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# Physical Activity Levels Predict Exercise-induced Hypoalgesia in Older Adults

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**Abstract**

Prior research indicates that older adults exhibit a deficient capacity to activate multiple pain inhibitory mechanisms, including pain inhibition after acute exercise termed exercise-induced hypoalgesia (EIH). The influence of physical activity levels and psychological processes on EIH in older adults remains unclear. **PURPOSE:** This study examined potential psychological and physical activity predictors of the magnitude of EIH following submaximal isometric exercise in healthy older adult men and women. **METHODS:** Fifty-two healthy older adults completed a test of EIH, the Pain Catastrophizing Scale, the Tampa Scale of Kinesiophobia, and wore an accelerometer on the hip for one week to assess physical activity levels. For the test of EIH, participants complete a 3-minute isometric handgrip at 25% of maximum voluntary contraction. Pressure pain thresholds (PPTs) and a 30-sec continuous heat pain test were completed before and immediately after the exercise. **RESULTS:** Mixed model ANOVAs revealed that older adults demonstrated significantly decreased PPTs following isometric exercise ($p$=.030), and no changes on the heat pain trials from pre to post test ($p$>.05). A multiple regression revealed that accumulated moderate to vigorous physical activity (MVPA) per week significantly predicted the change in PPT following exercise ($\beta$=0.35, $p$=.012). Participants who averaged greater MVPA experienced a greater increase in PPTs after exercise. No relationships were found with EIH and the psychological variables. **CONCLUSIONS:** Older adults did not exhibit EIH following submaximal isometric exercise. However, those who did more MVPA per week experienced a greater magnitude of pain inhibition following acute exercise.

**Key words:** Isometric exercise, moderate to vigorous physical activity, pressure pain thresholds, heat pain

## INTRODUCTION

The existing research is mixed in regards to changes in pain sensitivity (i.e., pain threshold) with aging (1,2), but has consistently shown that older adults exhibit dysfunctional central pain modulatory processing compared to younger cohorts (3,4,5,6). These dysfunctional pain modulatory processes likely increase the risk for persistent pain in older compared to younger adults. Specifically, studies using dynamic psychophysical tests such as conditioned pain modulation (4), offset analgesia (7), and exercise-induced hypoalgesia (EIH) (8) show that older adults exhibit deficient capacity for descending pain inhibition. Exercise-induced hypoalgesia is a phenomenon in which pain sensitivity and pain perception to noxious stimulation is temporarily reduced following an acute bout of moderate to vigorous exercise (9). We recently revealed that older adults, in contrast to younger adults, do not experience reduced pressure pain sensitivity following an acute bout of isometric exercise or aerobic exercise (8). Additionally, another EIH study demonstrated that while older adults exhibited EIH following isometric exercise, the pain reduction was smaller in magnitude compared to younger adults (10). While the mechanisms of EIH are not completely understood, animal and human data suggest involvement of the central nervous system and separate mechanisms than that regulating pain inhibition through conditioned pain modulation (11). Thus, collectively the research shows that aging is associated with a reduced capacity to activate multiple pain inhibitory mechanisms. Understanding modifiable factors associated with age-related dysfunctional central pain modulatory processing is essential to pain prevention and management strategies for this growing segment of the population.

A growing body of evidence suggests a relationship between central pain modulation and physical activity behavior, with more effective pain modulation associated with greater

physical activity (12-15). For example, Umeda et al. revealed that differences in EIH between African Americans and non-Hispanic Whites disappear after controlling for physical activity levels, suggesting that reduced physical activity in African Americans contributed to reduced EIH (16). Additionally, Naugle and colleagues recently showed that older adults who were more active exhibited greater pain inhibitory capacity on the CPM test and less facilitation of pain on the temporal summation test (13). However, whether regular physical activity behavior influences older adults' capacity for pain inhibition following acute exercise remains unknown.

Emerging evidence also suggests that psychological processes may influence the capability for central pain modulation, including EIH. Studies in younger adults show that higher pain catastrophizing is associated with less pain inhibition on the CPM test (17) and following acute isometric exercise (18). Furthermore, Brellenthin and colleagues demonstrated that a negative family environment, negative mood, and greater situational catastrophizing predicted worse EIH outcomes in young adults (19). No studies have investigated the impact of psychological processes on EIH in older adults.

The objective of this study was two-fold. First, the current study examined whether healthy older adults experience EIH following a submaximal isometric handgrip. Based on previous studies, we hypothesized that older adults would not experience significant inhibition of experimental pain following acute exercise. Secondly, an aim of this study was to examine potential psychological and physical activity predictors of the magnitude of exercise-induced hypoalgesia following submaximal isometric exercise in healthy older adult men and women. We hypothesized that older adults who did relatively more moderate to vigorous physical activity (MVPA) per week and reported less pain catastrophizing would experience greater inhibition of pain following isometric exercise.

## METHODS

### Participants

Participants were 53 healthy adults ranging in age from 60 to 77 (males=20, females=33). Table 1 presents the descriptive characteristics of the sample. The racial composition of the sample included 48 Caucasians, 1 Hispanic, and 4 African Americans. Participants were recruited through flyers within the local community. The following criteria excluded individuals from the study: 1) current use of narcotics or any tobacco products, chronic use of analgesics, 2) serious systemic disease or conditions that restricted normal daily activities (e.g., cancer, severe osteoarthritis), 3) cognitive impairment that would interfere with understanding of the study procedures as defined by a score of greater than 7 on the Six Item Cognitive Impairment Test, 4) uncontrolled hypertension, 5) cardiovascular, metabolic, or pulmonary disease, 6) neurological disease, 7) serious psychiatric conditions (e.g., schizophrenia and bipolar disorder), and 8) chronic pain or any ongoing pain problem (headaches, injury-related pain, etc.). Additionally, participants were instructed to refrain from consuming caffeine or any pain medications prior to the experimental sessions. While we excluded participants for current use of narcotics and chronic use of analgesics, we did not restrict use of other medications. Participants reported taking the following medications on the day of testing: 1) heart burn medication: proton-pump inhibitors (n=3); 2) cholesterol reducing medications: statins (n=5), antilipemic agent (n=1), and fibric acid (n=1); 3) antihypertensive medications: angiotensin II receptor antagonists (n=6), diuretics (n=2), beta blocker (n=1), calcium channel blockers (n=2), and ace inhibitor and channel blocker (n=1); 4) Hypothyroidism medication: thyroid hormones (n=7); 5) antidepressant (n=1); 6) Osteoporosis medication: estrogen modulator (n=1); 7) anti-

inflammatory (n=1); 8) allergy medicine: antihistamine (n=2); 9) antibiotics (n=1). We are unaware of any studies examining the effects of these medications on EIH.

**Procedures**

The Indiana University Human Subject Review Board approved this study. This study was part of a larger investigation examining the role of physical activity behavior in endogenous pain modulation in older adults (13). Participants completed a screening/orientation session and three experimental sessions. All sessions were scheduled on separate days and separated by at least 48 hours. During the experimental sessions, participants completed several questionnaires and the test of EIH. Additionally, physical activity behavior for one week was assessed with an accelerometer. These assessments are described below.

**Screening and Orientation Session**

The screening and orientation session lasted approximately 2 hours and took place on a different day than the experimental sessions. All participants were given information about the experimental procedures, and reviewed and signed a written informed consent form approved by the Indiana University Institutional Review Board prior to participation in the study. To determine eligibility, participants completed a health history questionnaire, supplemented by interview, blood pressure, and height and weight measurements. Participants were also administered the Six-item Cognitive Impairment Test to ensure that participants were free of cognitive impairment that may inhibit study participation (20). No participants were excluded following the orientation and training session. Once eligibility was determined, participants completed a quantitative sensory test training session which 1) allowed them to become

accustomed to the pain tests and laboratory setting and 2) determined individualized temperatures of the stimuli for the heat test stimulus of the exercise-induced hypoalgesia protocol such that participants would experience moderate pain (40-60 on a 0-100 numeric rating scale) during the heat trial. For this purpose, 10-sec trains of increasing heat stimuli were applied to the forearm until participants experienced a moderate level of pain (40-60 on a 0-100 visual analogue scale). Once this temperature was determined and following a 15-minute break, a 30-sec heat pain test was administered to ensure a moderate level of pain was experienced during this trial. The 30-sec heat pain test was administered again and with the temperature adjusted if pain levels did not reach a maximum of 40-60 out of 100. Participants also completed an assessment of maximal voluntary contraction (MVC) of handgrip muscles, and were given an accelerometer, instructions on how to wear the device, and a physical activity diary. Specific procedures for these assessments are described below.

MVC of the right hand flexor muscles was determined with a hand dynamometer (Jamar Plus digital hand dynamometer; Patterson Medical). The dynamometer handle was adjusted according to manufacture guidelines for each participant. Participants placed their right arm on a table surface with the elbow at a $90^{o}$ angle and firmly griped the hand dynamometer. Participants were asked to squeeze the dynamometer as hard as possible for 5 seconds. This procedure was repeated three times with a one minute rest between trials. The high score of the three MVC's was used to calculate the percent of MVC for the submaximal isometric handgrip that was performed in the test of exercise-induced hypoalgesia during the experimental sessions.

**Assessment of Physical Activity**

All participants were instructed to wear an accelerometer (Actigraph GT3X+) on the hip to measure physical activity levels. The Actigraph is a small lightweight tri-axial accelerometer

that is designed to detect tri-axial accelerations in the range of 0.05-2 G. Output from the ActiGraph is in the form of step counts, body positions and activity counts for a specific time period. Data were captured in 1-minute epochs, and non-wear time was defined as 60 minutes of consecutive zero counts. Participants were given the accelerometer and instructions on how to wear it during the screening session. They were instructed to wear the accelerometer for 7 consecutive days following the screening session except during sleep, showering/bathing, and swimming. A valid day was defined as having worn the device for more than 10 hours. Participants were also provided a Physical Activity Diary in which they recorded the start and finish times each day, as well as the duration and reason for any periods where they took the accelerometer off. Participants received reminders from research staff about wearing the accelerometers.

Activity count cut-points to determine the amount of time a participant spent in sedentary, light, or moderate to vigorous activity were defined as <100 counts/minute (sedentary), 100-1951 counts/minute (Light physical activity), and >1951 counts/minute (moderate to vigorous activity), respectively (21). These cut points have been used by other studies to measure physical activity behavior in older adults (22,23). Moderate physical activity and vigorous physical activity were combined into MVPA because very few older adults actually performed vigorous physical activity according to the accelerometer data. MVPA was expressed in minutes/day. National guidelines recommend that MVPA should be accrued in bouts of at least 10 minutes for potential health benefits (24). Therefore, we calculated total minutes of MVPA per day and MVPA accumulated in bouts ≥ 10 minutes. Light physical activity (LPA) and sedentary time were expressed in minutes per day and as a percentage of accelerometer wear time per day. Because light physical activity and sedentary time are highly related to

accelerometer wear time, percentage of wear time in LPA and sedentary time were used in the regression analyses.

***Exercise-induced Hypoalgesia (EIH).***

Exercise-induced hypoalgesia was assessed during one of the experimental sessions. The EIH procedures tested for changes in pressure and heat pain sensitivity (as described under experimental pain measures) following a 3-minute trial of submaximal isometric exercise at 25% of MVC (See Figure 1). Seven minutes separated the pre pain tests and the initiation of the isometric contractions for all participants. This period of rest was included to prevent within-session adaptation, as prior work has shown complete recovery of primary afferent responsiveness after 10 minutes of no pain stimulation (25). For the isometric contraction, participants placed their right arm on a table surface with the elbow at a $90^{o}$ angle and firmly griped the hand dynamometer. Participants were asked to squeeze the hand dynamometer at 25% MVC for 3 minutes. Participants saw the dynamometer read-out and adjusted their effort if necessary. Ratings of perceived exertion using Borg's 6-20 RPE scale (26) and heart rate were assessed every 20sec during the isometric exercise trial. Blood pressure was assessed immediately following the isometric contraction. Then the pressure and heat pain tests were administered again (post-pain tests). The pain tests were administered on the non-exercised (left) arm.

*Pain Test Stimuli:*

Two pain test stimuli were administered consecutively before and following the isometric contraction: pressure pain thresholds (PPTs) and a continuous heat pain test. We chose to always administer the PPTs first and the heat pain test second because PPTs were shorter in duration and

elicited a very low level of pain compared to the heat pain test. Thus, the PPTs were less likely to influence pain perception on the continuous heat pain test than vice versa (heat pain test and then PPTs). The first test stimulus was *Pressure Pain Thresholds (PPTs).* A digital, handheld, clinical grade pressure algometer was used for the mechanical procedures (AlgoMed, Medoc Advanced Medical Systems, Durham, NC, USA). The tip of the algometer consisted of a rubber flat 1.0 $cm^2$ probe. The experimenter applied a slow constant rate of pressure (30kPA/s) to the left ventral forearm. Participants were instructed to press a response button when the pressure sensation first became painful, at which the algometer was removed. Pressure pain threshold was defined as the amount of pressure in kilopascals (kPa) at which the participant first reported experiencing pain. Two trials were administered consecutively during each pre- and post-EIH test. These trials were averaged for a single pre- and post-test PPT score.

The second test stimulus was a *Continuous Heat Pain test*, where focal thermal stimuli (44-48.5$^{o}$C) were administered by a Pelteir-based thermode (TSA-II, Medoc; thermode size: 30mm x 30mm) to the forearm. For each 30-second continuous heat pain trial, the thermode was first brought to a neutral temperature (32$^{o}$C) and then ramped (2.0$^{o}$C/s) to the individualized temperature (44-48.5$^{o}$C) determined during the training session and maintained at that temperature for 30 s. The intensity of the pain produced by the contact thermode was rated continuously using an electronic visual analogue scale (eVAS). The eVAS consists of a low-friction sliding potentiometer (10cm travel) with the left endpoint defined as "no pain" and the right endpoint as "intolerable pain". Additional hash marks in increments of 10 are provided to simulate a 0-100 numerical rating scale. Participants were instructed to move the slider in proportion to their perceived pain intensity in real time. The Medoc software records the participants' pain ratings every 10-20 ms. The average pain rating for each 30-s trial was

calculated and used as the primary outcome measure for the heat pain test. Two trials were administered consecutively with a 1-minute inter-trial-interval during each pre- and post-EIH test. The pre- and post-EIH test trials were averaged for a single pre- and post-test heat pain score.

*Calculation of EIH.* A change score was calculated for each test stimulus (EIH-PPT and EIH-Heat) with the following formula: post EIH trial score – pre EIH trial score. For the EIH-Heat, a negative change score indicated a reduction in pain following the isometric contraction and thus pain inhibition. For the EIH-PPT, a positive change score indicated an increase in PPTs following the isometric contraction and thus pain inhibition.

**Psychological Questionnaires**

***Pain Catastrophizing Scale (PCS)***

The Pain Catastrophizing Scale consists of 13 items rated on a 5-point likert scale (27). The PCS asks the respondents to reflect upon past painful experiences and to rate the degree to which they experienced negative thoughts or feelings about pain. The PCS measures three dimensions of catastrophizing: rumination, helplessness, and magnification. The highest possible score on the PCS is 52, with prior studies showing a cutoff range of more than 20-24 points to be related with clinical relevance (28,29).

***Tampa Scale of Kinesiophobia-11 (TSK-11)***

The Tampa Scale of Kinesiophobia-11 (TSK) consists of 11 items used to measure fear of movement or re-injury associated with pain (30). The TSK is a reliable and valid method for determining fear of movement in both clinical and non clinical populations (31,32). The total

TSK score ranges from 11-44, with higher scores indicating greater fear of movement due to pain.

**Data Analysis**

As the primary purpose of the study was to determine predictors of EIH, a power analysis using G Power 3.0.10 was used to estimate the sample size needed for predicting the change in $R^2$ in a multiple linear regression model, when the independent variable of interest was added to the model. With an estimated moderate effect size ($f^2$=0.16) and including two covariates, a sample size of fifty-two participants would provide power of 0.80 at 0.05.

Descriptive statistics were calculated for age, each psychological questionnaire, thermode test temperature for the 30-s heat trials, MVC, average RPE score during the isometric trial, EIH-Heat score, EIH-PPT score, and average time per day spent in accumulated moderate to vigorous physical activity (MVPA) and MVPA accumulated in bouts ≥ 10 minutes (MVPA+10), light physical activity (LPA) and sedentary time, and percentage of accelerometer wear time spent in LPA and sedentary time. Shapiro-Wilk's test of normality indicated that all the above variables except for the RPE scores, LPA, percentage of wear time in LPA, and percentage of wear time in sedentary time were not normally distributed; thus Mann-Whitney U tests were conducted to determine if theses variables differed by sex. Independent t-tests were used to examine sex differences in the normally distributed variables.

One purpose of the study was to evaluate whether older adults exhibited significant pain reduction following isometric exercise. Thus, the pre PPTs, pre heat pain scores, post PPTs, and post heat pain scores were first evaluated for normal distribution. The Shapiro-Wilk's test of normality indicated normal distribution of the heat pain scores and the pre PPTs, but not the post

PPTs. Because the skewness (skewness=1.0±.33, z=3.03) and kurtosis (kurtosis=0.42±.65, z=.65) values for post PPTs were in the acceptable range for normal distribution (33), parametric tests were used to analyze this data. Two (Sex) × 2 (Trial: pre, post) mixed model ANCOVAs were conducted on the heat and pressure pain data to determine whether older men and women experienced EIH. Target force level was added as a covariate. Effect sizes were also calculated to determine the magnitude of pain reduction after exercise. Effect sizes were calculated for men and women separately and the sample as a whole. Cohen's *d* was defined as the posttest mean minus the pretest mean, divided by the pooled within group standard deviation ($\underline{d}$=[$X_{\text{posttest}}$ − $X_{pretest}$]/pooled standard deviation). Reductions in pain after exercise are reflected by positive effect sizes.

Second, spearman's rho bivariate correlation analyses were conducted to determine whether EIH was associated with demographic variables, test variables (RPE during isometric exercise, target force production), psychological variables, and physical activity variables. Third, separate hierarchical regressions were conducted to determine significant predictors of EIH-PPT and EIH-Heat. For each regression, age and pretest scores were entered as covariates in the first step. Age was added as a covariate due to prior research showing age associations for EIH. The pretest scores were added as covariates because the pretest PPT score was significantly correlated with EIH-PPT and the pretest heat score was significantly correlated with EIH-Heat. The physical activity variable (MVPA, MVPA+10, percentage of time in LPA, or percentage of time in sedentary time) was entered on the second step for each regression. Separate regressions were conducted for each physical activity variable.

## RESULTS

Table 1 presents the characteristics of the study sample as well as the means and standard deviations (SD) for all the primary measures of the study. The means are separated by sex. Target force production ($p<.001$), sedentary time per day ($p=.04$), and percentage of wear time in LPA ($p=.019$) were the only variables significantly different between sexes.

### Changes in pain sensitivity and ratings following isometric exercise

Data are presented as means ± SD's. For the PPTs, the mixed model ANOVA revealed a significant main effect of trial ($F(1,50)=5.0$, $p=.030$) and sex ($F(1,50)=3.2$, $p=.002$). Males (M=424.97 kPa ±144.7) exhibited greater pressure pain thresholds compared to females (M=280.42 kPa ±134.8). Additionally, PPTs decreased following the isometric exercise (Trial 1= 367.18 kPa ±131.8; Trial 2= 338.21 kPa ±134.0; $d=-.31$). The effect size for men was larger ($d=-.52$) than the effect size for women ($d=-.01$), indicating that the magnitude of pain facilitation following exercise was greater for men. However, the interaction of sex and trial was not significant, $F(1,50)=2.8$, $p=.098$. Figure 2a shows the average PPTs for the trials pre and post exercise.

No significant differences were found for the suprathreshold heat pain ratings [Main effect of Time: $F(1,50)=1.6$, $p=.206$, $d=0.27$; Main effect of Sex: $F(1,50)=0.28$, $p=.601$; Time by Sex interaction: $(1,50)=1.43$, $p=.24$]. Figure 2b shows the average heat pain ratings for the trials pre and post exercise. The effect size for men was $d=.15$ and for women $d=.36$.

### Correlations between EIH, demographic and test-related variables, and physical activity and psychological variables

Table 2 presents the correlations between EIH-PPT, EIH-Heat, age, BMI, target force level, RPE during exercise, MVPA, MVPA+10, percentage of accelerometer wear time spent in

LPA and sedentary time, PCS scores, and TSK scores. EIH-PPT was positively and significantly related to MVPA per day ($p$=.022), but not MVPA+10. Higher levels of MVPA were associated with greater EIH-PPT. MVPA was also significantly and negatively associated with BMI ($p$=.001), percentage of wear time spent in sedentary time ($p$=.011), and TSK score ($p$=.021). Therefore, those who had higher levels of MVPA also had lower BMI, less sedentary time, and lower fear of pain due to movement. MVPA+10 was negatively associated with BMI ($p$=.001). Percentage of time spent in sedentary time was also positively associated with TSK ($p$=.001) and BMI ($p$=.008), and negatively associated with percentage of time spent in LPA ($p$<.001).

**Predictors of EIH**

Table 3 presents the results of the regressions involving MVPA and MVPA+ to predict EIH. The model for prediction of EIH-PPT by MVPA was significant. After controlling for pre-exercise PPT and age, MVPA significantly predicted the magnitude of EIH-PPT. Participants who averaged greater MVPA per day experienced greater EIH, accounting for 11% of the variance. The model for prediction of EIH-PPT by MVPA+10 was also significant; however, the only significant predictor was PPT pre exercise score. The models involving the prediction of EIH-PPT by percentage of wear time in LPA ($p$=.076) and sedentary time ($p$=.126) were not significant.

The model for prediction of EIH-Heat by MVPA was also significant. However, only pre-exercise heat pain rating predicted EIH-Heat. The same results were found for MVPA+10 as a predictor of EIH-Heat. The model for prediction of EIH-Heat by percentage of wear time in LPA was significant (p=.008); however, this was driven by the significant effect of pretest heat pain score (age: β=.24, p=.065; pretest heat pain score: β=-.37, p=.005; LPA: β=.09, p=.461).

Similarly, the model for prediction of EIH-Heat by percentage of wear time in sedentary time was significant (p=.09), with the only significant predictor being pretest heat pain score (age: β=.24, p=.065; pretest heat pain score: β=-.37, p=.005; sedentary time: β=-.06, p=.620).

## DISCUSSION

The primary aims of the present study were to examine the relationship between physical activity levels and psychological variables with EIH in older adults. The results showed that, in general, older adults did not exhibit EIH following submaximal isometric exercise. However, those who accumulated more MVPA per week experienced greater EIH. These results point to potential benefits of physical activity in maintaining EIH capabilities with age.

Supporting previous research, the present study showed that older adults did not exhibit EIH following isometric exercise regardless of test stimulus (8). Exercise-induced hypoalgesia is a common phenomenon seen in younger adults but not consistently present in older adults or those with chronic pain (8,9). Within the present study, older adults failed to show significant heat pain reduction following isometric exercise. Furthermore, participants actually showed a decrease in PPT's following exercise. However, the effect sizes suggest that this pain facilitory effect of exercise was driven by the males, while females showed no change in PPT's following exercise. Prior research has shown a minimal to small magnitude of pressure pain reduction following isometric exercise in older adults that was significantly smaller in magnitude compared to younger adults (8,10). For example, Lemley and colleagues found a small pain reducing effect of an isometric contraction of 25% MVC that was held until task failure in older adults (10). Thus, the EIH effect could be stronger in older adults with isometric exercise of longer duration or greater intensity. Additionally, Naugle et al found small EIH effects in older

adults following isometric exercise and moderate and vigorous aerobic exercise; however, these effects were smaller than the effects of quiet rest (8). Conversely, Vaegter and colleagues did not find age differences in EIH following isometric or aerobic exercise; however, all participants were under the age of 65 years (34). Less research has examined EIH in older adults using heat stimuli, with mixed results (8). Nonetheless, the collective evidence to date suggests a diminished capacity for EIH in pain-free, generally healthy older adults.

As hypothesized, the amount of MVPA per day but not light physical activity or sedentary time for older adults predicted their level of EIH experienced following isometric exercise. However, MVPA only accounted for 11% of the total variance in EIH. Greater accumulated MVPA corresponded with a greater magnitude of EIH in older adults. Interestingly, only accumulated MVPA per day and not MVPA accumulated in at least 10 minute bouts significantly predicted EIH, suggesting that all bouts of MVPA are potentially important in maintaining function of this pain inhibitory system. Along these lines, Umeda et al. found lifestyle physical activity levels influenced EIH differences between African American and non-Hispanic White young adults, such that reduced lifestyle physical activity explained less efficient EIH in African Americans compared to non-Hispanic Whites (16). In contrast to Umeda et al. and the current study, Black and colleagues found no difference in EIH responses due to physical activity level or type in a group of college-aged women (35). The authors of this study point to two possible reasons for the lack of association between EIH and physical activity: 1) the insufficiently active group still did at least 13 minutes of vigorous physical activity per day and 2) the impact of physical activity on pain modulation may be greater in older adults, given the decline in physical activity and endogenous pain modulatory function with age. Research has also shown a relationship between physical activity levels and other tests of central pain

modulatory processing in older adults. Naugle et al. recently revealed that accumulated MVPA predicted temporal summation of pain (a test of endogenous pain facilitation), while light physical activity predicted conditioned pain modulation (a test of endogenous pain inhibition) (10). Overall, accumulating evidence supports the notion that physical activity helps to improve central pain-processing mechanisms, particularly in older adults.

Notably, the relationship between EIH and physical activity was observed with PPT's as the test stimulus and not the prolonged heat test stimulus. Prior research shows that EIH is partially a function of the experimental pain test (8,18), illustrating the complexity of the EIH phenomenon. Collectively, research on the mechanisms of EIH suggests this phenomenon may be produced by multiple analgesic systems (36,37), each of which may preferentially alter different types of nociceptive input. Future research needs to determine which pain test stimuli during the EIH protocol provide the most clinical significance.

Several potential mechanisms could exist through which regular MVPA enhances the ability to inhibit pain following acute exercise in older adults. First, a common mechanism used to explain EIH involves the activation of endogenous opioid system during exercise. Animal studies show that moderate to vigorous intensity exercise of sufficient duration decreases pain sensitivity in rodents likely through exercise-induced release of central and peripheral beta-endorphins (36,38,39). Additionally, a recent human study suggested, by genetic association, that opioid and serotonergic mechanisms jointly regulated central pain inhibitory signaling following isometric exercise (40). Rodent studies also suggest that aging is associated with decreased opioid peptides and opioid peptide receptor levels in the brain (41), which could contribute to a reduced capacity for EIH in older adults. Notably, regular aerobic exercise in rodents increases endogenous opioid content or release in the brain (42,43). Thus, regular aerobic exercise could

prevent or slow the age-related decline in opioid peptides and receptors in the central nervous system, and consequently help older adults maintain the ability to inhibit pain following acute exercise. This opioid-related explanation is clearly speculative and needs further support from animal and human mechanistic studies. Furthermore, a recent human study showed that the administration of an opioid antagonist does not influence the EIH response following isometric exercise, suggesting the involvement of a non-opioid mechanism (37). Another potential mechanism involves alterations of endocannabinoids with age and physical activity. Recently, another human EIH study evaluating isometric exercise suggested involvement of a non-opioid versus opioid mechanism (37,44). Crombie and colleagues discovered that endocannabinoid 2-arachidonoylglycerol (2-AG) concentrations were significantly elevated by isometric exercise and likely played a role in producing EIH (44). Interestingly, animal studies show that aging is associated with decreased 2-AG in the brain (45,46). However, few studies have examined the effects of chronic exercise on levels of endocannabinoids, providing conflicting results (47,48).

The current study did not find relationships between EIH and the psychological variables of pain catastrophizing and fear of movement due to pain. These findings are in contrast to previous research showing relationships between psychological variables and EIH following isometric exercise in younger adults (18,19). For example, Naugle and colleagues revealed that greater pain catastrophizing was associated with smaller reductions in pain following isometric exercise (18). Furthermore, Brellenthin et al. demonstrated that situational pain catastrophizing predicted magnitude of isometric EIH in younger adults (19). However, in both of the aforementioned studies, a significant relationship between EIH and pain catastrophizing was specific to the use of temporal summation of pain (i.e., repetitive heat pulses) as the test stimulus during the EIH protocol. Thus, it is possible that a relationship between EIH and pain

catastrophizing could exist in older adults with repetitive heat pulses used as the test stimulus. While fear of pain due to movement was not related to EIH, this variable was negatively associated with MVPA. Thus, older adults who had greater fear of pain also did less MVPA per day. Notably, the participants in our study had low levels of pain catastrophizing and fear of pain. It is possible that those with clinically relevant levels of pain catastrophizing and/or fear of pain may show a different relationship between EIH and these psychological variables.

A few limitations of this study should be noted. First, the present study is cross-sectional which prevents us from being able to show the direction of causality. Without following participants over an extended period of time, it is not possible to conclude whether enhanced exercise-induced hypoalgesia is caused by a greater level of MVPA or whether the greater EIH allows for greater amounts of MVPA. While the relationship is likely somewhat bidirectional, large longitudinal studies suggest that regular exercise can be protective against the development of chronic pain with aging (49-51). Furthermore, recording physical activity for seven days is a very insightful measure but this is only a tiny portion of participants 60+ years of activity or inactivity. Third, the older adults in this study were fairly active and healthy; thus, these results may not generalize to older adults with physical disability or chronic pain. Fourth, we did not measure pain during the isometric exercise, which could have varied greatly between participants. Prior research has demonstrated that painful exercise produces greater EIH compared to nonpainful exercise in healthy women, suggesting a possible role of conditioned pain modulation in EIH (52). Finally, the accelerometer data was captured in 1-minute epochs. Capturing data in 1-second epochs would have more accurately reflected total MVPA accumulated by participants. Despite these limitations, our data add to the accumulating evidence showing the importance of physical activity for efficient central pain modulatory processing,

particularly in older adults. This may be one mechanism through which physical activity may reduce the risk for chronic pain in older adults. Future research needs to determine whether increasing physical activity can prevent the age-related decline in central pain modulatory processing or even "normalize" deficient central pain modulatory processing in older adults.

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The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and the results of the present study do not constitute endorsement by ACSM.

**CONFLICT OF INTEREST**

There are not actual or potential conflicts of interest for any of the authors.

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## Figure Captions

**Figure 1.** Timeline of the EIH protocol. First, two trials of pressure pain thresholds and two trials of 30-sec heat pain tests were administered in consecutive order on the left/non-exercised forearm. Then participants sat quietly for 7 minutes followed by a 3-minute trial of a submaximal isometric handgrip exercise at 25% of MVC by the left arm. Blood pressure was immediately taken after completion of the handgrip exercise and then the pressure and heat pain tests were administered again on the left forearm.

**Figure 2.** PPT's (*top*) and Average Heat Pain ratings during the 30-s Heat pain trials (*bottom*) pre- and post-exercise in older men and women. Error bars represent standard deviations.

Figure 1

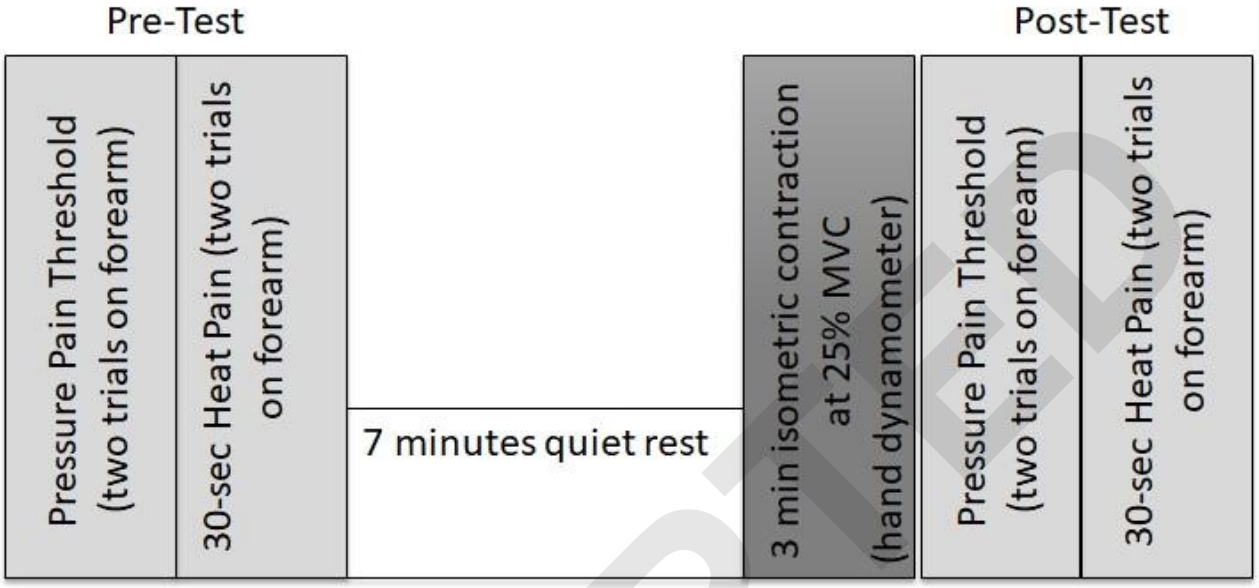
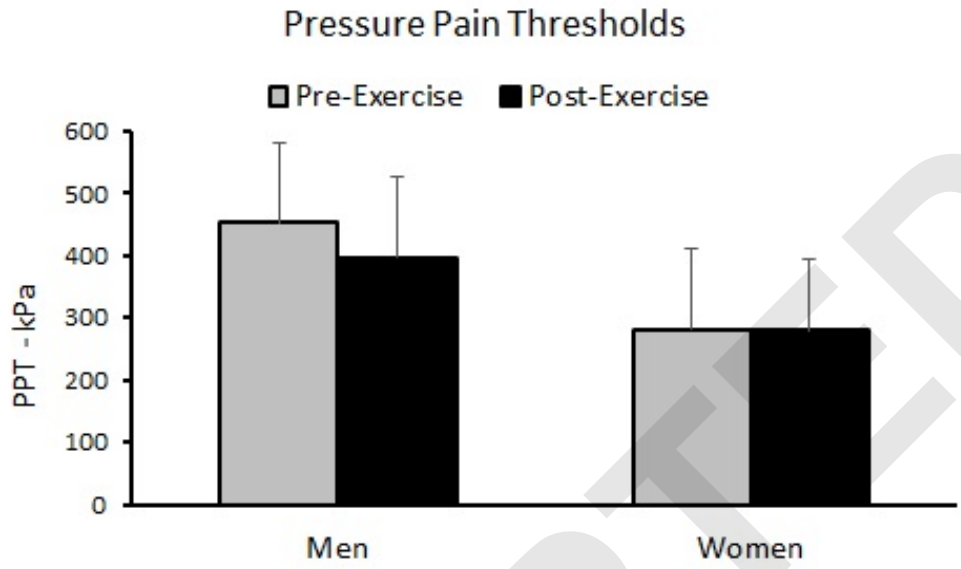


Figure 2



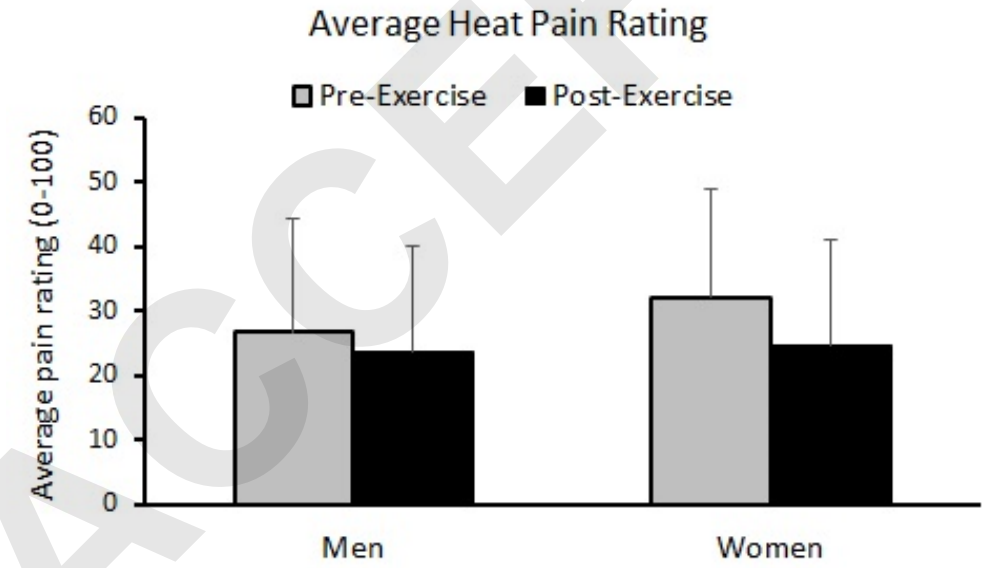



**Table 1.**

Means and standard deviations for primary study measures in participants

| Variable | Men (n=20) | Women (n=32) |
|---|---|---|
| Age, year | 67.6±5.3 | 67.2±4.9 |
| BMI | 26.9±3.4 | 26.0±5.0 |
| Target Force | 20.9±6.7 | 12.6±2.5 |
| RPE during exercise | 11.7±2.4 | 10.7±2.2 |
| 30-s Heat Trial Temperature, $C^o$ | 47.8±0.8 | 47.7±0.9 |
| TSK score | 19.7±5.1 | 18.3±4.1 |
| PCS score | 9.4±9.4 | 9.7±7.9 |
| MVPA per day | 28.3±20.9 | 21.2±14.5 |
| MVPA+10 | 14.9±19.0 | 10.2±11.4 |
| LPA per day, minutes | 257.6±65.1 | 280.1±51.4 |
| Sedentary time per day, minutes | 667.6±162.1 | 589.5±107.5 |
| Percentage of wear time in LPA | 27.2±6.9 | 31.8±6.3 |
| Percentage of wear time in Sedentary time | 69.7±7.5 | 65.8±6.9 |

Note: BMI=Body Mass Index; TSK = Tampa Scale of Kinesiophobia; PCS=Pain Catastrophizing Scale; MVPA=accumulated Moderate to vigorous physical activity; MVPA+10= MVPA accumulated in bouts ≥ 10 minutes; RPE=Ratings of perceived exertion; LPA=Light physical activity

**Table 2**

Spearman's rho bivariate correlation matrix between EIH and study measures

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. EIH-PPT | 1.00 | | | | | | | | | | | |
| 2. EIH-Heat | .27 | 1.00 | | | | | | | | | | |
| 3. Target Force | .23 | -.10 | 1.00 | | | | | | | | | |
| 4. RPE during exercise | .05 | .07 | .23 | 1.00 | | | | | | | | |
| 5. Pain catastrophizing | -.19 | -.10 | -.03 | .23 | 1.00 | | | | | | | |
| 6. MVPA | .33* | -.09 | .17 | .04 | -.03 | 1.00 | | | | | | |
| 7. TSK | -.09 | -.12 | -.10 | .12 | .18 | -.29* | 1.00 | | | | | |
| 8. BMI | -.14 | .11 | .10 | -.04 | -.03 | -.45** | .25 | 1.00 | | | | |
| 9. Age | -.20 | .23 | -.17 | .08 | -.13 | -.09 | .06 | .09 | 1.00 | | | |
| 10. % of LPA | -.04 | -.02 | -.05 | .11 | .02 | .07 | -.42** | -.24 | .01 | 1.00 | | |
| 11. % of Sedentary Time | .01 | .05 | .01 | -.12 | -.02 | -.35* | .46** | .36** | .01 | -.95** | 1.00 | |
| 12. MVPA+10 | .16 | -.11 | .02 | .01 | -.08 | .89** | -.21 | -.43** | .05 | -.01 | -.15 | 1.0 |

*Note*: *=p<.05; **=p<.001; EIH=Exercise induced hypoalgesia; PPT=Pressure pain threshold; TSK = Tampa Scale of Kinesiophobia; BMI=Body Mass Index; MVPA=Moderate to vigorous physical activity; MVPA+10= MVPA accumulated in bouts ≥ 10 minutes; RPE=Ratings of perceived exertion; LPA=Light physical activity.

**Table 3.** Hierarchical regression results in the prediction of (A) EIH-PPT and (B) EIH-heat by MVPA and MVPA+10

| Dependent Variables and Step number | R | $\Delta R^2$ | Standardized β | P value for β | Model P-value |
|---|---|---|---|---|---|
| **Prediction by MVPA** | | | | | |
| *A. Predicting EIH-PPT* | | | | | |
| 1. Age | .337 | .114 | -.134 | .324 | .012 |
| PPT Pre-exercise | | | -.337 | .016 | |
| 2. MVPA | .469 | .110 | .334 | .019 | |
| *B. Predicting EIH-Heat* | | | | | |
| 1. Age | .452 | .204 | .233 | .073 | .008 |
| HPR Pre-exercise | | | -.392 | .004 | |
| 2. MVPA | .460 | .008 | -.090 | .496 | |
| **Prediction by MVPA+10** | | | | | |
| *A. Predicting EIH-PPT* | | | | | |
| 1. Age | .337 | .114 | -.159 | .254 | .034 |
| PPT Pre-exercise | | | -.335 | .021 | |
| 2. MVPA+10 | .422 | .064 | .260 | .071 | |
| *B. Predicting EIH-Heat* | | | | | |
| 1. Age | .452 | .204 | .239 | .063 | .005 |
| HPR Pre-exercise | | | -.404 | .003 | |
| 2. MVPA+10 | .477 | .024 | -.158 | .224 | |

Note: PPT=Pressure pain threshold; HPR=Heat Pain rating; EIH=Exercise induced hypoalgesia; MVPA=moderate to vigorous physical activity; MVPA+10= MVPA accumulated in bouts ≥ 10 minutes.