RELATIONSHIPS BETWEEN PHYSICAL ACTIVITY AND PAIN

IN PEOPLE WHO ARE OVERWEIGHT, DIABETIC OR IN DISABLING PAIN

by

AMANDA LEE CARAVALHO

(Under the Direction of Patrick J. O'Connor)

ABSTRACT

Disabling pain interferes with daily life and can lead to chronic pain. This dissertation involved two studies evaluating the potential role physical activity (PA) could play in managing pain among people with disabling pain or at increased risk for disabling pain due to being overweight, diabetic or postmenopausal.

Study 1 used meta-analytic techniques to estimate the population effect size of randomized controlled trials of exercise training effects on bodily pain scores among overweight or diabetic samples. Twenty-one effects were calculated from eleven studies (n = 5826). A small, mean effect size delta (Δ) of 0.07 (95% CI, -0.07, 0.21; p = 0.30) was quantified. No significant moderators were found. Therefore, exercise training has a small effect on pain among overweight and diabetics samples.

Study 2 evaluated postmenopausal women with and without disabling pain and examined relationships between PA and both heat pain sensitivity and conditioned pain modulation. It was hypothesized that: (i) inactive women would rate the pain intensity and pain unpleasantness of all heat stimuli higher than active women, (ii) inactive women with disabling pain would rate the pain intensity and pain unpleasantness of heat stimuli higher at the higher heat stimulus

intensities compared to active women with disabling pain, and (iii) inactive women would show less pain modulation.

A mixed model ANOVA (2 x 4 x 2, PA x temperature x pain status) showed inactive women with disabling pain rated the pain unpleasantness of heat stimuli higher compared to active women with disabling pain ($F_{3,192}$ = 3.526, partial η^2 = .052, p= .016 for accelerometry and $F_{3,192}$ = 3.60, partial η^2 =.053, p = .015 for self-report). Significantly lower pain unpleasantness ratings were found at 49^{o}C only for the active women with disabling pain compared to inactive women in disabling pain (t_{11}=2.523, p=.028 for accelerometry and t_{11}=2.208, p=.049 for the self-report). The other hypotheses were not supported. Therefore PA is associated with reduced sensitivity to the unpleasantness of painful high intensity heat stimuli among women with disabling pain.

It is concluded that regular PA may be a useful for reducing pain unpleasantness in postmenopausal women in disabling pain.

INDEX WORDS: Pain, exercise, physical activity, pain processing, SF-36, conditioned pain modulation, postmenopausal, meta-analysis, overweight, diabetes

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BA, UNIVERSITY OF NOTRE DAME, 2008

MS, UNIVERSITY OF GEORGIA, 2010

A Dissertation Submitted to the Graduate Faculty of The University of Georgia

in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2013

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DEDICATION

I would like to dedicate this document to those who have guided me both in my personal life and in my pursuit of this degree. I dedicate the work put into this project to my parents who continue to guide me and support me through my endeavors. They gave me the opportunity to pursue my education and were constantly offering kind words of encouragement and love. They were my first teachers and continue to be people I hope to emulate.

I would also like to dedicate this document both to Drs. Radvansky and Kernis. Dr. Radvansky at the University of Notre Dame gave me my first opportunity to work in a psychology lab. It was through this experience that I learned of my love of psychology and research. He guided me through the process of applying to graduate school and sent me off well prepared for the challenges it would present.

Finally, this is dedicated to Dr. Kernis. It was Dr. Kernis who took a chance on me and accepted me into the Psychology Department here at the University of Georgia. He was excited for me to join his lab and welcomed me warmly into the "Kernis Lab." I greatly enjoyed learning more about "the self" while a member of his lab. His passing during my first year led me to the Kinesiology Department where I truly believe I was meant to be. May he continue to rest in peace.

ACKNOWLEDGEMENTS

"The Lord is my light and my salvation. Whom shall I fear? The Lord is my strength of my life. Of whom shall I be afraid? Though an army should encamp against me, my heart shall not fear. Though war should rise against me, even then I will be confident."

- Psalm 27:1,3

Dr. O'Connor deserves my utmost respect and gratitude. When I was an advisor-less graduate student in the Psychology Department, he gave me a home. I will never be able to repay him for the chance he took on me. My time in the Kinesiology Department has been greatly beneficial both academically and personally. I truly believe that I am a more critical reader, more scientific thinker, and more conscientious team member because of the experience here.

To my husband, John-Paul – thank you for your continued support. You have transitioned from a friend, boyfriend, fiancé, and now husband throughout my graduate school career and through each stage you have only gotten more supportive and loving. I have missed you this past year through your current deployment but know that when you get home we will be back to our fun adventures. While you are far from home, you still know exactly what to say (or not say) to help me through the stressful and disheartening moments of graduate school. I thank God everyday that you are by my side.

Thank you, again, to my parents for supporting me on this journey. I will never forget you asking me what I plan on doing with "just" a psychology degree when graduating from

college. And then when I decided to pursue a degree in Kinesiology I always enjoyed trying to explain what it is I do and what I plan on doing with that degree. I always appreciated hearing the jobs for which you think I would be qualified. In all seriousness though, I would not have been able to pursue this degree without your encouragement. Thank you.

To those who came before me – specifically Whitney Heppner and Matt Herring – thank you. You both have had a profound impact on my career and personal life. Whitney, you guided me through my struggles as a new graduate student and kept me in shape! Thank you for being my running buddy and mentor through my Masters. Matt, you helped tremendously as I transitioned not only from psychology to kinesiology but also from a Masters to a Doctoral student. You both continue to be great role models for what it looks like to be both productive in the lab and still have time for your family. I am grateful for the friendship that John-Paul and I have developed with both of you and your spouses. Whit & Zach and Matt & Lisa, you are great couples and dear life-long friends. Thank you.

Christie Ward Ritacco – thank you for accepting me as a teammate on this dissertation journey. I have learned a lot through working with you and hope to take the lessons I have learned to all of my future endeavors. I feel like I found a great lab-mate and friend in you. I am glad that we were both in the "business of graduating" at the same time. Oh the memories we have made!

To the Ex Psych crew – you are family to me. Not many people understand the ups and downs of graduate school. I am glad to share this experience with you. I am proud to call you colleagues and grateful to call you friends.

Thank you to all of the local baristas in town for keeping me caffeinated, the folks at Pawtropolis for keeping Coach occupied while I was writing, and to the blessed1 – Steven – for keeping my computer working!

Finally, I would be remiss if I did not acknowledge my Church community. Father Tom, Father Dave and the members of the Catholic Center have been my home away from home. This past year would have been even harder without your prayers and support. The Catholic Center will always have a special place in my heart.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Disabling pain, or pain that interferes with daily life, is a major public health problem that often leads to chronic pain. The point prevalence of chronic pain in the United States has been estimated as ~31% [15]; consequently, it negatively impacts over 116 million Americans [6]. The economic cost of chronic pain is substantial. After accounting for healthcare, disability and other related expenses the current estimate is that chronic pain costs over $150 billion dollars annually in the United States alone [4,11,18].

The risk of suffering from disabling pain is influenced by demographics, such as age, sex, ethnicity, socioeconomic status [12,15], genetics [17] and personality [5], physical characteristics, such as body weight [23], a physical injury [14,20], behaviors, including self-care and exercise [24], and the presence of a mental or physical health problem such as anxiety and depression [1-2,6,16], arthritis [13], fibromyalgia [28], breast cancer [8-9] and diabetes [25]. A heightened awareness of the need to better treat pain has emerged in recent years [3,10]. However, the myriad of limitations (long-term efficacy, cost, potential for abuse, side effects, cultural and political barriers) of a traditional pharmacological approach [22,27] means that interest in complementary and alternative approaches, including physical activity, remains strong [7,19,21,26].

This dissertation focuses on better understanding the potential role of physical activity in moderating pain experienced by those who are either reporting above average levels of disabling

pain or are at increased risk of suffering from disabling pain by virtue of being overweight or diabetic.

The next chapter presents a narrative review that summarizes some of the key background information related to the topic of this dissertation. The narrative review includes sections on: (i) the neurobiology of nociception and pain, (ii) the measurement of pain, (iii) quantitative sensory testing, a useful method for stimulating pain by precise activation of nociceptive, thermal skin afferents, (iv) conditioned pain modulation, a technique used to assess the endogenous pain modulation system, a spinal and supraspinal neural system for inhibiting pain that is thought to be impaired among many of those suffering from chronic pain, (v) physical inactivity and related risk factors (i.e., overweight, obesity, diabetes) for chronic pain, and (vi) a rationale for focusing on the potential role of physical activity in chronic pain among post-menopausal women.

Chapter 3 presents one of the two original studies constituting this dissertation. Chapter 3 summarizes a systematic review examining the impact of exercise on bodily pain among samples at increased risk for chronic pain – those who are overweight or diabetic. The purpose of this meta-analysis was to review randomized controlled trials of exercise training that contained pain data in diabetic or overweight groups. Eleven trials were found and used to calculate 21 effects based on self-reported prior month recollections of overall bodily pain presence or its interference with work or other daily activities (as measured through the bodily pain scale of the Short-form 36 Health Survey). The mean effect size delta (Δ) was 0.07 (95% CI, -0.07, 0.21; $p = 0.3008$) suggesting that the exercise intervention could reduce pain ratings but that it was not statistically significant. Although the results appear to be disappointing, the findings are not

altogether unexpected because the samples studied were not suffering from a high level of chronic pain.

Chapter 4 presents the second study of the dissertation. The study is based on what was learned from the narrative and meta-analytic reviews. The study attempts to determine whether recent physical activity performed by post-menopausal women moderates either (i) pain responses to a range of precisely presented heat pain stimuli or (ii) pain modulation capability. Novel features of the research include focusing on post-menopausal women, some were and some were not in disabling pain, and examining the potential impact of objectively measured physical activity on pain modulation ability rather than only obtaining and correlating recollections of pain and physical activity.

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CHAPTER 2

LITERATURE REVIEW

The purpose of this chapter is to succinctly review background literature relevant to the dissertation which is focused on the role of physical activity in pain experienced by post-menopausal women and those at risk of suffering from disabling pain by being overweight, obese or diabetic.

2.1 Pain versus nociception.

A noxious stimulus is one that damages tissue or threatens to do so [68]. Nociception is the sum of neural processes that encode noxious stimuli [68]. These neural processes usually include activation of brain neural circuits that underlie the perception of pain but this does not always happen. For example, local anesthesia can at least temporarily relieve pain in peripheral neuropathy [1] and a small number of individuals have a congenital insensitivity to pain [70].

Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in such terms [68]. Pain requires activation of specific brain neural circuits known to underlie pain. The usual stimulus for activation of these circuits is injury to tissues. However, these circuits can be activated in the absence of input from peripheral nociceptors. For example, individuals can report arm pain in absence of the arm and its peripheral afferents with the loss of a limb [34,73]. Because pain is subjective and there are a number of factors that affect how pain is experienced (i.e. past history with pain, attention, genetics, etc.) [67], it is important the pain be measured as precisely as possible.

2.2 Neurobiology of nociception and pain

Noxious stimuli are detected by nociceptors, or sensory receptors that respond solely or preferentially to pressure, chemical or temperature stimuli that threaten to injure tissue [68]. Two types of peripheral neurons encode noxious stimuli. Wide-dynamic range neurons "have a low threshold for activation and reach maximum discharges during noxious stimulation." High-threshold or nociceptive specific neurons "have a high stimulation threshold in the noxious range. These neurons require noxious stimuli for activation" [58,67-68].

Nociceptors are the receptive ends of nociceptive afferents. Sensory afferents are classified by their size and the absence or presence of a myelin sheath. Most nociceptive fibers in muscle and skin are the unmyelinated, smallest fibers classified as C or Type IV fibers. A significant portion of the larger lightly myelinated A-delta (aka Type III) fibers also respond to noxious stimuli. Electrophysiological and pharmacological studies indicate that both type III and IV primary afferent fibers release glutamate (amino acid) and substance P (peptide) as a neurotransmitter in communicating nociceptive information in the dorsal horn of the spinal cord. Here the nociceptive information can be augmented or attenuated through the actions of numerous interneurons [85]. Often the nociceptive information is then transmitted to the brain by projection neurons through one of three major pathways (i.e. spinothalamic, spinoreticular or spinomesencephalic tract) [85].

The spinothalamic tract has fibers that stem primarily from neurons in spinal laminas I and V. The tract then crosses the midline of the spinal cord and ascends in anterolateral white matter, contralateral to the noxious stimulus location. The lateral components of the tract projects through the medulla and pons then synapses in a somatotopically organized fashion in the ventroposterolateral (VPL) portion of the thalamus. The medial component of the spinothalamic

tract contains projections to the reticular formation at the medulla and pons. This includes major projections to the periaqueductal gray (PAG), hypothalamus, amygdala, and medial parts of the thalamus [32,104].

The spinoreticular and spinomesencephalic tracts have neural pathways that play an important role in affective aspects of nociception and pain. The spinoreticular tracts have projections to the reticular formation at the medulla and pons before synapsing in medial thalamic nuclei. The synapse to the nucleus paragigantocellularis which has inputs to the locus coeruleus is important for affective aspects of pain. Nociceptive neurons with cell bodies in lamina I and V project in the spinomesencephalic tract through the medulla and pons to the PAG [66].

The PAG contains direct projections to the hypothalamus and indirect inputs to various limbic structures such as the amygdala and anterior cingulate cortex. The LC, hypothalamus, amygdala, and cingulate cortex are brain areas with well-established roles in pain-related behavior like hypervigilance and freezing [24,31,56]. Animals placed in threatening situations freeze and exhibit a reduced responsiveness to noxious stimuli. When lesions are found in the amygdala, the fear-induced analgesia response is blocked. Several brain areas are activated by noxious cutaneous stimulation, and the effects are most consistently seen in the bilateral thalamus, contralateral anterior cingulate cortex, insular cortex, prefrontal cortex, and the anterior cingulate cortex. To be efficient, some authors collectively call these brain structures the pain matrix [64,103].

2.21 Pain modulation

Activation of nociceptors does not necessarily lead to the sensation of pain. For example, soldiers in combat may suffer an injury but not perceive the pain immediately [9]. On the other

hand, pain may be experienced despite a lack of noxious stimulation such as with phantom limb pain [34,63,67,73]. Such disconnections between stimuli and pain are thought to be in part influenced by alterations in the balance between pain-promoting and pain-inhibiting structures that influence pain perceptions.

Melzack and Wall [65] proposed that the gate control system is involved in modulating the perception of pain. Today it is well established that non-nociceptive afferent fibers (type I and II), the larger and faster fibers, synapse on dorsal horn interneurons and nociceptive projection neurons and can inhibit them [55,59,65,74].

Descending pain modulation increasingly is recognized as a brain system that influences pain. Descending pain modulation involves the activation of neurons with cell bodies in brain structures that project to the spinal cord and can decrease nociception and pain. Descending pain modulation can be activated in several ways but usually includes the activation of brain stem neurons in the dorsolateral pontine tegmentum (DLPT) or rostral ventromedial medulla (RVM) that descend to the spinal cord. Inducing fear or anxiety, for example, causes an analgesic response to a normally painful stimulus and this effect is blocked by destruction of the amygdala [71]. Stress can induce hypoalgesia and this effect is known to depend on hypothalamic activity [89]. The anterior cingulate cortex has been strongly implicated in pain reductions resulting from hypnosis and alterations in attention [38,76,80,87]. Pain itself also can induce hypoalgesia [69]. Nociceptive afferents include projections to the periaqueductal grey (PAG) activation of which is known to activate the DLPT and RVM. Activation of circuits involving these structures have been suggested as being responsible for athletes or soldiers who suffer an severe injury in competition or in battle yet report little or no pain at the time of the injury. This type of hypoalgesia, induced in a laboratory, is one focus of this dissertation.

These types of descending pain modulation responses are thought to be normal, healthy responses to noxious stimuli. Impairments in this system may be a risk factor for chronic pain [97]. Methods developed to test this system were first used in experimental animals and called Diffuse Noxious Inhibitory Control (DNIC). Today, similar experiments are conducted with humans and the technique is called Conditioned Pain Modulation (CPM).

2.22 Conditioned Pain Modulation

The CPM system works through a spinal-medullary-spinal pathway [11,53,81,97]. The wide dynamic range neurons mentioned earlier appear to play an important role. Since they can be activated by both noxious and innocuous stimuli the wide dynamic range neurons are important for both excitatory and inhibitory influences [52,54,97]. The wide dynamic range neurons present a continuous supply of signals to the brain making it difficult to extract a signal from this noise [15]. It has been suggested that the CPM system may function as a filter, allowing the brain the focus on the more painful stimuli [15,54,97-98].

A conditioned pain modulation response can be invoked relatively easily in a laboratory setting using two painful stimuli presented at the same time. First, a noxious stimulus is presented alone. This is the test stimulus. Later, a second (conditioning) stimulus is presented concomitantly. The addition of a second stimulus triggers the CPM system to activate and inhibit the pain response to the test stimulus.

Evidence suggests that those with certain diseases or disorders have impaired pain inhibitory systems [97]. The most consistent evidence has been found in those suffering from fibromyalgia [23,46,48,51], chronic tension-type headache [77], painful osteoarthritis of the hip [49], and irritable bowel syndrome [17]. Impairments are not though, consistently found for all types of chronic pain. For example, those with chronic low back pain were found to have a

normal CPM system when compared to healthy controls [46]. When the impairments are found it is unclear as to whether chronic pain impairs the CPM response or if an impaired CPM system leads to chronic pain [5]. Regardless, using this method potentially would help to explain the mechanisms by which an individual suffers from chronic or disabling pain.

2.3 Measurement of pain

Although portions of the nociceptive system can be assessed objectively (e.g., brain activation via fMRI during a painful stimulus, the nociceptive flexion reflex), there are no accepted objective measures of pain. That is, pain is always a subjective report. Pain is a complex construct that can be measured and evaluated in a number of different ways. For example, pain can be described in terms of when it is first perceived through pain threshold evaluation, as the maximum limit that someone can withstand through pain tolerance measures, or through self-report evaluation of the intensity of the pain or the affective dimension (e.g., the unpleasantness).

2.31 Pain Intensity

The intensity of pain is the most commonly measured aspect of pain. Perception of pain is often rated using a 0-10 numerical scale or a 100 mm horizontal line as part of a Visual Analog Scale (VAS). There is strong validity evidence to support the use of these two types of pain measurement tools [42]. Individuals rate their pain intensity as analogous to the length of the line with length being determined by the rater as the distance from the left edge of the line. It is important for both these types of scales that the full range of perceptual experience is allowed; consequently, common anchors used for the continuous scale are “No Pain” to “Worst Possible Pain”.

2.32 Pain Affect

A VAS or 0-10 scale can also be used to measure pain affect. Pain affect refers to the degree to which a stimulus is unpleasant or bothers an individual. Therefore, only the verbal anchors are changed (e.g. “Not Bothersome at All” to “Extremely Bothersome”) [42,75]. The benefit of using these two scales is that the researchers can quantify both the intensity and unpleasantness score. Some pain treatments, such as opioids, influence affect to a greater extent than intensity probably because the treatment is influencing brain circuits underlying the affective dimension of pain to a greater extent than the circuits underlying pain intensity [28,79].

2.33 Psychophysics-based Pain Assessments

Some pain questionnaires have been developed based on experiments involving quantitative semantics and psychophysics. Prominent examples of this approach are the instruments developed by Richard Gracely including the Descriptor Differential Scale (DDS) [27] and the Gracely Intensity and Unpleasantness Box Scales [28]. These scales are advantageous because of their ratio qualities and use of verbal descriptors. The scales allow researchers to compare pain syndromes across acute, chronic, and experimental pain [28].

2.34 Qualitative Pain Measures

There are other important aspects of pain that can be assessed including its location, duration (pain is referred to as chronic if it lasts for 3 months or longer) and its qualitative aspects. With regard to location, a common approach is to present an individual with the silhouette of a body and then ask the person to shade in all the locations that are experiencing pain. The number of locations shaded in has been shown to be positively correlated with pain medication use and negatively correlated with activity level [42,60]. With regard to qualitative aspects of pain, the dominant approach has been to use the McGill Pain Questionnaire [62]. This

instrument asks individuals to describe sensory (intensity) aspects of pain with the help of a list of words like “throbbing”, “sharp”, and “tender” and to describe affective dimensions of pain with words like “sickening” and “fearful”. Where the Gracely Intensity and Unpleasantness Box Scales are helpful in comparing pain syndromes across different types of pain, the McGill Pain Questionnaire approach type of verbal scale is helpful for identifying unique aspects of specific types of chronic pain [28].

2.35 Multidimensional Pain Measures

The McGill Pain Questionnaire is an example of a multidimensional pain measure because it inquires about several different aspects of pain. A multidimensional assessment approach is often thought to be advantageous because it provides information beyond pain intensity alone [20]. A prominent example of a comprehensive multidimensional pain tool is the Multidimensional Pain Inventory [47]. This 52-item questionnaire has three different sections. The first provides information regarding interference in daily life due to pain, perceived support from a spouse or significant other, pain severity, perceived life control and affective distress. The second section pertains to how the individual perceives the responses received from the spouse or significant other when that person knows the individual is in pain. Finally, the third section allows the individual to report the frequency of participation in common daily activities like household chores, outdoor work, activities away from the home and social activities [12,40,47]. Acceptable internal reliability coefficient for the scales ranges from .70 to .90 and the test-retest reliability has also been evaluated and determined acceptable with the 2-week interval range of .62 to .91 [12,47]. The questionnaire will help to evaluate the many dimensions of adapting to chronic pain [12]. Within samples of participants with chronic low back pain, temporomandibular disorders, fibromyalgia, and headaches, three profile patterns were identified

using the MPI. The patterns are labeled Dysfunctional, Interpersonally Distressed, and Adaptive Coper [12,92-93,99]. Dysfunctional patterns include relatively high levels of pain severity in addition to relatively low levels of life control and activity. Interpersonally Distressed characteristics include relatively low levels of perceived support from significant others. Finally, Adaptive Copers have relatively low levels of pain severity and relatively high levels of life control and activity, thus the opposite of those with Dysfunctional profile [12].

Perhaps the most widely used multidimensional measure of pain is the bodily pain subscale of the Medical Outcome Study SF-36 Health Survey [101]. This survey has eight different subscales pertaining to Physical Functioning, Role Limitations due to Physical Problems, Social Functioning, Bodily Pain, General Mental Health, Role Limitations due to Emotional Problems, Vitality and General Health Perceptions. There are two questions in the Bodily Pain subscale: one that asks about the magnitude of pain during the past four weeks and the other asks how much that pain interfered with normal activities within the same four weeks [8,101]. All the SF-36 subscales have been demonstrated to be highly reliable and valid (ICC = .90) [8,100-101].

Standardized and precise instructions along with practicing rating appear to reduce error in obtaining pain ratings. Evaluating recollections of pain can be prone to error. Memories of pain can be different than the experience of pain at the moment [57,91]. People have difficulty remembering pain intensity accurately after several days and studies show that ratings of pain based on recall are higher compared to average momentary assessments [14]. Therefore, there is a benefit to rating standardized noxious pain induced in the laboratory at the moment pain is experienced. This type of induction of pain is not identical to pain experienced in response to

real world situations but it does have the advantages of giving all of the participants the same stimulus and being able to avoid recall bias.

2.4 Standardized noxious stimuli used in the laboratory

There are a variety of standardized noxious stimuli that can be used in a research setting [3,10,50,86] including pressure [13,72], exercise [18], injections of algesic substances [30,105], heat [72,84], and cold [72,107]. Each approach has advantages and disadvantages. For example, third molar extraction has the advantage of mimicking well a real world noxious stimulus [7] while electrical stimulation of tooth pulp has the advantage of being able to activate only one type of nociceptive sensory afferent (A-delta) [39]. This section will focus on the two stimuli that have been used in the dissertation – noxious heat and cold.

Stimuli above 45°C temperature activate skin nociceptors, nociceptive nerve tracts and brain areas involved in generating and processing pain [4]. Determining a stimulus-response curve describing the relationship between heat stimuli and ratings of the pain intensity and pain affect of each stimulus is a useful technique for assessing both individual responsiveness to heat and group differences in pain processing [22,28,79]. Using a specialized device that employs a Peltier effect, such as the TSA II Neurosensory Analyzer, individuals can be presented with a series of precisely controlled and quickly delivered heat stimuli. When participants are asked to rate multiple heat stimuli presented in a random order using a VAS or 0-10 scale prior research shows that there is a strong positive relationship between the stimulus temperatures and both pain intensity and affect ratings [79]. Rater bias or poor perceptual performance can be discovered using this method if the stimulus-response curve is not normal (i.e. the intensity ratings do not increase appropriately as the temperature increases) [29,79]. Because of the ability to deliver precise stimuli and the consistent dose-response pain results from noxious heat stimuli

presented to the skin demonstrated in prior studies [3,22,72] this approach is likely to have greater sensitivity for finding differences between groups hypothesized to differ in pain processing than other commonly used approaches such as pain recollections or perceived impact of pain on functioning.

Another useful technique for understanding pain processing is to determine how a person rates or copes with a single heat stimulus maintained above pain threshold. Typically, this involves temperatures that evoke low-to-moderate intensity pain. Higher intensity painful stimuli sometimes are used to most strongly activate conditioned pain modulation system but the temperature stimuli used must not be so high as to be unethical.

2.5 Risk Factors for Disabling Pain

There are a number of factors proposed to be associated with the experience of disabling pain. An impaired CPM response was already mentioned as one. Other factors that will be explored as potential moderators of pain include overweight/obesity and physical inactivity.

2.51 Obesity

There is currently a lack of strong evidence showing a causal relationship between obesity and pain. The association has been investigated; however there is a need for high quality randomized controlled trials to fully explore this relationship. A recent meta-analytic review showed that overweight or obese adults who participated in an exercise intervention as part of a randomized controlled trial demonstrated a small improvement in their Short Form - 36 Bodily Pain scores (ES = .07; CI -.07, .21). This meta-analysis is included in the following chapter.

The prevalence of overweight (BMI 25.0-29.9 kg/m2) and obese (BMI ≥ 30 kg/m2) individuals in the United States is approximately 66% for women aged 40-59 [25]. The average percent body fat percentage for older women is approximately 38% [96]. Overweight and obese

individuals are at a higher risk for experiencing several types of chronic pain, including low back pain, headaches, osteoarthritis and chronic widespread pain conditions such as fibromyalgia [106]. It has been hypothesized that contributing factors include increased sensitivity to noxious stimuli, chronic inflammation, poor diet and physical inactivity [41,61].

2.52 Physical activity

According to the Physical Activity Guidelines for Americans [94], adults should strive to achieve either 150 min·week^{-1} of moderate intensity physical activity or 75 min·week^{-1} of vigorous intensity physical activity or a combination of both moderate and vigorous activity [94,90]. In trying to decide if American adults are meeting these guidelines consideration must be given to how physical activity is measured. Self-reports can provide information about mode, duration and intensity of physical activity in an efficient and inexpensive manner; consequently, self-reports are widely used. Increasingly, accelerometers are being used because they provide an objective precise measure. All measures are imperfect. For example, self-reports estimates can be inaccurate and accelerometry counts fail to assess extra work results from adding weight (e.g., carrying groceries).

Tucker and colleagues [90] found a discrepancy between data from self-reports of physical activity when compared to accelerometry data. Based on completion of self-report questionnaires, adults reported 324.5 ± 18.6 min·week^{-1} of moderate intensity and 73.6 ± 3.9 min·week^{-1} of vigorous intensity activity. However, when evaluating the more objective data collected through accelerometers adults only participated in 45.1 ± 4.6 min·week^{-1} of moderate and 18.6 ± 6.6 min·week^{-1} of vigorous activity [90]. Therefore in order to obtain a thorough evaluation of physical activity patterns the argument is often made that it is worthwhile to collect both the self-report and objective data.

Ellingson and colleagues [22] classified healthy women into two groups based on physical activity (i.e. meeting physical activity guidelines or insufficiently active) using accelerometry data. The sedentary women averaged approximately 87 ± 24 min·day^{-1} in moderate activity and 4 ± 3 min·day^{-1} in vigorous activity) while those meeting guidelines average approximately 118 ± 29 min·day^{-1} in moderate activity and 16 ± 14 min·day^{-1} in vigorous activity. Each woman was then randomly presented with 7 different hot thermal stimuli ranging from 43-49°C. Those who were more physically active rated all of the temperatures except 43°C as significantly less intensely painful (Cohen's d = .51 – 1.12) and significantly less unpleasant (Cohen's d = .70-1.24) compared to the sedentary women.

There is a great deal of related research based largely on pain recall indicating that physical activity can reduce the perception of already existing pain. The evidence stems from multiple randomized controlled trials and convincingly shows that pain is reduced after training among those suffering from osteoarthritis [82], chronic low back pain [36], fibromyalgia [35], and peripheral artery disease [102].

Few experiments have examined the potential role of physical activity in endogenous pain modulation ability. CPM methods were used on women with fibromyalgia – a disorder known to be associated with chronic pain – and it was found that physical activity modified their pain modulating abilities [23]. Women who were more physically active experienced better pain regulation than the women who were less active or sedentary. More research is needed to determine if physical activity should be accounted for when assessing those with chronic painful conditions.

2.6 Post-Menopausal Women and Disabling Pain

The prevalence of disabling pain that interferes with daily life increases with age [45,88] and is higher for females [88]. With the average age of natural menopause being approximately 50 [6,26], women in their midlife who are transitioning through menopause may be at an increased risk for suffering from pain. Aging women are characterized by a decrease in physical activity [90], an increase in weight gain [16,25,37], an increase in chronic pain [43] and greater impairments in endogenous pain modulation [21].

2.61 Overweight/Obesity and Postmenopausal Women

Middle age women gain approximately .55 kg (~1lb) per year [16,33]. With the increase in weight comes an increased risk for bodily pain [41,44]. This can also lead to the development of the metabolic syndrome and thus an increased risk for cardiovascular disease [16]. More specifically this risk increases with an accumulation in centrally located fat. With menopause comes the loss of estrogen, which is associated with an increase in central fat [16,78]. The typical total percent body fat for older American women aged 60-85 years is estimated at approximately 38% [96].

In addition to a potential increase in central fat mass there is also a risk of decreased muscle mass known as sarcopenia [2] and a decrease in muscular strength [83]. Preservation of lower body lean mass and maintaining a lower percent body fat has great implications for decreasing the risk of physical disability especially in older women [95]. One way to combat these body composition changes is through physical activity.

2.62 Physical Activity in Postmenopausal Women.

Women who naturally enter into menopause face changes that potentially lead to decreased health-related fitness [6]. This risk is increased if women are already sedentary before

entering menopause. The risk of physical disability is reduced for women in midlife who are physically active [19]. Tucker and colleagues [90] report that only about 6.5% of women between the ages of 50-59 meet the recommended 150 activity minutes·week^{-1}.

A recent three year longitudinal study of midlife women (n=2400) used self-report measurements of both physical activity and health-related quality of life (including a self-report assessment of pain) and found that for every 1 point increase of physical activity, women were likely to have a 10% lower bodily pain score [19]. These results are promising but still need to be evaluated with more objective measures of both physical activity and pain. The measure used in the previously mentioned study asked women to recall the past year's physical activities.

2.7 Conclusion

In conclusion, the evidence strongly suggests that regular exercise is a plausible treatment for disabling pain. The literature points towards a number of risk factors for the development of disabling pain. Two questions then arise from this review concerning those at risk for disabling pain and those who are already experiencing disabling pain. First, for those only at risk for disabling pain, can exercise training reduce pain symptoms and second, if individuals are already suffering from disabling pain, does physical activity modify their pain experience such that those who are more physically active suffer less intense pain than those who are insufficiently active?

The next chapter addresses the first question by systematically reviewing randomized controlled trials that investigate the use of exercise on individuals with diabetes or who are overweight. The fourth chapter attempts to address the second question by evaluating the relationship between physical activity and pain among postmenopausal women.

2.8 References

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CHAPTER 3

EFFECT OF EXERCISE TRAINING ON PAIN IN DIABETIC OR OVERWEIGHT SAMPLES: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS[1]

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ABSTRACT

Exercise training reduces the risk of developing type 2 diabetes and reduces pain among those experiencing chronic pain. Pain is common among diabetics and those at risk for developing diabetes, including those who are overweight. The aim of this meta-analysis was to estimate the population effect size for exercise training reducing pain among diabetic, overweight and obese groups. Studies published in English between January 1, 2000 and April 10, 2012 were included if (1) an exercise training intervention was compared to a non-exercise control, (2) the sample involved diabetics or was characterized by a mean BMIs > 25 kg/m^2, and (3) bodily pain data from the SF-36 Health Survey were reported. Exercise training reduced pain by a small, nonsignificant magnitude (mean effect size delta (Δ) of .07, 95% Confidence Interval, -0.07, 0.21) in samples largely free of chronic pain. No significant moderators were found. It is concluded that exercise training has a small effect on pain among overweight and diabetics samples that were largely free of chronic pain. Exercise training has potential for reducing pain among diabetic and overweight individuals. Future research should focus on diabetic, overweight, obese and other groups experiencing chronic pain or at increased risk for chronic pain and include pain assessments that minimize the potential for recall bias.

Keywords: Meta-analysis, physical activity, overweight, diabetes, SF-36

3.1 Introduction

Chronic pain affects approximately 31% of Americans [13]. The economic costs of chronic pain have been estimated to be $560-635 billion per year in the United States [5], a staggering number. Chronic pain is undertreated and poorly understood [12]. Overweight and obese individuals are at a higher risk for experiencing several types of chronic pain, including low back pain, headaches, osteoarthritis and chronic widespread pain conditions such as fibromyalgia [30]. The prevalence of overweight (BMI 25.0-29.9 kg/m2) and obese (BMI ≥ 30 kg/m2) individuals in the United States continues to rise with current estimates at 70% and 34%, respectively for individuals aged 40-59 [11]. It is poorly understood why chronic pain among obese individuals is often independent of body mass and hypothesized contributing factors include increased sensitivity to noxious stimuli, chronic inflammation, poor diet and physical inactivity [12].

It is well known that being overweight is a risk factor for developing diabetes. Approximately 25% of diabetics also suffers from painful neuropathies [6], often located in the feet [1]. Exercise has been shown to be effective both in reducing the risk of developing diabetes and in treating diabetes after it has been diagnosed. Exercise training can reduce several types of chronic pain, including low back pain [9,18], fibromyalgia [8,14] and osteoarthritis [27], but rarely has it been the focus of investigations aimed at pain experienced by overweight, obese or diabetic people. The objectives of this review were to estimate the population effect of exercise training on bodily pain scores and to determine if the effect varied according to BMI status (i.e. overweight or obese) or the diagnosis of diabetes.

3.2 Methods

The current review and meta-regression analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [22].

3.21 Data Sources and Searches

Google Scholar and PubMed were searched for articles published between January 1, 2000 and April 10, 2012 using the following terms and logic: *exercise training AND pain AND SF-36 AND randomized controlled trial with diabetes OR HbA1c OR overweight OR obese.*

3.22 Study Selection

Inclusion criteria were (1) published in English, (2) an exercise training intervention compared to a non-exercise control, (3) presence of diabetes or samples with BMIs > 25 kg/m^2, (4) use of SF-36.

Exclusion criteria included: (1) a non-RCT design, (2) exercise interventions compared only to other exercise interventions, and (3) type 1 diabetes.

3.23 Data Collection Process

The following information was extracted from each study included: (1) number of participants assigned to the exercise intervention who were analyzed at the end of the study, (2) number of participants assigned to the control condition analyzed at the end of the study, (3) baseline means and standard deviations (SD) for both groups on the SF-36 bodily pain scale, and (4) post-intervention means and SDs (or mean change scores from baseline) for both groups on the SF-36 bodily pain scale.

The studies were also coded for potential moderators which included duration of the study, inclusion of diabetics and exercise type. In one instance a paper only reported the Physical Component Score for which bodily pain is one of the subscales. The corresponding author

provided the bodily pain subscale means and SDs in response to a request [25]. Figure 3.1 illustrates the process used to evaluate potential studies to include in the current meta-analysis.

3.24 Study Characteristics

Twenty-one effects were calculated from eleven studies that involved a total of 5826 participants (2978 were in the intervention condition). Sixteen effects came from studies of diabetics and all effects included participants who were overweight or obese. Ten effects were based on studies that used a combination of aerobic and resistance training while 11 used a single exercise mode. The exercise duration ranged from 8 weeks to 2 years and the age of the participants ranged from 35-75 years.

3.25 Effect Size Calculation

Effect sizes were calculated using Hedges and Olkin [10] methodology. The mean change scores from the control group was subtracted from the exercise intervention group mean change scores and then divided by the pooled standard deviation of the baseline scores. Effect sizes were then adjusted for small sample bias [10]. Calculations were organized so that pain reductions that were larger after exercise compared to the changes after the control condition resulted in a positive effect. A positive effect represents a beneficial change. All of the studies reported means and SDs or were provided upon request.

3.26 Data Synthesis and Analysis

In order to perform a moderator analysis a meta-regression using a random effects model was planned to reduce the probability of committing a type I error. SPSS 20 was used to analyze the mean effect size delta (Δ) and test of variation in effects (moderators) using macros (MeanES and MetaReg) [20].

Heterogeneity analyses were performed using both the Q and I^2 statistics. If the Q reached significance ($p < 0.05$) then the sample was determined to be heterogeneous. The I^2 values of 25%, 50%, and 75% represented low, moderate and high homogeniety, respectively.

Publication bias was assessed by graphing a funnel plot [28]. All of the effects were calculated twice and discrepancies (i.e. differences in calculated effect sizes or coding) were addressed and corrected.

3.27 Primary Moderators and Analysis

Based on a review of the literature and the number of effects being evaluated it was decided to code the effects based on presence or absence of diabetes in the sample and the type of exercise used in the intervention. These moderators were then coded in order to be entered into the multiple linear regression analysis with maximum likelihood estimation.

3.3 Results

Half of the effects (N=11) favored exercise training for pain relief however only one confidence interval did not include zero [24]. The magnitude and direction of the effects are illustrated in Figure 3.2. Table 3.1 presents an annotated description of the effects. The mean effect size Δ was 0.07 (95% CI, -0.07, 0.21; $p = 0.3008$). The random effects model indicated a homogenous sample ($Q = 17.43$, $p = 0.625$; $I^2 = 0\%$). The funnel plot (Figure 3.3) indicates that there was only one effect that could be a result of publication bias [28]; however, after performing a sensitivity analysis by excluding that one effect [24], the overall effect was still not significant.

3.31 Primary Moderator Analyses

The overall test for homogeneity was not significant indicating that it would be inappropriate to run the planned moderator analyses.

3.4 Discussion

In general the results presented in this review suggest that there is a small and positive albeit non-significant effect for exercise reducing pain based on the bodily pain subscale of the SF-36. These results though not statistically significant are still promising. The articles included in the analysis do report positive findings for their other main outcome variables (i.e. improvements in quality of life). Therefore, exercise is still highly promoted for improvements in overall quality of life among those with diabetes [4].

Exercise is also increasingly being used for the treatment of pain. For example, exercise has been found to be helpful in the reduction of pain for a number of individuals suffering from several types of chronic pain as in fibromyalgia [8], low back pain [9], and osteoarthritis [27]. However, the purpose of this meta-analysis was not to evaluate the effect of exercise for individuals already known to suffer from chronic pain but rather to investigate the effect of exercise in a sample of individuals who were at an increased risk for developing chronic pain (i.e. diabetic or overweight) [30]. In fact, according the SF-36 manual, for the bodily pain subscale the mean score for the US adult population is 75.2 ± 23.7. The average starting bodily pain score for those included in the current analysis was very similar at 70.1 ± 21.2. This further suggests that these individuals included in the current meta-analysis were not individuals who were suffering above average pain levels. This fact likely contributed to the small effect size.

3.41 Limitations

The current meta-analysis only evaluated pain using the SF-36 bodily pain score despite there being a number of different ways to quantify pain. Had more precise measures been included, for example, assessments that did not depend on pain recollections, which are known to introduce error, [19,29] the observed effect could have been more substantial.

Another potential limitation is the wide variety of exercise interventions. For the purposes of this review, exercise type was coded as either a combination of resistance training and endurance training or as “other”. The “other” group included a wide range of interventions from Tai Chi [15] to counseling patients on physical activity [7,17]. With only 21 effects to evaluate it was challenging to make meaningful distinctions between the different types of interventions and still have enough effects in each group for statistically powerful analyses.

3.42 Conclusion / Implications

Exercise interventions appear to have a small effect on reducing pain ratings among overweight/obese or diabetic individuals based on the bodily pain scale, but the effect may be underestimated. Future studies should use a standardized pain stimulus, which could lead to more precise and exact pain ratings as opposed to a pain questionnaire asking recollections about pain during the past month. The current meta-analysis also suggests the benefit of looking at individuals who suffer from chronic pain. The benefits of exercise could perhaps be more apparent for those already demonstrating impairments due to chronic pain. Perhaps then the use of standardized painful stimuli on a sample with chronic pain will result in greater pain reductions following an exercise intervention.

3.5 References

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Table 3.1: Annotated Descriptors of Unweighted Hedges *d* Effect Sizes

Source	Total N	Diabetes	Exercise Type	Hedges d Effect Size (95% CI)
Lambers et al., 2008[16]	28	Yes	Aerobic	-0.76 (-1.70, 0.18)
Lambers et al., 2008 [16]	29	Yes	RT and aerobic	-0.61 (-1.54, 0.32)
Reid et al., 2010 [25]	110	Yes	RT	-0.25 (-0.89, 0.38)
Reid et al., 2010 [25]	109	Yes	RT and aerobic	-0.08 (-0.72, 0.57)
Reid et al., 2010 [25]	109	Yes	RT and aerobic	-0.07 (-0.71, 0.57)
Martin et al., 2009 [21]	188	No	Aerobic	-0.05 (-0.64, 0.54)
Lawton et al., 2008 [17]	1089	Yes	Counseling on PA	-0.05 (-0.58, 0.48)
Reid et al., 2010 [25]	103	Yes	Aerobic	-0.05 (-0.70, 0.60)
Rejeski et al., 2002 [26]	137	Yes	RT and aerobic	-0.05 (-0.66, 0.57)
Lawton et al., 2008 [17]	1089	Yes	Counseling on PA	-0.04 (-0.57, 0.50)
Reid et al., 2010 [25]	103	Yes	Aerobic	0.05 (-0.60, 0.70)
Martin et al., 2009 [21]	239	No	Aerobic	0.05 (-0.53, 0.63)
Reid et al., 2010 [25]	110	Yes	RT	0.07 (-0.57, 0.71)
Lam et al., 2008 [15]	46	Yes	Tai Chi	0.10 (-0.68,0.87)
Morey et al., 2009 [23]	641	No	RT and aerobic	0.11 (-0.43, 0.65)
Elley et al., 2003 [7]	750	Yes	Counseling on PA	0.15 (-0.39, 0.69)
Martin et al., 2009 [21]	187	No	Aerobic	0.19 (-0.40, 0.79)
Rejeski et al., 2002 [26]	141	Yes	RT and aerobic	0.25 (-0.37, 0.86)
Aylin et al., 2009 [3]	36	Yes	RT and aerobic	0.51 (-0.34, 1.35)
Atlantis et al., 2004 [2]	44	No	RT and aerobic	0.66 (-0.14, 1.46)
Nicolucci et al., 2011 [24]	538	Yes	RT and aerobic	0.78 (0.24, 1.33)

RT = Resistance Training; PA = Physical Activity

Figure 3.1: Selection of Studies for Review

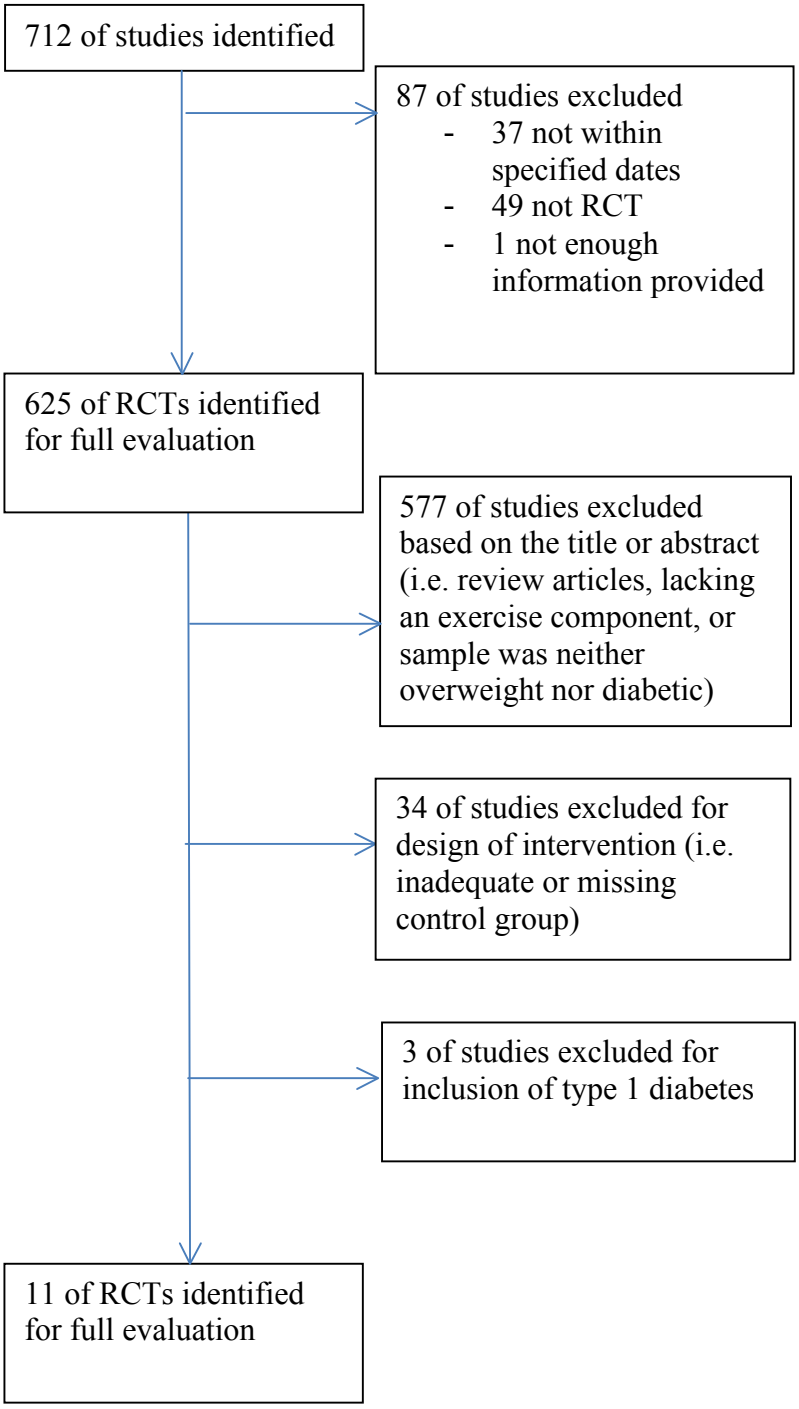


Figure 3.2: Forest plot of unweighted distribution of Hedges *d* effect sizes.

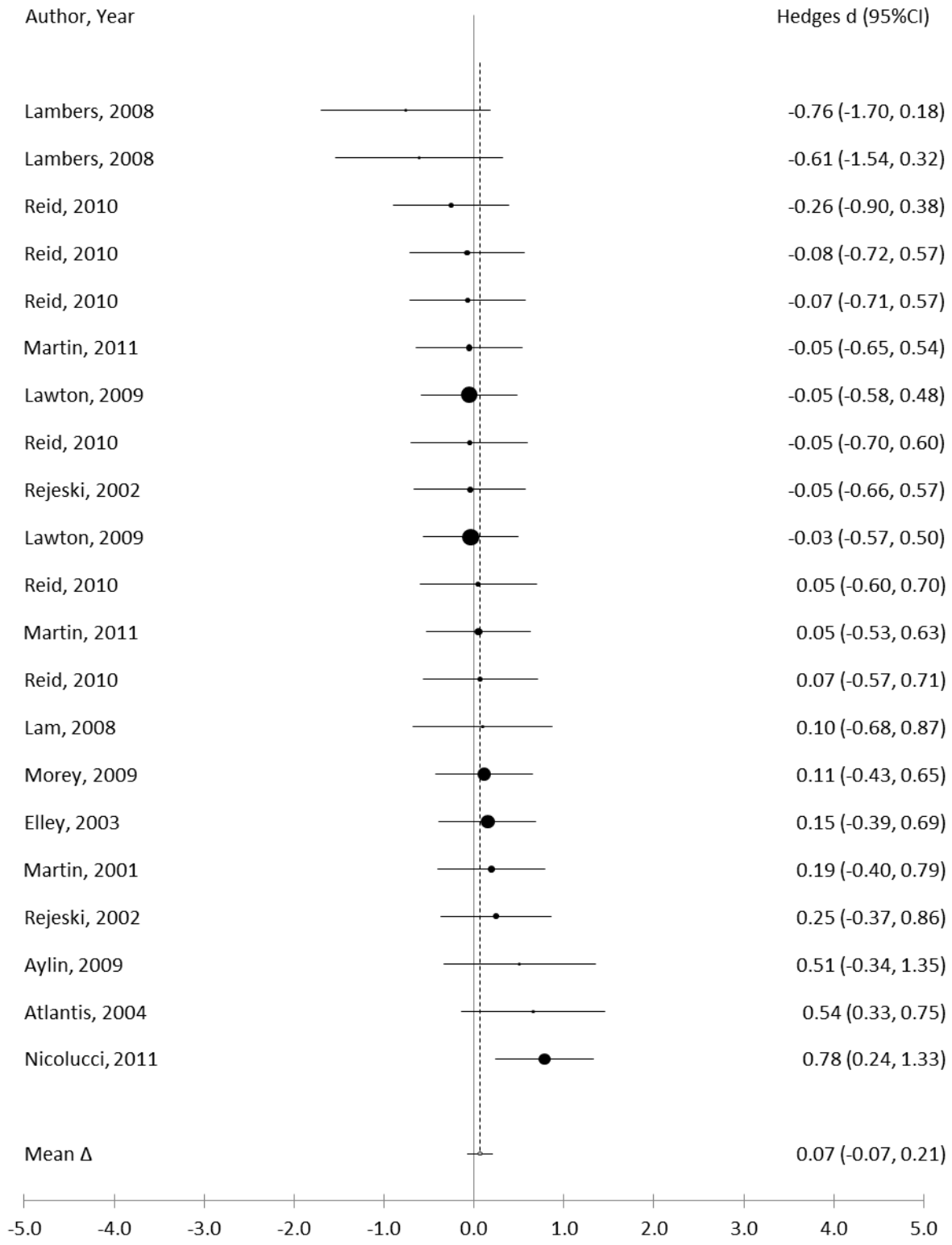
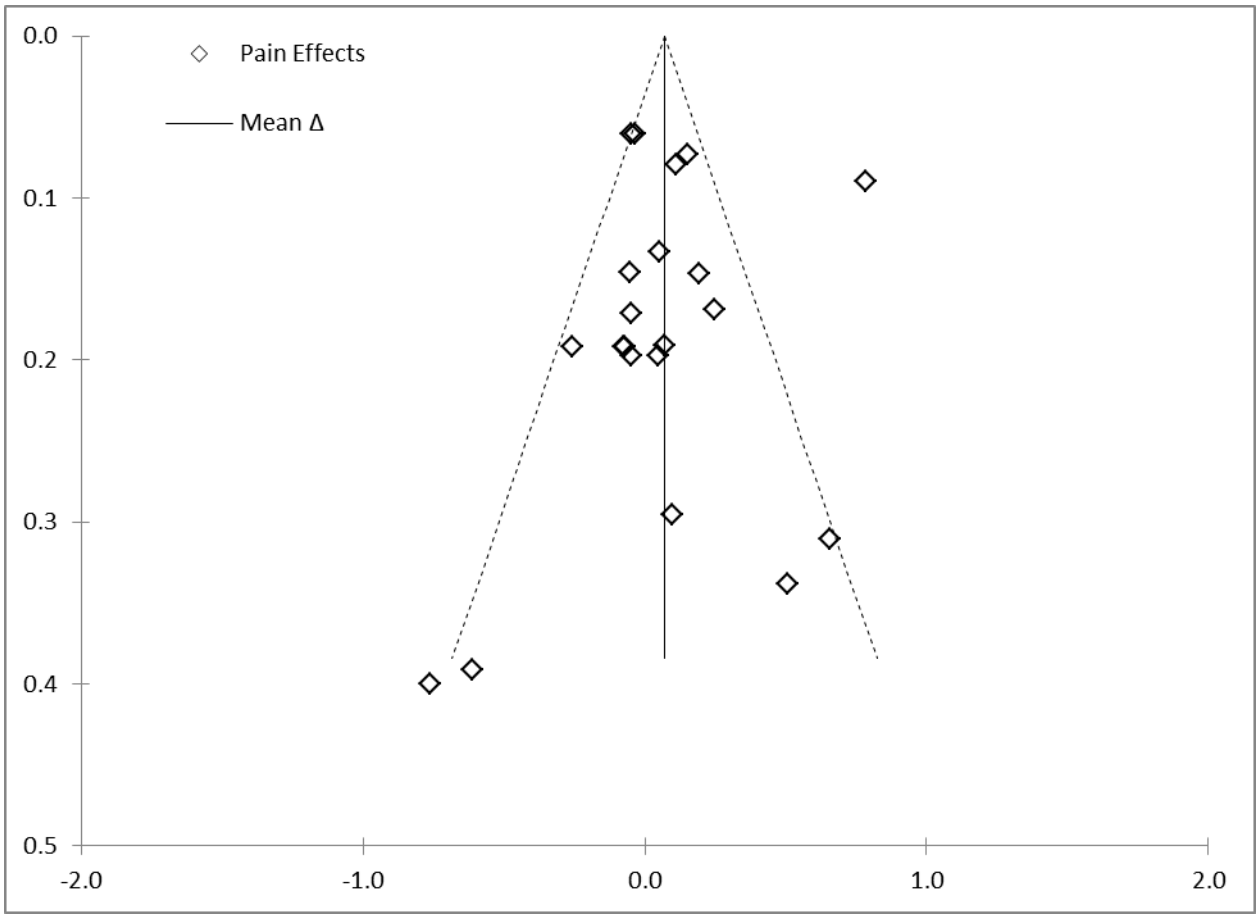


Figure 3.3: Funnel plot



CHAPTER 4

PHYSICAL ACTIVITY, PAIN RESPONSES TO HEAT STIMULI, AND CONDITIONED PAIN MODULATION IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT DISABLING PAIN[1]

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ABSTRACT

Disabling pain refers to pain that is both persistent and interferes with one's daily life [70]. Postmenopausal women are at high risk for disabling pain [28,69-70] and for being inactive [72]. Relatively little is known about relationships between physical activity and pain in postmenopausal women and the available evidence is conflicting. The overall aim of the current study was to enhance understanding of relationships between physical activity and pain among postmenopausal women using two approaches. First, 68 postmenopausal women rated the intensity and unpleasantness of painfully hot stimuli presented to the hand. Second, 31 women participated in a conditioned pain modulation (CPM) task to assess endogenous pain modulation. It was hypothesized (i) that inactive women would report higher pain intensity and unpleasantness ratings compared to active women, and (ii) that the inactive women with disabling pain would report higher pain intensity and unpleasantness at the high but not low stimulus intensities. For the CPM test, more efficient pain modulation was hypothesized for active compared to inactive women. Inactive women with disabling pain rated the pain unpleasantness of noxious heat stimuli higher at the highest heat stimulus intensity compared to active women with disabling pain as evidenced by a statistically significant interaction ($F_{3,192}$ = 3.526, partial η^2 = .052, p= .016 for accelerometry and $F_{3,192}$ = 3.60, partial η^2 =.053, p = .015 for self-report physical activity) from a mixed model ANOVA (2 x 4 x 2, physical activity status X stimulus temperature X pain status). The three-way interaction was explained by significantly lower pain unpleasantness ratings at 49^{o}C only (t_{11}=2.523, p=.028 for accelerometry and t_{11}=2.208, p=.049 for the self-report physical activity) for the active women with disabling pain compared to inactive women in disabling pain (7.0 ± 4.8 [unpleasant] vs. 13.3 ± 3.9 [very distressing]). The results were unchanged when prescription pain and antidepressant medication

use variables were added as covariates. The other hypotheses were not supported by the data obtained. It was concluded that physical activity is associated with a reduced sensitivity to the unpleasantness of painful high intensity heat stimuli among women with disabling pain. The results suggest that that regular physical activity may be a useful treatment or adjunct for reducing pain unpleasantness in postmenopausal women suffering from disabling pain.

Keywords: Heat pain, pain modulation, exercise, disabling pain, SF-36

4.1 Introduction

Disabling pain refers to pain that is both persistent and interferes with one's daily life [69]. Factors thought to increase the risk of developing disabling pain include genetics [50], personality [8] and cognitive factors such as catastrophizing [16], low socioeconomic status [6], injury, acute pain, physical or mental illness [5,12,43], obesity [40], physical inactivity [1,19,27], age [69], being female [70] and poor endogenous pain control [21].

Pain is often inadequately treated because of a host of institutional (e.g., reimbursement-related), clinician-level (e.g., poor training in pain management) and individual barriers (e.g., expense, lack of health insurance) [12]. Regular physical activity is potentially useful for pain management. Dozens of randomized controlled trials have shown that adopting a program of regular physical activity reduces self-reported recollections of recent (prior month) pain among people suffering from a variety of painful medical conditions including those common among middle-aged and older adults such as low back pain [35], fibromyalgia [34], and osteoarthritis [64].

Postmenopausal women are at high risk for disabling pain [28,69-70] and pain sensitivity is higher among individuals with chronic pain [11,41,59]. Relatively little is known about relationships between physical activity and pain in postmenopausal women and the available evidence is conflicting. One 3-year prospective cohort study of 2,400 middle-aged women found that the physically active women reported less disabling pain regardless of menopausal status [19]. Another study examined 430 sedentary, overweight and obese postmenopausal women as part of a 6 month randomized controlled trial. Compared to a non-exercise control group, pain scores consistent with sex- and age-norms at baseline were not improved by aerobic exercise training that expended 4, 8, or 12 kcals per kg of body weight each week. Those amounts of

physical activity approximated 50%, 100%, and 150% of levels recommended by the National Institutes of Health. The results suggest that 6 months of exercise training has little effect on improving pain when postmenopausal women are experiencing normal pain for their age [52]. Key limitations of both of these studies were that the affective dimension of pain was not measured and that pain was assessed only from memories of disabling pain averaged over the prior month.

The importance of pain affect is increasingly being realized by pain clinicians and researchers [60,62,75]. Pain affect refers to the unpleasant feelings that co-occur during painful experiences. Although pain affect and pain intensity ratings are positively related they are generated by different neural mechanisms [60] and can be dissociated using biological (e.g., opioid medications) and psychological (e.g., attention, hypnosis, mood) approaches [33,45]. Because exercise has emotional, mood and affective consequences [37-38,57,68] and alters blood flow to brain regions involved in affective processing (e.g., insular and prefrontal corticies) to a greater extent than those involving in the coding of sensory intensity (e.g., sensory corticies), physical activity could plausibly be more strongly related to pain affect than pain intensity [24,54,65,78].

Rather than solely relying on memories of pain over days or weeks, examining dose-response relationships between well-controlled noxious stimuli and pain ratings obtained immediately following stimulus presentations could help to resolve some of the conflicting findings from studies of physical activity and pain. While this approach appears to not yet have been used with postmenopausal women, physical fitness has been associated with pain responses to cold and hot stimuli in women with fibromyalgia [15], and physically active, healthy young women showed less pain compared to inactive women in response to seven hot temperatures

applied to the hand [23]. The effects were larger for pain unpleasantness (mean d = .89) than pain intensity (mean d = .71) and largest at the highest temperature (e.g., mean d = .34 and 1.04 at 43 and 49°C, respectively).

Pain among inactive postmenopausal women may be the result of an inability to endogenously moderate their pain. This ability can be assessed using a conditioned pain modulation (CPM) procedure involving two noxious stimuli [80]. One stimulus, termed the test stimulus, is presented twice. The first time it is presented alone. The second time it is presented concomitantly with a different noxious stimulus termed the conditioning stimulus. Pain intensity ratings to the test stimulus usually are lower when presented with the conditioning stimulus but groups with pain disorders show less pain reduction during the conditioning stimulus. That is their CPM is inefficient. This technique has been used to demonstrate that those with painful chronic conditions [3,73], older adults [21,77] and females [26,71] have less efficient CPM. Postmenopausal women are at increased risk of having suboptimal endogenous pain modulation ability for several reasons included their age [21,77] and increased risk for chronic pain [73]. The role of physical activity in CPM is unknown. There appears to be only one related study exploring the role of physical activity in pain modulation. A distracting cognitive task was used to modulate pain in 11 women with fibromyalgia. Physical activity, assessed using accelerometry, was significantly related to brain hemodynamic responses during the cognitive task in brain areas known to be involved in the processing of pain affect - the prefrontal cortex, posterior cingulate cortex, insular cortex and periaqueductal grey [23,60].

The overall aim of the current study was to better understand relationships between physical activity and pain among postmenopausal women. Hypotheses for the heat pain test were that compared to physically active women: (i) inactive women would report higher pain intensity

and pain unpleasantness, and (ii) inactive women with disabling pain would report higher pain intensity and unpleasantness at high but not low stimulus intensities. The hypothesis for the CPM test was that compared to physically active women, inactive women would report a smaller reduction from baseline in pain intensity ratings during the second test stimulus. That is, active women would show a more efficient conditioned pain modulation.

4.2 Methods

4.21 Participants

Post-menopausal women aged 45-65 were recruited, primarily through electronic listservs and word-of-mouth, from the Athens-Clarke County metropolitan area to participate in a body composition and health study. Exclusion criteria were: a) body weight greater than 136 kg, b) body mass index not within 20-34.9 kg/m^2, c) body weight not stable for the prior 3 months (not within 2.27 kg), d) unwilling to undergo body composition assessment, e) current smoker, f) living in a nursing home, g) history of COPD or severe asthma, h) uncontrolled diabetes, i) diagnosis of HIV, j) history of dizziness, k) diagnosis of mental illness, l) use of an assistive device to walk, and m) any contraindication to exercise.

Eligible and willing participants arrived at the laboratory after an overnight fast, signed an approved informed consent and completed the following: a) an arm venipuncture to obtain a blood sample, b) questionnaires to provide demographic, health, medication use, and self-reported physical activity information, c) a heat pain test, d) body composition assessment involving dual energy x-ray absorptiometry, e) a conditioned pain modulation test, and f) a resting blood pressure measurement. Testing took about 120 minutes and the participants received a copy of their body composition results and a chance to win a 3-month membership at the laboratory's fitness center for their involvement.

4.22 Questionnaires

4.221 Disabling Pain and Health Status

The presence and absence of disabling pain during the prior month was determined from the two-item bodily pain scale of the SF-36 Health Survey [76]. The items categorize the degree of pain intensity (none, very mild, mild, moderate, severe, very severe) and the extent to which pain interferes with normal work (not at all, a little bit, moderately, quite a bit, extremely). The SF-36 manual [76] provides both a scoring rubric, which combines the pain intensity and interference data into a single score, and age- and sex-specific norms from a representative sample of the non-institutionalized general US population (N=2,474). This information was used to generate criterion groups who did or did not report disabling pain. Those below the norm on bodily pain were categorized has having disabling pain, those above were categorized as being free from disabling pain. (Note that higher bodily pain scores represent higher health status.) Those with disabling pain reported at least mild pain and at least some interference. Those free from disabling pain either reported no pain or very mild pain that did not interfere with their normal work.

The SF-36 measures seven other aspects of health: physical functioning, role physical, role emotional, general health, vitality, social functioning and mental health. There is a large body of evidence supporting the validity of the SF-36 scales [76].

4.222 Pain Locations

The Pain Body Locations Scale was used to identify the number of body locations currently in pain [51]. The scale consists of dorsal and ventral outlines of a human figure with the body divided into 45 numbered regions. Participants circled those numbers where they were feeling pain. The number of locations circled was summed to yield a criterion score from 0 to 45.

Pain location scores have been positively related to pain medication use, disability and comorbid physical conditions [17-18,51].

4.223 Pain Intensity (0-10)

Pain intensity during both pain tests was measured using a 0-10 numerical graphical rating scale. This scale is a valid, reliable and widely used measure of pain intensity [39].

4.224 Pain Affect and Intensity (0-20)

Pain affect and pain intensity were measured during the heat pain test using the well validated Affect and Intensity Box Scales [31]. These 0-20 category scales were designed to yield results that mimic ratio scales through careful semantic choices and placement of the verbal anchors. These scales were included to compare the results to the most similar work in the related literature [23].

4.225 Self-Reported Physical Activity

Self-reported physical activity was measured using the Global Physical Activity Questionnaire (GPAQ) [4]. The GPAQ asks participants about the number of minutes of physical activity during work, travel, and recreational pursuits for a typical week. The GPAQ provides reproducible data over 3-7 days (Kappa 0.67 – 0.73) and has moderate-to-strong concurrent validity with the International Physical Activity Questionnaire (r = 0.45 – 0.65) [7]. The criterion measure used here was the total number of physical activity minutes per week. The participants were classified into active and inactive groups based on whether they reported being, or not being, active for 150 or more minutes per week [13].

4.23 Objective Physical Activity

New-Lifestyles NL-1000 *(Pensacola, FL)* monitors were used to measure physical activity. The small (2.5 x 1.5 x 0.9 in), light weight (<2 oz) instrument is a piezoelectric

pedometer that uses a mechanism similar to accelerometers. The NL-1000 has a Moderate-to-Vigorous Physical Activity™ timer that records the accumulated time spent in physical activity above a defined intensity. The intensity used in this study was above 3.6 metabolic equivalents (level 4-9 on the instrument). Estimates of moderate-to-vigorous physical activity from the NL-1000 were found to be not meaningfully different from, and moderately-to-highly correlated with, other accelerometer-based measures of moderate-to-vigorous physical activity [53,55].

Participants were asked to wear the NL-1000 on the anterior of their non-dominant hip during all waking hours for 7 continuous days and return to the lab after one week. The times of day the participants put the monitor on and took the monitor off were recorded in a log. When participants returned to the lab, the number of minutes of moderate-to-vigorous physical activity for each of the prior 7 days was obtained from the instrument's memory and recorded. Five days with at least 10 hours of wear time were required for the data to be included in the analyses. Only two people who were included in the analyses did not have at least one weekend day included in their valid days. Because 7-days of NL-1000 data were available for only 52% of the participants, the current Physical Activity Guidelines for Americans [13] were not used to create physical activity groups for statistical analysis. The current guidelines focus on the total number of minutes accumulated over an entire week. The criterion measure of physical activity based on the NL-1000 data was whether participants did or did not spend an average of 30 minutes per day in moderate-to-vigorous physical activity over the 5-7 days of wear time. This categorization is consistent with prior physical activity recommendations [36,58].

4.24 Procedure

Both pain tests were conducted in the same quiet, windowless, dimly lit chamber. Standardized instructions about the procedures and their timing were given to the participants

and any questions they had were answered. Pain intensity was defined as the perceived degree of hurt. A music analogy was used to help participants understand the difference between pain intensity and affect. The participants were told that rating pain intensity was like rating the loudness of a song while pain affect was akin to rating how unpleasant the music made them feel. Each participant received practice in making ratings (with non-noxious thermal stimuli) prior to rating noxious stimuli.

4.241 Heat Pain Test

The goals of this test were: i) to use a range of hot temperatures to generate mean pain intensity ratings that were at least mild and not unethically intense (> 7 and <16 on the 0-20 intensity scale) that also on average produced at least a slightly unpleasant affective response (> 4 on the 0-20 unpleasantness scale), and ii) to determine eligibility for the second pain test.
A 30 X 30 mm thermode was strapped to the thenar eminence of the right hand. The thermode was rapidly heated and cooled using a computer controlled Peltier heat pump (TSA-II Neuro Sensory Analyzer, Medoc). The thermode began at a baseline temperature of 35°C and both increased to target temperatures and returned to baseline at a rate of $8°C \cdot s^{-1}$. Seven different target temperatures (43, 44, 45, 46, 47, 48 and 49°C) were presented in random order, maintained for seven seconds and then returned to the baseline temperature for a one-minute inter-stimulus interval. During the inter-stimulus intervals pain intensity and pain affect ratings were obtained.

4.242 Conditioned Pain Modulation (CPM) Test

CPM eligibility required that each participant be presented with a heat stimulus to the thenar eminence that was predicted to produce a moderate intensity pain of 6 on the 0-10 scale based on the results of the heat pain test. That is, we sought to expose all the participants to a

similar magnitude of perceived pain by using individualized heat stimuli. Some individuals elected to not participate in a second pain test, others were excluded (e.g., they failed to rate any of the heat stimuli as ≥ 6 during the heat pain test).

Twenty-minutes after the heat pain test, during which time body composition tests were conducted, 36 participants completed the CPM protocol. Adequate data were obtained from 34 women. First, the heat stimulus predicted to be rated as 6 was presented to the right hand for 30 seconds. In CPM studies it is recommended that this be termed the *test stimulus* [80]. The test stimulus was rated for pain intensity using the 0-10 scale every 10 seconds. Pain affect was not measured so that the reliability of the pain intensity measures could be quantified. This was a priority because investigators have focused on pain intensity and some have used the first rating while others have used the last rating, the peak rating or an average of several ratings. Whether all or any of these approaches is adequate is uncertain because the reliability of CPM measures rarely has been quantified.

After five-minutes of seated rest during which the participants remained in the testing chamber, the painfully cold *conditioning stimulus* was presented. Participants put their left hand up to the distal portion of the ulna and radius into a circulating cold water bath (12°C) for 60 seconds. The water was contained in a cooler (Igloo, Island Breeze 9 QT, USA) and circulated with a pump (Pondmaster, 110 gph, Islandia, NY). The water temperature was assessed before and after using a mercury thermometer. For the last 30 seconds of the conditioning stimulus, the right hand was simultaneously exposed to the hot test stimulus a second time. Participants rated their pain intensity every 10 seconds. During the first 30 seconds, three pain intensity ratings of the cold conditioning stimulus were given. For the final 30 seconds, three pain intensity ratings of the hot test stimulus were provided. After 60 seconds the left hand was removed from the

water and the test stimulus returned to the baseline temperature. If at any point the participants wanted to stop the heat stimulus they were instructed to click a mouse on which their hand was resting. Clicking the mouse would return the heat stimulus to baseline immediately. Similarly, if the cold water stimulus was intolerable, the participants were instructed to take their hand out of the cold water. All participants were able to tolerate the test stimulus and 2 participants took their hand out of the cold water before the 60 second test was complete.

4.25 Preliminary and descriptive analyses

To ensure accuracy, data were entered into a spread sheet twice and any discrepancies were resolved. Data were analyzed using the Statistical Package for Social Sciences (SPSS 21.0 IBM Corp., Armonk, NY). The distribution of the primary outcome variables (pain ratings) met the statistical assumptions (e.g., normality, homescedasticity) required for the primary analyses. Because a goal of the heat pain test was to generate pain that was at least rated as mild in intensity and slightly unpleasant, the pain ratings at 43, 44 and 45°C were excluded from the analysis [2,75]. Twelve of 80 women who completed the heat pain test women were excluded from the heat pain test analysis for the following reasons: missing physical activity data (n=6), taking multiple antidepressant/antianxiety medications (n=4), and missing health history information (n=2).

The CPM analysis was completed with a sample of 31 because of missing physical activity data for 3 participants. There were 4/372 missing pain intensity ratings during the CPM tests from 4 individuals (1 missing rating for each person). The last value carried forward (or backward, n=1) approach was used to impute the missing data. The reliability of the repeated pain intensity ratings made during the CPM test was assessed by calculating the intraclass correlation (ICC). The ICC models (3,2 and 3,3) involved single measures at each of two or three

rating times and focused on consistency rather than absolute agreement. A two-way mixed model was used in which the participants were considered random effects and the 10-, 20- and 30-second ratings were considered fixed effects.

Independent t-tests or chi-square tests were used to determine whether the subgroup with disabling pain differed from the subgroup without disabling pain on descriptive or SF-36 variables.

4.26 Primary Statistical Analysis

Hypotheses for the heat pain intensity and pain unpleasantness data were tested using a series of 2 X 2 X 4 (Physical Activity Status [inactive vs. active] X Pain Status [disabling pain vs. no disabling pain] X Stimulus Temperatures [46,47,48,49°C]) mixed model ANOVAs and ANCOVAs with repeated measures on the stimulus temperatures. Physical activity status was analyzed using both accelerometer and self-report data. To determine whether group differences in the use of pain-related prescription medication or antidepressant use might explain significant ANOVA results, when necessary a follow-up ANCOVA was used based on self-reported use of prescription pain medication and antidepressant medication (coded as 0 or 1 for not using or using) as covariates.

Because statistical power was too low for a meaningful test of the CPM data comparing active and inactive women with and without disabling pain (sample size was as low as 2 per cell), hypotheses for the CPM data were limited to comparisons between active and inactive women. The CPM data were tested using 2 X 2 (Physical Activity Status [inactive vs. active] X Time [Test Stimulus 1, Test Stimulus 2]) mixed model ANOVAs with repeated measures on Time. To rule out the potential effect of variations in the test stimulus temperature models were run with that variable as a covariate.

Adjustments for sphericity, when needed, were made using Huynh-Feldt epsilon. The effect size magnitudes are reported as d for group differences and partial eta squared for interactions.

4.3 Results

4.31 Information Describing the Sample

Tables 4.01 to 4.06 present information describing the sample. Scores from the SF-36 show that the total sample reported better than average health status compared to age- and sex-specific norms. The total sample also was more physically active than many groups of women with a mean age of 59 for example 54% reported 150 minutes or more of physical activity per week and 38% showed an average of 30 minutes or more of moderate to vigorous activity per day based on activity monitoring. The sample was largely white, highly educated, normotensive, and medication free. Twenty-six percent of the sample reported taking antidepressant medication. Compared to those with no disabling pain, the subgroup with disabling pain had a significantly greater number of body locations in pain, worse health status scores on every measure of the SF-36, and a higher percentage taking prescription pain medications (NSAIDs, n=3; opioid analgesics, n=2; GABA analogs, n=2; CNS depressants, n=1).

The descriptive pain intensity and unpleasantness ratings at each temperature for the pain subgroups as a function of physical activity status categorized by activity monitoring and self-report are presented in Tables 4.07 and 4.08, respectively. The same data are presented in Figures 4.1 to 4.4. Effect size differences between active and inactive groups are presented in Table 4.09.

4.32 Heat Pain Test Intensity Rating Results

Sixty-eight women were included in the heat pain test analyses. The ANOVA that used physical activity groups based on activity monitoring found a significant main effect for temperature ($F_{3,192}$ = 37.533, partial η^2 =.370, p< .001). All other main effects and interactions were insignificant (Figure 4.1). The ANOVA that used physical activity groups based on self-report found a significant main effect for temperature ($F_{3,192}$ = 44.480, partial η^2 =.410, p< .001). All other main effects and interactions were insignificant (Figure 4.2).

Across the four temperatures, the mean intensity ratings for the entire sample increased linearly from 7.2 (very mild) to 8.4 (mild) to 10.5 (moderate) and to 12.7 (barely strong).

4.33 Heat Pain Test Unpleasantness Results

The ANOVA that used physical activity groups based on physical activity monitoring found a significant main effect for temperature ($F_{3,192}$ = 53.751, partial η^2 =.456, p< .001), an interaction of temperature and physical activity ($F_{3,192}$ = 5.070, partial η^2 =.073, p = .002), and a three-way interaction among temperature, pain status and physical activity status ($F_{3,192}$ = 3.526, partial η^2 =.052, p=.016). All other main effects and interactions were insignificant. The interaction is illustrated in Figure 4.3; descriptive information about the women in disabling pain is presented in Table 4.10. The three-way interaction remained significant when the covariates were included in the analysis.

Several post-hoc tests were performed to understand the three-way interaction. A physical activity status x temperature post-hoc was insignificant. Separate one-way repeated measures ANOVA analyses indicated significant temperature main effects for inactive women in disabling pain (n=9; $F_{3,24}$ = 28.890, partial η^2 =.783, p < .001) and for the active women in disabling pain (n=4, $F_{3,9}$ = 3.901, partial η^2 =.565, p = .049). The three-way interaction was

explained by significantly lower pain unpleasantness ratings at 49°C only (t_{11}=2.523, p=.028) for the physically active women with disabling pain compared to inactive women in disabling pain (7.0 ± 4.8 vs. 13.3 ± 3.9).

The ANOVA that used physical activity groups based on self-reported physical activity found a significant main effect for temperature ($F_{3,192}$ = 64.989, partial η^2 =.504, p< .001), an interaction of temperature and physical activity ($F_{3,192}$ = 3.60, partial η^2 =.053, p = .015), and an interaction among temperature, pain status and physical activity status ($F_{3,192}$ = 4.174, partial η^2 =.061, p=.007). All other main effects and interactions were insignificant. The interaction is illustrated in Figure 4.4; descriptive information about the women in disabling pain is presented in Table 4.11. The three-way interaction remained significant when the covariates were included in the analysis.

Post-hoc tests were performed to understand the three-way interaction. Separate one-way repeated measures ANOVA analyses indicated significant temperature main effects for inactive women in disabling pain (n=8; $F_{3,24}$ = 24.756, partial η^2 =.780, p < .001) and for the active women in disabling pain (n=5; $F_{3,12}$ = 6.744, partial η^2 =.628, p=.006). The three-way interaction was explained by significantly lower pain unpleasantness ratings at 49°C only (t_{11}=2.208, p=.049) for the physically active women with disabling pain compared to inactive women with disabling pain (8.0 ± 4.7 vs. 13.5±4.2).

Across the four temperatures, the mean unpleasantness ratings for the entire sample (n=68) were lower than the associated intensity ratings and increased linearly from 4.3 to 5.6 (slightly annoying) to 7.0 (unpleasant) and to 9.9 (very unpleasant).

4.34 Conditioned Pain Modulation Results

Descriptive information about the women included in the CPM analyses (n=31) are presented in Tables 4.12 and 4.13. The reliability results are summarized in Table 4.14. All the intraclass correlations were significant statistically. For each stimulus type (test stimulus [TS-1], conditioning stimulus and the test stimulus during the conditioning stimulus [TS-2]), the ICC was higher when the last two ratings were used than when all three ratings were used. Therefore, the average of the last 2 ratings during the test stimulus, both before and during the conditioned stimulus, was used as the criterion measure in the CPM test. Pain intensity ratings during the CPM test are presented in Table 4.15.

The ANOVA that used physical activity groups based on physical activity monitoring (n=20 inactive and n=11 active) found a significant main effect of time ($F_{1,29} = 12.656$, partial $\eta^2 = .304$, p=.001). The activity main effect and activity x time interaction were not significant. The results were unchanged when the test stimulus temperature was used as a covariate.

The ANOVA that used physical activity groups based on self-reported physical activity (n=12 inactive and n=18 active) found a significant effect of time ($F_{1,28} = 13.461$, partial $\eta^2 = .325$, p = .001). The activity main effect and interaction with time were not significant. The results were unchanged when the test stimulus temperature was used as a covariate.

Before and during the conditioning stimulus, pain intensity ratings for the entire group during the test stimulus were 7.1 ± 1.5 and 6.1±1.4, respectively.

4.4 Discussion

4.41 Heat Pain

The hypothesis that inactive postmenopausal women would report higher pain intensity and pain unpleasantness than low active postmenopausal women was not supported. This hypothesis was based in part on a preliminary report showing inactive women reported higher

pain intensity and pain unpleasantness ratings to heat stimuli compared to active women [23]. Although this study is similar to the present one in many respects (heat stimuli used and its rate of rise, body site of heat application, pain scales used) there are several differences, including age, sample sizes, medication use and the presence of disabling pain, that could have accounted for the disparate findings.

The women in the present study were on average 30 years older than in the prior preliminary study [23]. Age-related reductions in the density of sensory receptors or impairments of myelinated or unmyelinated nociceptive fiber function can lead to changes in heat pain threshold [10,30,48] but how that would alter a possible moderating effect of physical activity on ratings of noxious stimuli above pain threshold is uncertain. The women in the present study showed expected mean pain intensity and pain unpleasantness rating responses; that is, their ratings increased with increases in the intensity of the heat stimulus. And a ceiling effect did not impact the results because the highest pain ratings were well below the highest possible ratings.

The present study tested more than twice as many active women and fourfold as many inactive women as the prior preliminary study; thus, the present study is less apt to have been influenced by small sample bias. While the prior study tested a small sample of drug-free participants, a large percent of people in the United States, especially middle-aged and older adults [42,61] regularly take prescription medication. The total sample of the present study included 26% who were taking antidepressants and 7% who were taking prescription pain medications. While medications in these classes can influence pain responses to heat stimuli [22,25,66], all of the findings reported in this investigation were unchanged when the use of these medications was accounted for statistically.

Approximately 20% of participants in the current study were classified as being in disabling pain, a prevalence that is slightly lower than expectations based on the related literature. Current estimates report that about 70% of midlife women report being in pain and that about 32% indicate that the pain they experience is interfering with their daily life; that is, their pain is disabling [69-70].

The hypothesis that inactive women with disabling pain would report higher pain intensity and pain unpleasantness at high but not low stimulus intensities was not supported for pain intensity but was supported for pain unpleasantness. This hypothesis was made based both on evidence that pain sensitivity is higher among individuals with chronic pain [11,41,59] and a preliminary report showing inactive women reported higher pain intensity and unpleasantness ratings to heat stimuli and that larger effect size differences were found at the higher stimulus intensities [23]. For pain unpleasantness in the present study, the largest effect size difference between active and inactive groups was found at the highest temperature (49°C) but the magnitude of the effect was substantially smaller compared to the prior preliminary report (.38-.49 versus 1.10) [23]. Regardless, the results of these two studies suggest that physical activity impacts pain unpleasantness to a greater extent than pain intensity. Several studies have reported that experimentally-induced mood shifts, using odors, movies or hypnosis preferentially influence pain unpleasantness [49,63,74]. While it has been suggested that the naturally occurring muscle pain that occurs during an acute bout of moderate-to-vigorous intensity exercise could cause adaptions in brain areas that underlie pain intensity [14], brain responses and adaptations associated with exercise-induced mood shifts also could plausibly contribute to reduced pain unpleasantness responses to noxious stimuli of the type observed here. Generally consistent with this possibility is that acute exercise preferentially activates brain regions

involved in processing affective dimensions of pain such as the anterior cingulate cortex (ACC), and the insular cortex [24,60,65,67,78].

The higher unpleasantness ratings at 49°C for the inactive women with disabling pain (described on average as very distressing) compared to the active women (unpleasant) were present whether physical activity status was determined from objective physical activity monitoring or self-report. The correlation between self-reported minutes of physical activity per week and the average daily minutes of moderate-to-vigorous physical activity estimated from the NL-1000 was low (r=.39) which is consistent with prior studies including those of postmenopausal women (r=.33) [29]. Nevertheless, there was substantial overlap between the two methods in classifying the physical activity status of women in disabling pain. For example, all of those in disabling pain judged to be physically active by accelerometry were also classified as active by self-report (4/4 or 100%) while the majority of those in disabling pain judged to be physically active by self-report were also classified as active by accelerometry (4/5 or 80%). For the women included in the CPM analyses, 11 were classified as active by accelerometry with 9 of those women also being classified as active by self-report (9/11 or 82%). An additional 9 women who were classified as inactive by accelerometry were classified as active by self-report. In integrating the present finding into the extant and future related research literature, it is important to recognize the apparent high level of physical activity for the total sample. Based on activity monitoring, 38% of total sample was considered active while 54% was classified as active based on self-report. Tucker and colleagues [72] estimate that only about 6.5% of the U.S. population aged 50-59 are adequately active based on accelerometry and current physical activity guidelines while nearly 59% of the U.S. population aged 50-59 are adequately active based on self-report measurements.

4.42 Conditioned Pain Modulation (CPM)

An efficient pain modulation system is indicative of a healthy, well-functioning pain processing system. The second aim of the current study evaluated the efficiency of postmenopausal women's endogenous pain modulation ability. Postmenopausal women were a focus of this investigation because they are at increased risk of having suboptimal endogenous pain modulation ability for several reasons including their age [21,77] and high prevalence of, and increased risk for, chronic pain [73]. We reasoned that if physical activity can improve pain modulation ability then it might be especially meaningful in a group with poor endogenous pain control ability. It was hypothesized that the physically inactive postmenopausal women would show poorer pain modulation compared to physically active postmenopausal women. The data obtained showed that physical activity status was unrelated to endogenous pain modulation ability.

There are several possible explanations as to why physical activity status was unrelated to endogenous pain modulation ability. There is a body of evidence showing a reduced ability for endogenous pain modulation among groups older than 40 years [21,44,47,77]. The failure to show a moderating effect of physical activity in the present study could be explained if the mechanism responsible for this age-related effect is uninfluenced by physical activity (e.g., age-related alterations in skin nociceptive afferents).

The fact that many of the postmenopausal women reported pain is a second potential explanation for the lack of a physical activity relationship with conditioned pain modulation efficacy. There is a substantial body of literature showing that groups characterized by chronic pain show inefficient pain modulation. A meta-analysis showed that across 30 studies, patients in chronic pain showed conditioned pain modulation that was substantially less efficient compared

to controls; the mean size of the standardized effect for reduced pain modulation among those in pain (.78) was large [47]. Poor CPM efficiency could contribute to chronic pain among postmenopausal women [20] or the presence of chronic pain plausibly could result in a habituation of the endogenous pain modulation system and make it insensitive to additional noxious stimuli. This possibility is not supported by the present results because most of the sample tested here demonstrated endogenous pain modulation and the magnitude of this effect was not influenced by the presence of disabling pain.

Because of the unique and relatively small sample tested the present results should not be used to suggest that physical activity has no effect on conditioned pain modulation. Pain modulation ability was found to be moderated by physical activity status in one study of women with fibromyalgia [24]. The plausibility of physical activity relationships with endogenous pain modulation were supported in that study by the observation that physical activity level was significantly and positively related to brain responses during distraction from heat pain in brain regions implicated in pain modulation (i.e., dorsolateral prefrontal cortex, dorsal posterior cingulate, and the periaqueductal grey) [23-24,54].

The reliability of CPM has been inadequately documented and there is no consensus methodology for assessing it; for example, whether the pain producing stimuli should be heat, cold, pressure or something else. One study found low, insignificant correlation among CPM responses generated by different noxious stimuli [56] suggesting that CPM is not a unitary phenomenon. When the same CPM methodology was used 8 times over a period of 7-10 months with healthy women the test-retest reliability (ICC = .39) was low [79]. Higher reliability has been shown across 3 days (ICC = .66) and within the same day (ICC = .85) when cold was used as the conditioning stimulus [46].

Typically CPM reliability has been assumed so information aimed at optimizing reliability of this technique could be useful. Often the pain ratings used for the CPM calculation have been the peak pain rating, a single pain rating or the average of all pain ratings during stimulus presentation. A limitation of utilizing the peak pain rating or a single rating is the inability to assess reliability. There appears to be no research conducted determining the number of ratings needed to obtain reliable pain ratings during either the test stimulus or the conditioning stimulus. It is plausible that pain ratings obtained during the first 10-seconds of a heat stimulus could differ from those obtained 20-30 seconds post-stimulus. Heat pain is mediated by vanilloid receptors (VR1). Vanilloid receptors are activated by painful skin temperatures above 45^{o}C and transmit nociceptive information to dorsal root ganglion (DRG) neurons [9]. In-vivo recordings from DRG cells show about 50% of cells decrease their activity in response to a constant noxious heat stimulation during the first 10-seconds of the stimulation after which the activity is stable [32]. This type of adaptation to a constant heat stimulus plausibly could influence pain perceptions associated with the stimulus. Demonstrated here was that the reliability of the average of last 2 ratings (obtained at 20 and 30 seconds after the initiation of the heat test stimulus) was more reliable for both the test stimulus (ICC of .73 versus .63) and the conditioning stimulus (ICC of .82 versus .74) than the average of all three ratings. These results suggest that better CPM data can be obtained by ignoring pain ratings obtained during the first 10-seconds of a stimulus or not averaging data obtained in the early and late post-stimulus phases. More evidence with larger samples and different testing modalities is needed to generalize these findings to all CPM testing.

4.43 Limitations

This investigation had several limitations. Women using prescription pain or antidepressant medication were included in the study. The potential moderating effect of using these medications was controlled statistically based on self-report. Financial constraints prevented us from conducting drug tests to confirm the presence or absence of a numerous drugs that could have influenced the results. The heat pain test findings are based on a small number of physically active women with disabling pain. This is not surprising because we did not focus on recruiting active women with disabling pain and by definition function is impaired by pain that is disabling. Pain unpleasantness data were not obtained during the CPM testing but related literature and the present findings suggest that physical activity may have a larger impact on pain unpleasantness than pain intensity. Intensity of physical activity was described as moderate-to-vigorous activity. Limitations of the activity monitor kept us from examining the role of vigorous activity levels on the outcomes. While the GPAQ does have this capability, we only had 1 participant meet the criteria to be classified as vigorously active. Therefore, we were unable to assess the potential associations between vigorous activity and pain ratings. The cross-sectional design allowed for associations between physical activity and pain unpleasantness to be described but the causal direction of the associations is uncertain.

4.44 Conclusion and implications

It was concluded that physical activity is associated with a reduced sensitivity to the unpleasantness of painful high intensity heat stimuli among women with disabling pain. The results suggest that that regular physical activity may be a useful treatment or adjunct for reducing pain unpleasantness in postmenopausal women suffering from disabling pain.

4.5 References

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Table 4.01 Descriptive information (mean ± SD)

	Total sample (n=68)	Subgroup with disabling pain (n=13)	Subgroup without disabling pain (n=55)	Effect size for subgroups (d)	Significance (p-value)
Age	59 ± 4	58 ± 4	59 ± 4	.16	.618
Percent body fat	39 ± 7	41 ± 8	39 ± 6	.28	.340
Percent Causasian	94	85	96	---	.149$^{\alpha}$
Years of education	19 ± 4	18 ± 3	19 ± 4	.29	.871
Systolic blood pressure	128 ± 12	131 ± 13	127 ± 12	.43	.179
Diastolic blood pressure	76 ± 9	76 ± 8	76 ± 9	.03	.923
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	27 ± 19	20 ± 20	28 ± 18	.42	.171
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	38	31	40	.22	.533 $^{\alpha}$
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	372 ± 432	295 ± 414	392 ± 437	.22	.472
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	54	39	58	.08	.199 $^{\alpha}$
Percent taking hormone replacement therapy medication	10	8	11	.21	.723 $^{\alpha}$
Percent taking antidepressents	26	46	22	.62	.086 $^{\alpha}$
Percent taking prescription pain medication	7	38	0	1.95	< .001 $^{\alpha}$
Number of body locations in pain	4 ± 4	8 ± 6	3 ± 4	1.25	< .001

α=Chi-square assessed significance otherwise t-tests were used

Table 4.02 Descriptive information (mean ± SD)
Physical activity based on objective activity monitoring data

	Total sample (n=68)	Active (n=26)	Inactive (n=42)	Effect size for subgroups (d)	Significance (p-value)
Age	59 ± 4	59 ± 4	58 ± 4	.25	.166
Percent body fat	39 ± 7	35 ± 6	42 ± 6	1.00	< .001 α
Percent Causasian	94	96	93	.02	.564 α
Years of education	19 ± 4	19 ± 3	18 ± 4	.25	.177
Systolic blood pressure	128 ± 12	128 ± 13	127 ± 12	.08	.829
Diastolic blood pressure	76 ± 9	76 ± 9	76 ± 9	0.00	.773
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	27 ± 19	47 ± 13	14 ± 8	1.74	< .001
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	38	100	0	---	---
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	372 ± 432	552 ± 384	259 ± 426	.68	.006
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	54	33	87	.54	< .001 α
Percent taking hormone replacement therapy medication	10	15	7	.42	.285 α
Percent taking antidepressents	26	8	38	.88	.003 α
Percent taking prescription pain medication	7	0	12	.67	.024 α
Number of body locations in pain	4 ± 4	3 ± 4	5 ± 5	.50	.043

α=Chi-square assessed significance otherwise t-tests were used

Table 4.03 Descriptive information (mean ± SD)
Physical activity based on self-report activity data.

	Total sample (n=68)	Active (n=37)	Inactive (n=31)	Effect size for subgroups (d)	Significance (p-value)
Age	59 ± 4	60 ± 4	57 ± 4	.75	.029
Percent body fat	39 ± 7	37 ± 6	43 ± 6	.86	< .001
Percent Causasian	94	97	90	.04	.218
Years of education	19 ± 4	19 ± 4	18 ± 4	.25	.208
Systolic blood pressure	128 ± 12	127 ± 13	129 ± 12	.17	.545
Diastolic blood pressure	76 ± 9	75 ± 9	77 ± 9	.22	.347
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	27 ± 19	35 ± 18	17 ± 15	.95	< .001
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	38	62	10	1.02	< .001 $^{\alpha}$
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	372 ± 432	651 ± 421	50 ± 56	1.39	< .001
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	54	100	0	---	---
Percent taking hormone replacement therapy medication	10	14	6	.41	.331 $^{\alpha}$
Percent taking antidepressents	26	19	33	.35	.123 $^{\alpha}$
Percent taking prescription pain medication	7	3	13	.86	.101 $^{\alpha}$
Number of body locations in pain	4 ± 4	4 ± 4	5 ± 5	.25	.251

α=Chi-square assessed significance otherwise t-tests were used

Table 4.04 SF-36 Subscale Scores (mean ± SD)

	Norms for females age 55-64	Total sample (n=68)	Subgroup with disabling pain (n=13)	Subgroup without disabling pain (n=55)	Effect size for subgroups (d)	Significance (p-value)
Bodily pain	67 ± 25	79.0 ± 19.9	45.7 ± 15.8	86.9 ± 10.2	2.07	< .001
Physical function	73 ± 27	84.3 ± 17.0	57.7 ± 16.5	90.6 ± 9.4	1.93	< .001
Social functioning	79 ± 27	90.0 ± 20.4	63.6 ± 28.1	96.2 ± 11.7	1.59	< .001
Vitality	58 ± 23	65.6 ± 19.6	41.0 ± 21.8	71.4 ± 13.9	1.55	< .001
Role physical	72 ± 40	86.5 ± 21.0	61.1 ± 30.9	92.6 ± 12.0	1.50	< .001
General health	63 ± 23	78.6 ± 17.3	59.4 ± 19.7	83.1 ± 13.2	1.37	< .001
Mental health	73 ± 20	82.2 ± 14.2	71.5 ± 19.5	84.7 ± 11.4	0.93	.002
Role emotional	80 ± 35	90.1 ± 15.8	82.1 ± 22.7	92.0 ± 13.3	0.63	.041

Note: Higher scores represent better health status

Table 4.05 SF-36 Subscale Scores (mean ± SD)
Physical activity based on objective activity monitoring data.

	Norms for females age 55-64	Total sample (n=68)	Active (n=26)	Inactive (n=42)	Effect size for subgroups (d)	Significance (p-value)
Bodily pain	67 ± 25	79.0 ± 19.9	82.7 ± 13.2	76.7 ± 22.9	.30	.182
Physical function	73 ± 27	84.3 ± 17.0	90.6 ± 12.7	80.4 ± 18.3	.60	.008
Social functioning	79 ± 27	90.0 ± 20.4	93.3 ± 15.0	87.9 ± 23.1	.27	.239
Vitality	58 ± 23	65.6 ± 19.6	71.5 ± 16.1	62.0 ± 20.9	.49	.051
Role physical	72 ± 40	86.5 ± 21.0	92.7 ± 9.6	82.8 ± 25.1	.47	.026
General health	63 ± 23	78.6 ± 17.3	82.0 ± 14.8	76.4 ± 18.5	.32	.198
Mental health	73 ± 20	82.2 ± 14.2	83.7 ± 15.1	81.3 ± 13.7	.17	.512
Role emotional	80 ± 35	90.1 ± 15.8	91.4 ± 14.8	89.3 ± 16.6	.13	.607

Note: Higher scores represent better health status

Table 4.06 SF-36 Subscale Scores (mean ± SD)
Physical activity based on self-report activity data.

	Norms for females age 55-64	Total sample (n=68)	Active (n=37)	Inactive (n=31)	Effect size for subgroups (d)	Significance (p-value)
Bodily pain	67 ± 25	79.0 ± 19.9	82.2 ± 13.8	75.1 ± 25.0	.35	.167
Physical function	73 ± 27	84.3 ± 17.0	89.7 ± 12.2	77.7 ± 19.7	.71	.005
Social functioning	79 ± 27	90.0 ± 20.4	94.6 ± 13.2	84.4 ± 25.7	.50	.050
Vitality	58 ± 23	65.6 ± 19.6	69.6 ± 15.8	60.8 ± 22.8	.45	.073
Role physical	72 ± 40	86.5 ± 21.0	91.0 ± 10.5	81.3 ± 28.3	.46	.078
General health	63 ± 23	78.6 ± 17.3	82.4 ± 13.0	74.0 ± 20.6	.48	.055
Mental health	73 ± 20	82.2 ± 14.2	82.4 ± 13.7	81.9 ± 15.0	.04	.887
Role emotional	80 ± 35	90.1 ± 15.8	91.7 ± 13.0	88.2 ± 18.7	.22	.378

Note: Higher scores represent better health status

Table 4.07 Pain ratings in response to heat stimuli during the heat test (Mean ± SD). Physical activity based on objective activity monitoring data.

			Temperatures °C			
			46	47	48	49
Intensity	No disabling pain	Inactive (n=33)	6.9 ± 4.8	8.3 ± 4.9	11.3 ± 4.1	12.4 ± 3.8
		Active (n=22)	8.0 ± 4.7	8.2 ± 4.7	10.8 ± 4.4	12.3 ± 4.5
	Disabling pain	Inactive (n=9)	5.3 ± 3.4	9.1 ± 3.7	11.1 ± 5.4	14.8 ± 4.0
		Active (n=4)	8.8 ± 3.2	8.3 ± 4.8	10.1 ± 4.4	13.5 ± 2.6
Unpleasantness	No disabling pain	Inactive (n=33)	4.6 ± 3.6	6.1 ± 3.8	7.2 ± 3.9	9.9 ± 3.7
		Active (n=22)	4.3 ± 3.4	5.2 ± 3.7	6.8 ± 4.4	8.9 ± 3.8
	Disabling pain	Inactive (n=9)	3.3 ± 2.3	5.7 ± 2.6	7.6 ± 4.3	13.3 ± 3.9
		Active (n=4)	3.8 ± 3.8	3.8 ± 4.1	5.3 ± 5.0	7.0 ± 4.8

Table 4.08 Pain ratings in response to heat stimuli during the heat test (Mean ± SD). Physical activity based on self-report activity data.

			Temperatures °C			
			46	47	48	49
Intensity	No disabling pain	Inactive (n=23)	7.4 ± 4.4	8.7 ± 4.7	10.5 ± 4.6	12.3 ± 4.2
		Active (n=32)	7.3 ± 5.0	8.0 ± 4.8	10.3 ± 4.2	12.4 ± 4.1
	Disabling pain	Inactive (n=8)	5.0 ± 3.5	9.5 ± 3.8	10.5 ± 5.4	14.5 ± 4.2
		Active (n=5)	8.6 ± 2.8	7.8 ± 4.3	12.2 ± 4.1	14.2 ± 2.8
Unpleasantness	No disabling pain	Inactive (n=23)	4.7 ± 3.4	6.4 ± 3.6	7.7 ± 3.7	9.7 ± 3.6
		Active (n=32)	4.3 ± 3.6	5.2 ± 3.8	6.6 ± 4.3	9.3 ± 3.8
	Disabling pain	Inactive (n=8)	3.2 ± 2.4	5.9 ± 2.7	7.4 ± 4.6	13.5 ± 4.2
		Active (n=5)	3.8 ± 3.3	3.8 ± 3.6	6.0 ± 4.6	8.0 ± 4.7

Table 4.09 Effect size difference in pain ratings between active and inactive. Positive effect sizes are associated with lower pain ratings for the active women and negative effects are associated with higher pain ratings for the active women.

		Effect size (d)	
	Temperature °C	Unpleasantness	Intensity
Objective physical activity monitoring (n=26 active; n=42 inactive)	46	0.04	-0.33
	47	0.28	0.06
	48	0.17	-0.11
	49	0.49	0.09
Self-reported physical activity (n=37 active; n=31 inactive)	46	.03	-0.16
	47	.36	.21
	48	.27	-0.02
	49	.38	.06

Table 4.10 Descriptive information for women in disabling pain (mean ± SD)
Physical activity based on objective activity monitoring data

	Total sample (n=13)	Active (n=4)	Inactive (n=9)	Effect size for subgroups (d)	Significance (p-value)
Age	58 ± 4	60 ± 3	57 ± 5	.75	.441
Percent body fat	41 ± 8	34 ± 6	44 ± 7	1.25	.038
Systolic blood pressure	132 ± 13	133 ± 16	131 ± 12	.15	.812
Diastolic blood pressure	76 ± 8	77 ± 8	76 ± 8	.13	.821
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	20 ± 21	46 ± 15	8 ± 8	1.33	.009
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	31	100	0	--	--
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	295 ± 414	451 ± 279	225 ± 458	.55	.818
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	39	100	11	1.75	.001 $^{\alpha}$
Percent taking hormone replacement therapy medication	8	0	11	.54	.380 $^{\alpha}$
Percent taking antidepressents	46	0	68	.99	.011 $^{\alpha}$
Percent taking prescription pain medication	39	0	56	.73	.084 $^{\alpha}$
Number of body locations in pain	8 ± 6	5 ± 5	9 ± 6	.67	.283

α=Chi-square assessed significance otherwise t-tests were used

Table 4.11 Descriptive information for women in disabling pain (mean ± SD)
Physical activity based on self-report activity data.

	Total sample (n=13)	Active (n=5)	Inactive (n=8)	Effect size for subgroups (d)	Significance (p-value)
Age	58 ± 4	60 ± 3	57 ± 5	.75	.206
Percent body fat	41 ± 8	34 ± 6	45 ± 6	1.38	.006
Systolic blood pressure	132 ± 13	131 ± 14	133 ± 12	.15	.844
Diastolic blood pressure	76 ± 8	76 ± 7	76 ± 8	0	.953
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	20 ± 21	38 ± 28	9 ± 9	1.38	.005
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	31	80	0	1.84	.001 $^{\alpha}$
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	295 ± 414	646 ± 498	75 ± 92	1.38	.062
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	39	100	0	--	--
Percent taking hormone replacement therapy medication	8	0	13	.30	.312 $^{\alpha}$
Percent taking antidepressents	46	20	63	1.05	.125 $^{\alpha}$
Percent taking prescription pain medication	39	20	50	.76	.299 $^{\alpha}$
Number of body locations in pain	8 ± 6	7 ± 6	8 ± 6	.17	.757

α=Chi-square assessed significance otherwise t-tests were used

Table 4.12 Descriptive information for conditioned pain modulation analyses (mean ± SD) Physical activity based on objective activity monitoring data.

	Total sample (n=31)	Active (n=11)	Inactive (n=20)	Effect size for subgroups (d)	Significance (p-value)
Age	58 ± 4	58 ± 4	59 ± 4	.25	.742
Percent body fat	39 ± 6	36 ±6	41 ±6	.83	.032
Systolic blood pressure	125 ± 11	125 ± 8	125 ± 13	0	.992
Diastolic blood pressure	73 ± 8	72 ± 7	73 ±9	.13	.768
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	24 ± 17	43 ±10	14 ±9	1.71	< .001
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	36	100	0	--	--
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	401 ± 423	460 ± 339	365 ±473	.22	.572
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	58	82	45	.89	.069 $^{\alpha}$
Percent taking hormone replacement therapy medication	29	36	25	.30	.394 $^{\alpha}$
Percent taking antidepressents	13	9	15	.35	.530 $^{\alpha}$
Percent taking prescription pain medication	26	9	45	1.21	.037 $^{\alpha}$
Number of body locations in pain	5 ± 5	5 ± 7	5 ± 4	0	.991

α=Chi-square assessed significance otherwise t-tests were used

Table 4.13 Descriptive information for conditioned pain modulation analyses (mean ± SD) Physical activity based on self-report activity data.

	Total sample* (n=30)	Active (n=18)	Inactive (n=12)	Effect size for subgroups (d)	Significance (p-value)
Age	58 ± 4	59 ± 4	58 ± 5	.25	.586
Percent body fat	39 ± 6	38 ±6	42 ± 7	.67	.118
Systolic blood pressure	125 ± 11	125 ± 11	126 ± 13	.09	.851
Diastolic blood pressure	73 ± 8	72 ± 7	75 ± 10	.38	.326
Activity monitor: average moderate-to-vigorous activity minutes·day^{-1}	24 ± 17	27 ±16	20 ± 18	.41	.266
Percent active (≥ 30 mins·day^{-1}) based on the activity monitor	37	50	17	.89	.069 $^{\alpha}$
GPAQ total: moderate-to-vigorous physical activity minutes·week^{-1}	401 ± 423	641 ± 402	61 ± 75	1.37	< .001
Percent active (≥ 150 mins·week^{-1}) based on the GPAQ	60	100	0	--	--
Percent taking hormone replacement therapy medication	13	11	17	.26	.531 $^{\alpha}$
Percent taking antidepressents	27	28	42	.34	.344 $^{\alpha}$
Percent taking prescription pain medication	13	11	17	.26	.531$^{\alpha}$
Number of body locations in pain	5 ± 5	6 ± 1	4 ± 1	.40	.724

*Only 30 people completed the GPAQ questionnaire; α=Chi-square assessed significance otherwise t-tests were used

Table 4.14 Descriptive data and pain rating reliability during the CPM test (n=31)

Stimulus type (seconds after start of the stimulus)	Pain intensity mean ± SD	Reliability ICC for 3 ratings	Reliability ICC for last 2 ratings
Test stimulus (10)	7.1 ± 1.5	.620	
Test stimulus (20)	7.1 ± 1.5		
Test stimulus (30)	6.9 ± 1.7		.730
Conditioning (10)	6.3 ± 1.4	.731	
Conditioning (20)	7.1 ± 1.6		
Conditioning (30)	7.6 ± 1.7		.942
TS during CS (10)	5.6 ± 1.3	.738	
TS during CS (20)	6.1 ± 1.5		
TS during CS (30)	6.0 ± 1.4		.819

TS = Test stimulus; CS = Conditioning stimulus; ICC = Intraclass correlation

Table 4.15 Pain intensity ratings during the CPM test.

		Active	Inactive
Objective physical activity monitoring (n=11 active; n=20 inactive)	TS temperature (°C)	47.7 ± 1.1	47.4 ± 1.1
	Rating^ of TS-1	6.8 ± 1.8	7.2 ± 1.4
	Rating^ of cold water	7.6 ± 1.7	7.5 ± 1.6
	Rating^ of TS-2 (during cold water CS)	5.7 ± 1.7	6.3 ± 1.3
	CPM (TS-1 minus TS-2)	1.1 ± 1.8	1.0 ± 1.5
Self-reported physical activity (n=18 active; n=12 inactive)	TS temperature (°C)	47.9 ± 0.9	47.0 ± 1.1
	Rating^ of TS-1	7.2 ± 1.6	6.9 ± 1.4
	Rating^ of cold water	7.7 ± 1.6	7.1 ± 1.7
	Rating^ of TS-2 (during cold water CS)	6.3 ± 1.6	5.6 ± 1.2
	CPM (TS-1 minus TS-2)	0.9 ± 1.9	1.3 ± 1.0

^ = average of last 2 intensity ratings

TS = Test stimulus; CS = Conditioning stimulus; CPM = Conditioned pain modulation

Figure 4.1 Pain intensity ratings (means ± SE) for active (n=4) and inactive (n=9) women (A) in disabling pain and (B) active (n=22) and inactive (n=33) women not in disabling pain.
Activity categories are based on objective activity monitoring.

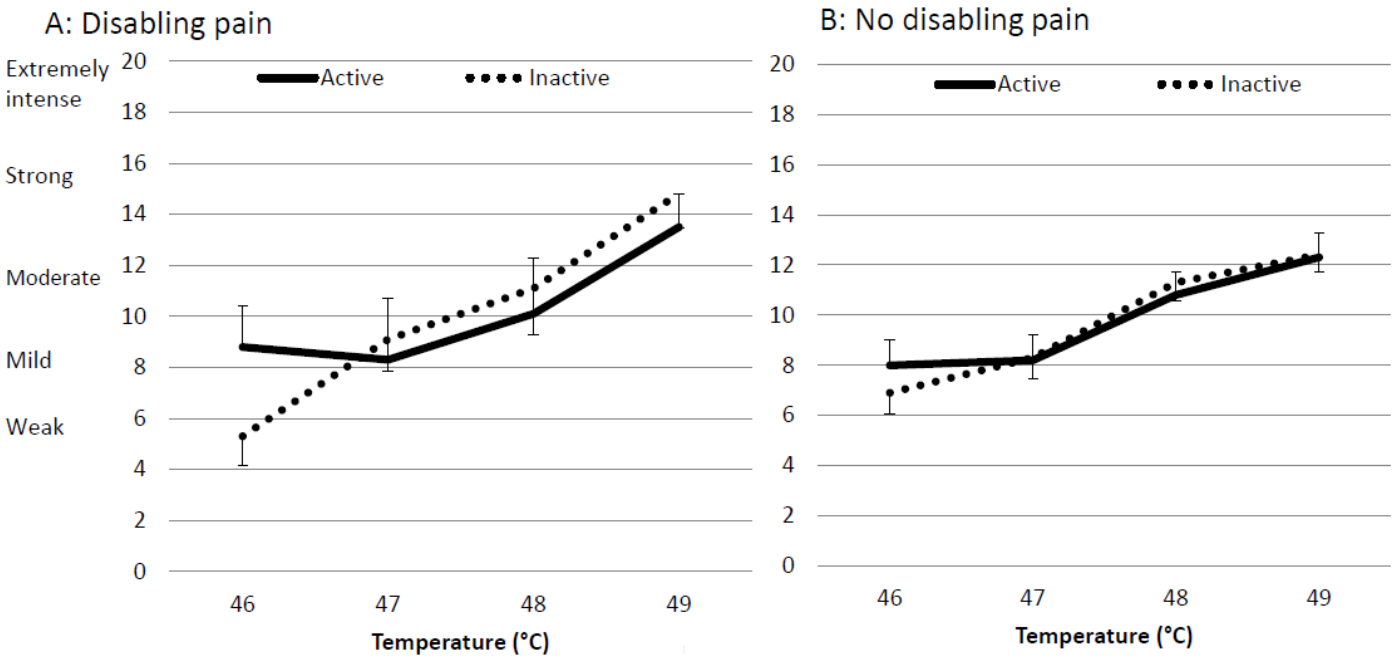


Figure 4.2 Pain intensity ratings (means ± SE) for active (n=5) and inactive (n=8) women (A) in disabling pain and (B) active (n=32) and inactive (n=23) women not in disabling pain.
Activity categories are based on self-reported physical activity.

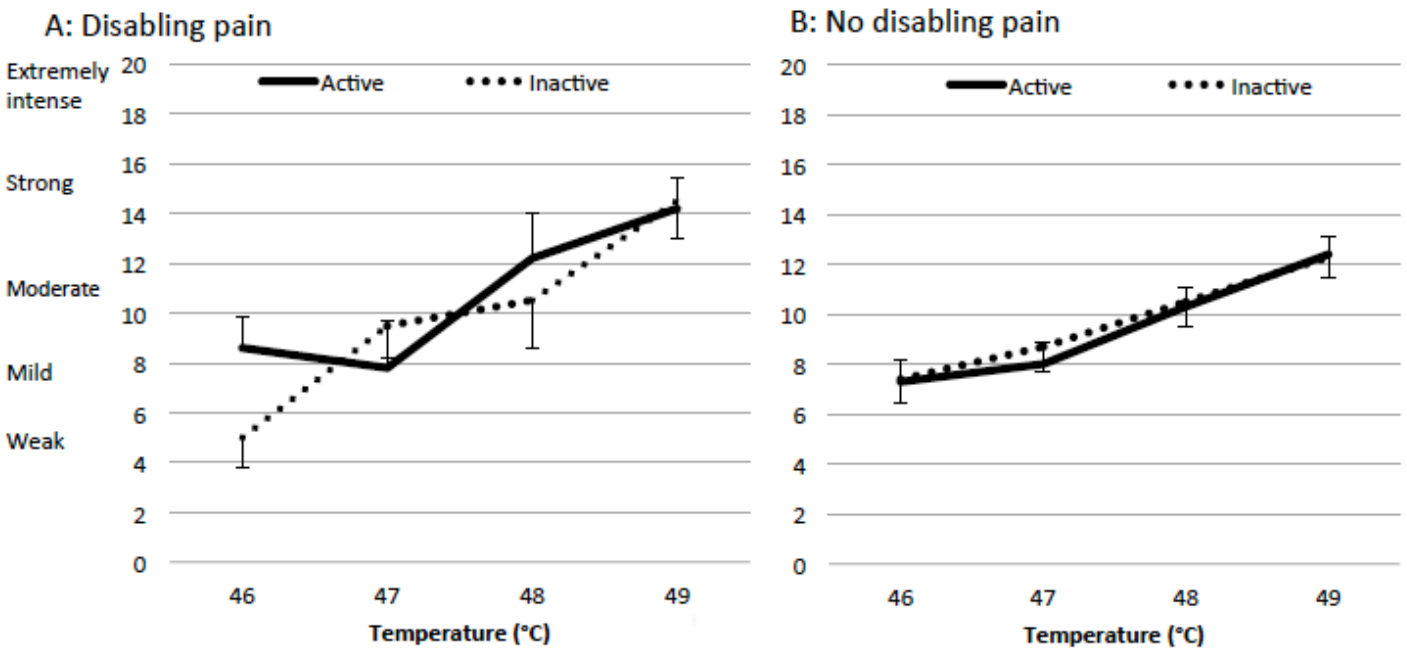


Figure 4.3 Pain unpleasantness ratings (means ± SE) for active (n=4) and inactive (n=9) women (A) in disabling pain and (B) active (n=22) and inactive (n=33) women not in disabling pain.
Activity categories are based on objective activity monitoring.

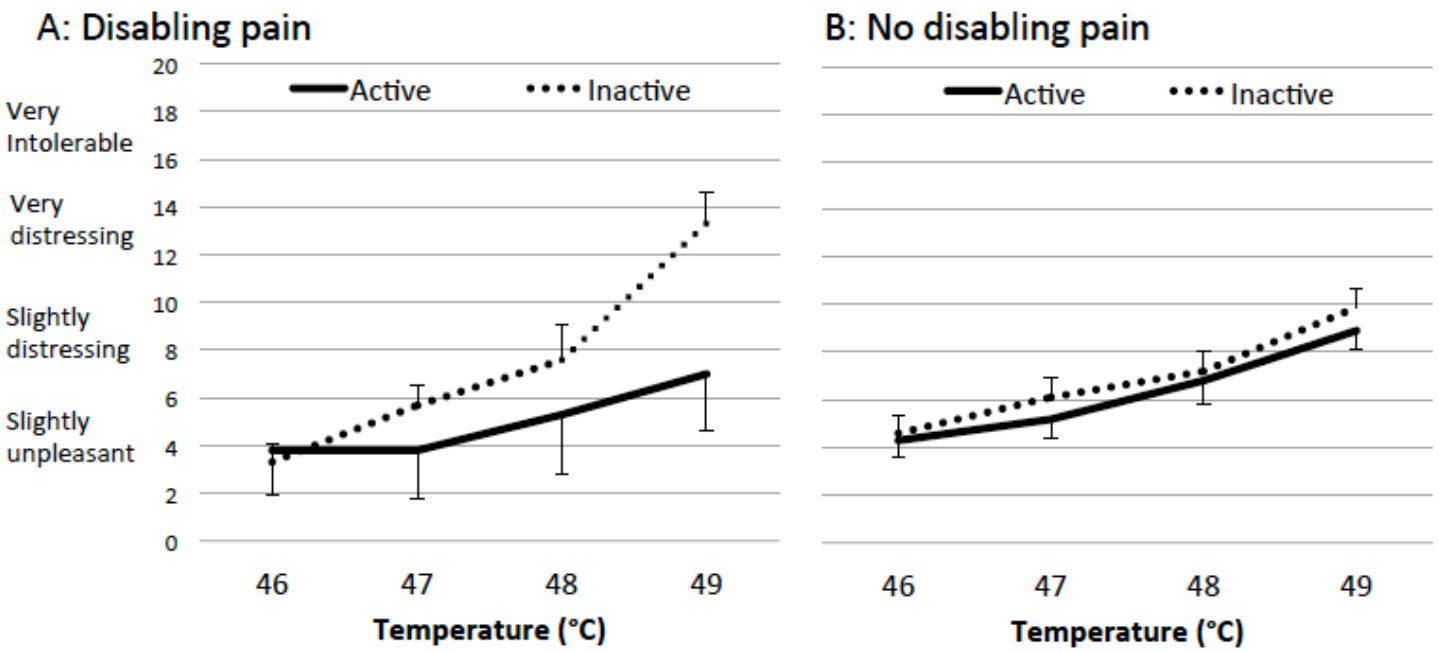
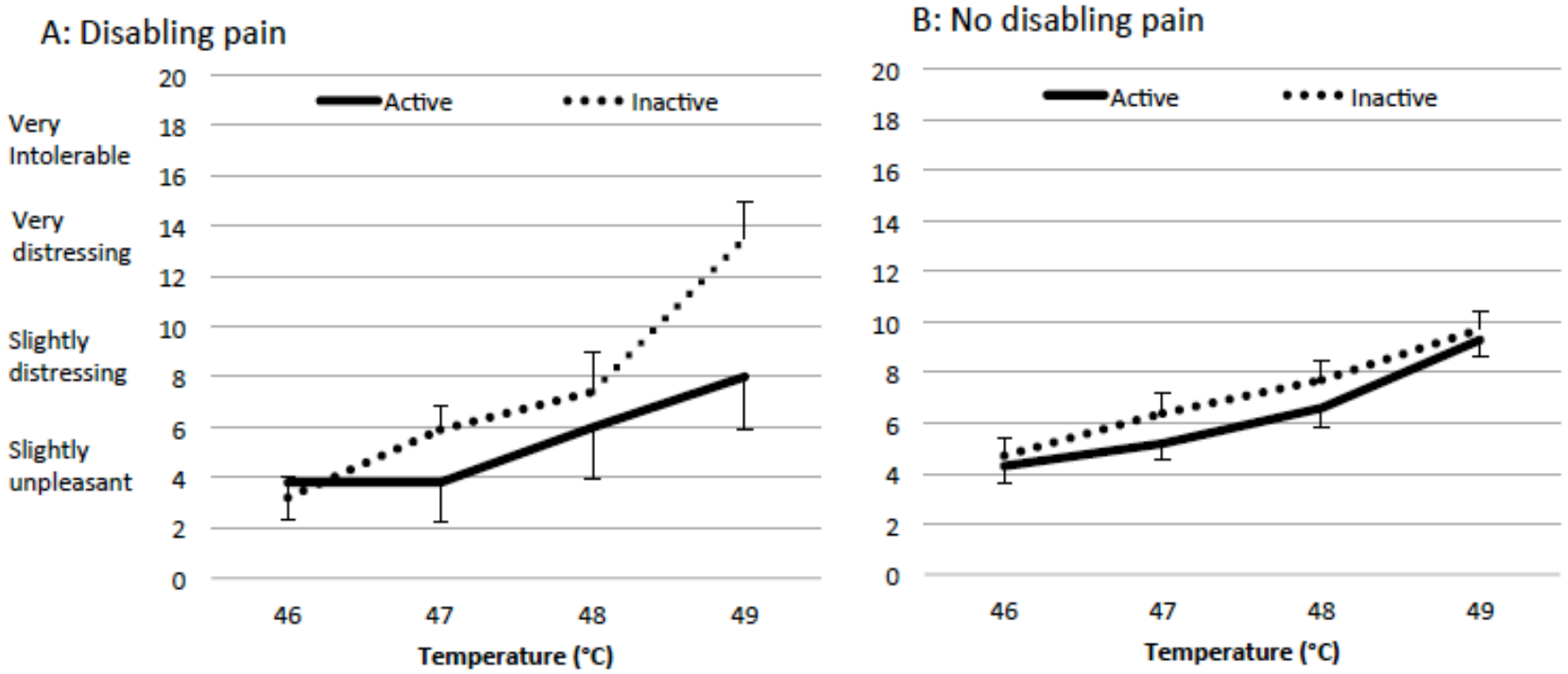


Figure 4.4 Pain unpleasantness ratings (means ± SE) for active (n=5) and inactive (n=8) women (A) in disabling pain and (B) active (n=32) and inactive (n=23) women not in disabling pain.
Activity categories are based on self-reported physical activity.



CHAPTER 5

CONCLUSION

The purpose of this dissertation was to better understand the potential role of physical activity in moderating pain. More specifically the focus was on those at increased risk of suffering from disabling pain due to being older, postmenopausal, overweight or diabetic and then to evaluate pain in those who were already reporting being in disabling pain.

The findings of this dissertation support the plausibility that physical activity could play an important role in pain processing. It was first found that there was a small effect of exercise training on bodily pain scores but that the relationship was not statistically significant. The second study concluded that recent physical activity may be interacting with the presence of disabling pain such that those who are in pain and are active will be less bothered by high stimulus intensities than those who are inactive. While it is still plausible that physical activity may influence a person's endogenous pain modulation ability, we did not find significant differences among our active and inactive women with the methods used in this study.

5.1 Implications for those at risk of suffering from disabling pain

In chapter 3 eleven randomized controlled trials were evaluated to better understand the potential effect that exercise training could have on bodily pain scores for those who were overweight or diabetic. Those trials let to the calculation of 21 effects. The bodily pain scores were recollections of the past month's pain severity and impact on daily life as measured through the Short-form 36 Health Survey [22]. The mean effect size delta (Δ) was 0.07 (95% CI, -0.07,

0.21; p = 0.3008) suggesting that the exercise intervention could reduce pain ratings among those in pain but that it was not statistically significant.

In general the results presented in this review suggest that there is a small and positive albeit non-significant effect for exercise reducing pain based on the bodily pain subscale of the SF-36 [22]. The articles included in the analysis do report positive findings for their other main outcome variables such as improvements in quality of life. Therefore, exercise is still highly promoted for those with diabetes [1].

While exercise is becoming an increasingly more popular treatment for reducing pain like fibromyalgia [5], low back pain [6], and osteoarthritis [16] that was not the purpose of this meta-analysis. I sought to understand the effect of exercise in a sample of individuals who were at an increased risk for developing chronic pain (i.e. diabetic or overweight) [24]. The average starting bodily pain score for those included in the current analysis was very similar at to the mean score for the US adult population (70.1 ± 21.2 compared to 75.2 ± 23.7) [21]. This suggests that the individuals included in the current meta-analysis were experiencing few pain symptoms. This fact likely contributed to the small effect size.

Because the SF-36 is so widely used and well validated, the current meta-analysis evaluated only studies that used that measure. Had more precise measures been included, such as questionnaires that did not depend on pain recollections during the prior month or immediate reporting of pain in response to standard noxious stimuli the observed effect could have been more substantial [10,19].

The 21 effects included in the analysis utilized a wide variety of exercise interventions. However, because there were a limited number of effects and there were concerns about statistical power, exercise type was coded as either a combination of resistance training and

endurance training or as “other”. The “other” group ranged from interventions using Tai Chi [7] to counseling patients on physical activity [3,8].

The findings from this review point to the need for standardized pain stimuli, which would lead to more precise and exact pain ratings. Questionnaires are a valuable tool but the benefit of rating a stimulus during or immediately post presentation removes the inherent error of recollection. The findings also point to the need to better understand the role of different types and doses of physical activity on people who are already suffering from some type of pain (e.g. disabling pain).

5.2 Implications for those in disabling pain

The purpose of the second study was to better understand the relationships between current physical activity and pain processing among a group of women potentially at an increased risk for disabling pain by being older, inactive females [17-18]. The second study used two approaches to assess these relationships. The first approach used noxious heat and hypothesized that (i) inactive women would report higher pain intensity and unpleasantness ratings compared to active women and (ii) that the inactive women with disabling pain would report higher pain intensity and pain unpleasantness at the high but not the low stimulus intensities. The second approach used a conditioned pain modulation technique and hypothesized that active women would have more efficient pain modulation compared to inactive women.

The primary results from the heat pain test showed that inactive women in disabling pain also had the highest pain unpleasantness ratings at the highest stimulus intensity compared to the active women in disabling pain ($F_{3,192} = 3.526$, partial $\eta^2 = .052$, $p = .016$). The implication is that being active does improve the affective dimension of pain when postmenopausal women are in disabling pain.

The results from the CPM task suggest efficient pain modulation on average in our sample ($F_{1,29}$ = 12.656, partial η^2 = .304, p= .001) but that the modulation was not moderated by physical activity.

There were a number of novel features to the cross-sectional study. First recollections of pain can be prone to error. Because memories of pain can be different than the immediate experience [10,19], participants rated a standard thermal stimuli. The assessment of both pain intensity and pain unpleasantness during the heat test allowed for inferences to be made about the potential mechanism by which physical activity works to improve pain processing since it is known that the brain processes pain intensity and pain unpleasantness differently [13,12,15]. The current study only found a significant effect of physical activity for the pain unpleasantness ratings thereby implying that physical activity may be influencing the affective dimension of pain to a greater extent than the pain sensitivity dimension.

Finally, the CPM task is a useful tool for understanding endogenous pain modulation – a mechanism thought to be impaired in older adults [2,23] and those in chronic pain [4,20]. The CPM methodology has been used with a number of different modalities and protocols [14]. However, there is not a consensus standardized set of parameters by which to administer the CPM task and the reliability of the aspects of test parameters has only recently been evaluated [9,11]. The current study attempted to better understand the reliability of the pain ratings taken during each phase of the task. I found here that the reliability of the last two ratings taken 20 and 30 seconds after the start of the stimulus for both the test stimulus and the conditioning stimulus was more reliable than using the average of all 3 ratings taken during the entire presentation of the stimulus.

5.3 Future direction

Future studies investigating the relationships between physical activity and pain processing should build on these findings. Immediate pain ratings to noxious stimuli will eliminate the potential error in recollections of pain. Incorporating pain unpleasantness ratings may improve our understanding of the role in which physical activity might play in pain processing. Finally, larger studies should incorporate the CPM task in order to better evaluate the differences in the modulation across physical activity levels, pain sufferers, and healthy persons. Reliability studies should continue to be pursued in order to establish a consensus optimal method to assess modulation.

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