (M/F)**	**Pain induction stimulus/location**	**Mode of exercise**	**Exercise intensity**	**Exercise Duration**	**Pooled ES (intensity, threshold)**
Gurevich et al., 1994	15/0	Pressure/index finger	step exercise	75% VO_{2max}	12 minutes	0.92, NA
Koltyn et al., 1996	14/2	Pressure/forefinger	cycle ergometer	65–75% VO_{2max}	30 minutes	1.18, 1.47
Kemppainen et al., 1988	8/0	Cold pressor/hand	cycle ergometer	Incremental 50–200 Watt	24–32 minutes	1.17, 0.46
Sternberg et al., 2001	10/10	Cold pressor/arm	Treadmill	85% VO_{2max}	10 minutes	0.64, NA
Vierck et al., 2001	10/10	Heat thermal/glabrous skin of hand	Treadmill	To exhaustion	11–12 minutes	0.83, NA
Hoffman et al., 2004	5/7	Pressure/index finger	Treadmill	75% VO_{2max}	10 minutes	0.08, NA
Hoffman et al., 2004	5/7	Pressure/index finger	Treadmill	75% VO_{2max}	30 minutes	0.65, NA
Hoffman et al., 2004	5/7	Pressure/index finger	Treadmill	50% VO_{2max}	30 minutes	0.51, NA
Ruble et al. 2005	6/8	Thermal heat/glabrous skin of hand	Treadmill	75% VO_{2max}	30 minutes	0.20, 0.04
Ruble et al., 2005	6/8	Thermal cold/glabrous skin of hand	Treadmill	75% VO_{2max}	30 minutes	0.11, 0.04
Meeus et al., 2010	21/10	Pressure/arm, hand, back, calf	cycle ergometer	Incremental 20–130 Watt	22–29 minutes	NA, 0.23

Note. NA=Not available.

Table 2

Summary of pain threshold effect sizes by exercise and pain stimuli type in healthy participants

Pain response measure	Number of studies	Subjects	Mean effect size	Effect size SD	Unbiased effect size[a]
Aerobic					
Pressure	2	47	0.84	0.89	0.58
Thermal heat	1	10	0.04		0.04
Thermal cold	2	18	0.34	0.43	0.30
All aerobic Threshold	4	57	0.48	0.61	0.43
Isometric					
Pressure	9	222	1.27	0.78	1.05
Dynamic resistance					
Pressure	2	4	0.86	0.18	0.83

[a] Weighted by sample size.

Table 3

Summary of pain intensity effect sizes by exercise and pain stimuli type in healthy participants

Pain response measure	Number of studies	Subjects	Mean effect size	Effect size SD	Unbiased effect size[a]
Aerobic					
Pressure	3	43	0.67	0.42	0.69
Thermal heat	2	38	0.55	0.40	0.59
Thermal cold	3	42	0.81	0.80	0.61
All aerobic Intensity	7	105	0.68	0.50	0.64
Isometric					
Pressure	5	140	0.81	0.76	0.73
Thermal heat	1	12	1.35		1.35
Electrical	1	24	0.40		0.40
All isometric Intensity	7	176	0.83	0.71	0.72
Dynamic resistance					
Pressure	2	34	0.83	0.37	0.75

[a] Weighted by sample size.

Table 4

Studies examining pain perception following acute bouts of isometric exercise in healthy participants

Author, year	Sample Size (M/F)	Pain induction stimulus/location	Exercise location	Exercise intensity	Exercise Duration	Pooled ES (intensity, threshold)
Koltyn et al., 2001	15/16	Pressure/forefinger	hand grip	max	5 seconds	0.83, 0.93
Koltyn et al., 2001	15/16	Pressure/forefinger	hand grip	40–50% MVC	2 minutes	0.84, 1.28
Kosek & Lundberg, 2003	12/12	Pressure/contracting MQ	knee extension	1 kg on ankle	Exhaust (~12 min)	NA, 1.77
Kosek & Lundberg, 2003	12/12	Pressure/resting MQ	knee extension	1 kg on ankle	Exhaust (~12 min)	NA, 1.68
Kosek & Lundberg, 2003	12/12	Pressure/contralateral MI	knee extension	1 kg on ankle	Exhaust (~12 min)	NA, 0.99
Kosek & Lundberg, 2003	12/12	Pressure/contracting MI	elbow flexion	1 kg on wrist	Exhaust (~12 min)	NA, 1.48
Kosek & Lundberg, 2003	12/12	Pressure/resting MI	elbow flexion	1 kg on wrist	Exhaust (~12 min)	NA, 2.64
Kosek & Lundberg, 2003	12/12	Pressure/contralateral MQ	elbow flexion	1 kg on wrist	Exhaust (~12 min)	NA, 1.12
Staud et al., 2005	0/11	Heat thermode/ip forearm	hand grip	30%MVC	90 seconds	1.21, NA
Staud et al., 2005	0/11	Heat thermode/co forearm	hand grip	30%MVC	90 seconds	1.48, NA
Kadetoff & Kosek, 2007	0/17	Pressure/MQ	knee extension	39 N, ~10%MVC	Exhaust (~10 min)	NA, 2.0
Kadetoff & Kosek, 2007	0/17	Pressure/deltoideus	knee extension	39 N, ~10%MVC	Exhaust (~10 min)	NA, 2.2
Koltyn & Umeda, 2007	0/14	Pressure/ ip forefinger	hand grip	40–50% MVC	2 minutes	2.81, 0.99
Koltyn & Umeda, 2007	0/14	pressure/ co forefinger	hand grip	40–50% MVC	2 minutes	1.59, 1.09
Hoeger Bement et al., 2008	11/11	Pressure/ index finger	elbow flexor	25% MVC	task failure	0.68, 0.85
Hoeger Bement et al., 2008	11/11	Pressure/ index finger	elbow flexor	25% MVC	2 minutes	0.22, 0.32
Hoeger Bement et al., 2008	11/11	Pressure/ index finger	elbow flexor	80% MVC	task failure	0.36, 0.27
Hoeger Bement et al., 2008	11/11	Pressure/ index finger	elbow flexor	Max	2–3 seconds	0.31, 0.51
Ring et al., 2008	24/0	Electrical/Sural nerve	hand grip	15% MVC	4.5 minutes	0.31, NA
Ring et al., 2008	24/0	Electrical/Sural nerve	hand grip	25% MVC	4.5 minutes	0.49, NA
Hoeger Bement et al., 2009	0/20	Pressure/ index finger	elbow flexor	25% MVC	task failure	NA, 0.72
Umeda et al., 2009	0/23	Pressure/forefinger	handgrip	25% MVC	1 minute	−0.16, 0.33
Umeda et al., 2009	0/23	Pressure/forefinger	handgrip	25% MVC	3 minutes	0.11, 0.54
Umeda et al., 2010	25/25	Pressure/forefinger	handgrip	25% MVC	1 minute	0.94, 0.70
Umeda et al., 2010	25/25	Pressure/forefinger	handgrip	25% MVC	3 minutes	0.95, 0.76
Umeda et al., 2010	25/25	Pressure/forefinger	handgrip	25% MVC	5 minutes	1.06, 0.57
Lannersten & Kosek, 2010	0/21	Pressure/contracting MI	shoulder rotation	20–25% MVC	5 minutes	NA, 2.56
Lannersten & Kosek, 2010	0/21	Pressure/resting MI	shoulder rotation	20–25% MVC	5 minutes	NA, 1.85

Author, year	**Sample Size (M/F)**	**Pain induction stimulus/location**	**Exercise location**	**Exercise intensity**	**Exercise Duration**	**Pooled ES (intensity, threshold)**
Lannersten & Kosek, 2010	0/21	Pressure/contralateral MQ	shoulder rotation	20–25% MVC	5 minutes	NA, 1.09
Lannersten & Kosek, 2010	0/21	Pressure/contracting MQ	knee extension	20–25% MVC	5 minutes	NA, 1.61
Lannersten & Kosek, 2010	0/21	Pressure/resting MQ	knee extension	20–25% MVC	5 minutes	NA, 2.05
Lannersten & Kosek, 2010	0/21	Pressure/contralateral MI	knee extension	20–25% MVC	5 minutes	NA, 1.60

Note. M=males; F=females; ES= effect size; MQ= m. quadriceps; MI=m. infraspinatus; ip=ipsilateral; co=contracting; min=minutes; NA=Not available

Table 5

Studies examining pain perception following acute bouts of dynamic resistance exercise in healthy participants

Author, year	Sample Size (M/F)	Pain induction stimulus/location	Mode of exercise	Exercise intensity	Exercise Duration	Pooled ES (intensity, threshold)
Koltyn & Arbogast	7/6	Pressure/middle finger	bench press, leg press pull downs, arm ext	3 sets of 10, 75% 1RM	45 minutes	1.08, 0.99
Focht & Koltyn, 2009	21/0	Pressure/middle finger	bench press, leg press pull downs, arm ext	3 sets of 10, 75% 1RM	45 minutes	0.56, 0.74

Note. RM=repetition max; ext = extensions; NA=Not available

Table 6

Studies examining pain perception following aerobic exercise in chronic pain populations

Author, year	Participants (M/F, pain cond.)	Pain induction stimulus/location	Mode of exercise	Exercise intensity	Exercise Duration	Pooled ES (intensity, threshold)
Newcomb et al., 2011	0/21, FMS	Pressure/index finger	cycle ergometer	Self-selected	20 minutes	0.45, 0.79
Newcomb et al., 2011	0/21, FMS	Pressure/index finger	cycle ergometer	60–75% HR_{max}	20 minutes	0.39, 0.01
Vierck et al., 2001	0/10, FMS	Heat thermal/glabrous skin of hand	Treadmill	To exhaustion	11–12 minutes	−1.13, NA
Meeus et al., 2010	21/5, CFS	Pressure/arm, hand, back, calf	cycle ergometer	Incremental 20–130 Watt	22–29 minutes	NA, −0.32
Meeus et al., 2010	11/10, CLB	Pressure/arm, hand, back, calf	cycle ergometer	Incremental 20–130 Watt	22–29 minutes	NA, 0.08
Hoffman et al. 2005	4/4, CLB	Pressure/index finger	cycle ergometer	50–70% VO_{2max}	25 minutes	1.50, NA
Cook et al. 2010	15/0, CMP	Heat thermal/glabrous skin of hand	cycle ergometer	70% VO_{2max}	30 minutes	NA, 0.31
Cook et al. 2010	15/0, CMP	Pressure/middle finger	cycle ergometer	70% VO_{2max}	30 minutes	NA, 0.07

Note. Cond=condition; FMS=Fibromyalgia Syndrome; CFS=Chronic Fatigue Syndrome; CLB=Chronic Low Back Pain; M=males; F=females; ES= effect size; NA=Not available; CMP=Chronic musculoskeletal pain.

Table 7

Studies examining pain perception following isometric exercise in chronic pain populations

Author, year	**Participants (M/F, pain cond.)**	**Pain induction stimulus/location**	**Mode of exercise**	**Exercise intensity**	**Exercise Duration**	**Pooled ES (intensity, threshold)**
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/contracting MI	iso. shoulder rotation	20–25% MVC	5 minutes	NA, −0.67
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/resting MI	iso. shoulder rotation	20–25% MVC	5 minutes	NA, 0.15
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/contralateral MQ	iso. shoulder rotation	20–25% MVC	5 minutes	NA, 0.68
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/contracting MQ	iso. knee extension	20–25% MVC	5 minutes	NA, 0.96
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/resting MQ	iso. knee extension	20–25% MVC	5 minutes	NA, 1.48
Lannersten & Kosek, 2010	0/20, sh myalgia	Pressure/contralateral MI	iso. knee extension	20–25% MVC	5 minutes	NA, 1.62
Lannersten & Kosek, 2010	0/20, FMS	Pressure/contracting MI	iso. shoulder rotation	20–25% MVC	5 minutes	NA, −0.55
Lannersten & Kosek, 2010	0/20, FMS	Pressure/resting MI	iso. shoulder rotation	20–25% MVC	5 minutes	NA, −0.95
Lannersten & Kosek, 2010	0/20, FMS	Pressure/contralateral MQ	iso. shoulder rotation	20–25% MVC	5 minutes	NA, −0.46
Lannersten & Kosek, 2010	0/20, FMS	Pressure/contracting MQ	iso. knee extension	20–25% MVC	5 minutes	NA, −0.97
Lannersten & Kosek, 2010	0/20, FMS	Pressure/resting MQ	iso. knee extension	20–25% MVC	5 minutes	NA, −0.05
Lannersten & Kosek, 2010	0/20, FMS	Pressure/contralateral MI	iso. knee extension	20–25% MVC	5 minutes	NA, −0.14
Staud et al. 2005	0/12, FMS	Heat thermode/ip forearm	hand grip	30% MVC	90 seconds	−1.68, NA
Staud et al. 2005	0/12, FMS	Heat thermode/co forearm	hand grip	30% MVC	90 seconds	−2.20, NA
Hoeger Bement et al. 2011	0/15, FMS	Pressure/index finger	iso elbow flexor	25% MVC	Task failure	NA, 0.15
Hoeger Bement et al. 2011	0/15, FMS	Pressure/index finger	iso elbow flexor	25% MVC	2 minutes	NA, −0.36
Hoeger Bement et al. 2011	0/15, FMS	Pressure/index finger	iso elbow flexor	Max	3–5 seconds	NA, 0.02
Kadetoff & Kosek, 2007	0/17, FMS	Pressure/MQ	knee extension	39 N, ~15%MVC	Exhaust (~8 min)	NA, 1.16
Kadetoff & Kosek, 2007	0/17, FMS	Pressure/deltoideus	knee extension	39 N, ~15%MVC	Exhaust (~8 min)	NA, 2.7

Note. Cond=condition;. iso= isometric; FMS=Fibromyalgia Syndrome;M=males; F=females; ES= effect size; MQ= m. quadriceps; MI=m. infraspinatus; ip=ipsilateral; co=contracting; min=minutes; NA=Not available; sh=shoulder.