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Exploring the relationship between sex, pain catastrophizing and abdominal pain sensitivity in a healthy, pain-free population

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EXPLORING THE RELATIONSHIP BETWEEN SEX, PAIN CATASTROPHIZING AND ABDOMINAL PAIN SENSITIVITY IN A HEALTHY, PAIN-FREE POPULATION

by

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ABSTRACT

Given a significant lack of literature focused on abdominal pain sensitivity between the sexes, this paper aims to explore how biological males and females processing abdominal pain stimuli differently. Additionally, the differences between males and females as it pertains to pain catastrophizing is explored. To examine sensory processing differences, the German Research Network's quantitative sensory testing protocol was conducted on the abdomens of 186 healthy, pain-free participants (66.1% female, 33.9% male). Ultimately, there were significant results that suggested a difference in the sensory processing of males and females. Females were more sensitive to pressure and thermal pain stimuli than males, which was consistent with prevailing literature. In regards to pain catastrophizing, the results from this study suggested no difference between males and females in a healthy, pain-free population, which was inconsistent with prevailing literature. The results of this study suggest that clinicians should use a more individualized approach with pain patients, with the consideration that each patient responds to pain stimuli differently, partially due to their biological sex.

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LIST OF ABBREVIATIONS

CPP……Chronic pelvic pain

IBS……... Irritable Bowel Syndrome

QST……Quantitative sensory testing

INTRODUCTION

"Women have traditionally been avoided as subjects in pain research, partly because of the assumption that results derived from males can be transferred to females."

(Arendt-Nielsen et al., 2004)

Current literature in the field of chronic pain research is disproportionately descriptive of the male experience (Arendt-Nielsen et al., 2004). While it acknowledges that females experience chronic pain more frequently, for a longer duration, and at a higher intensity, little has been studied in terms of specific differences between how females and males respond to pain stimuli. In this paper, we will attempt to identify the possible links between the biological sexes and responses to pain stimuli.

Key terms

Before exploring potential causes of abdominal pain between the sexes, it is important to define key terms that will be of use in this study. We will use "sex" as defined by Leslie and Kasza (Leslie & Kasza, 2020), specifically, a biological state defined by chromosomes, gonads, genitals and secondary sexual characteristics. Sex is determined at conception, but from the time that sex is assigned antenatally or at birth, humans begin to experience the effects of their gender and sex (Leslie & Kasza, 2020). "Gender", on the other hand, will be defined as a set of feelings, attitudes and behaviors linked to one's identity as a woman, man, other gender or no gender. While the role that

gender and societal norms plays in the study and treatment of chronic pelvic pain (CPP) will be discussed, the main aim of this study is to identify possible links between the biological mechanisms of the sexes and abdominal pain sensitivity. Much of the literature referenced in this paper uses the terms "women" and "men" interchangeably with "females" and "males"; however, for the purposes of keeping the study biologically-based, we will use the terms "female" and "male". Additionally, "pain catastrophizing" will be defined as a tendency to focus excessively on pain and exaggerate its threat value (Suso-Ribera et al., 2017).

Background information

Currently, there is little research on sex differences in pain sensitivity, as well as even less research on abdominal pain sensitivity specifically. Through the current research, however, it is widely accepted that females are more sensitive to pain stimuli than males (Arendt-Nielsen et al., 2004). Biologically, there are several reasons why females and males experience and process abdominal pain stimuli differently. Two major reasons for these differences are the different visceral organ structure and the different hormonal makeup of the sexes (Traub & Ji, 2013).

Hormonal Influences

It has been found that there is a higher prevalence of abdominal pain in biological females (Unruh, 1996). One reason for this discrepancy is due to the hormonal cycle. Specifically, in reproductive-aged females, the fluctuation of certain hormones has been shown to affect the times at which pain is more frequently present and more severe. In healthy women, it was concluded that the affective component of pain may be enhanced during the low-estrogen phase of the menstrual cycle (See **Figure 1)** (de Leeuw et al., 2006).

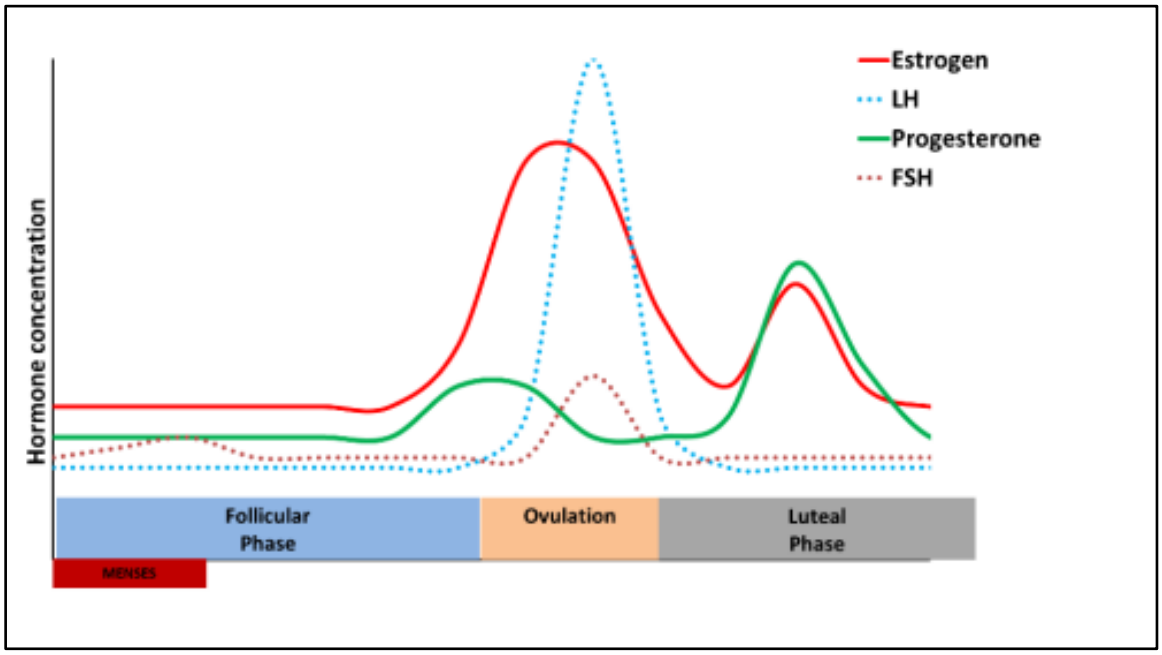

Figure 1. Female hormone cycle diagram. This diagram visually represents the fluctuations of specific reproductive hormones throughout the female menstrual cycle (*Mittuniversitetet*, n.d.).

Females may additionally experience menstrual cramp pain, or pain with ovulation. In fact, in America and Europe, menstrual and pelvic pain account for the most

common complaints during the reproductive period (Arendt-Nielsen et al., 2004). Another reproductive condition that exclusively affects biological females is endometriosis, which is a condition experienced by 5-10% of reproductive-aged females. It is due to abnormal growth of endometrial tissue outside of the uterus (Nunnink & Meana, 2007). This condition causes high levels of prolonged pelvic pain in females, and is only diagnosed surgically.

Visceral Pain

Visceral pain is due to autonomic innervations in the intraperitoneal organs (Chiantera et al., 2017). In regards to visceral pain, females experience not only more frequent pain, but more severe levels of pain and longer duration of pain as well (Arendt-Nielsen et al., 2004). Conditions such as irritable bowel syndrome (IBS), biliary colic and esophagitis, while not exclusive to females, are more common in females (Thompson et al., 1999). This could be due to the increased gastrointestinal transit time as compared to males (Arendt-Nielsen et al., 2004). There is additionally research indicating that a history of sexual trauma in the early life of a female correlates to the development of chronic pain conditions later in life (Fuentes & Christianson, 2018). As females are more likely to experience childhood sexual trauma (Tolin & Foa, 2008) – although this statistic may be skewed due to reporting bias – this could be a contributing factor to the increased prevalence of chronic pain in adult females. **Figure 2** below gives several examples of

visceral and abdominal pain conditions, and the prevalence of these conditions between males and females.

GENDER VARIATION IN PREVALENCE OF ABDOMINAL PAIN

Author(s) and Sample	Variable(s)	Outcomes	
		Female	Male
Andersson et al. (1993) n = 1,806, 49%f, ages 25–74 years, Sweden.	Prevalence of chronic abdominal pain of more than 3 months duration.	No gender difference.	
Apley and Naish (1957) n = 472f, 528m, age 5–15 years, England.	Prevalence of recurrent abdominal pain - at least 3 attacks sufficient to interfere with activities.	12.3%	9.5%
Aro et al. (1987, 1989) n = 999f, 1002, mean age 15 years, Finland.	Prevalence of abdominal pain, quite often, often or continuously, during 1 year (excluding pain due to menstruation).	2.5%	2.5%
Faull and Nicol (1986) n = 439, gender distribution not given, age 6 years, England.	Prevalence of abdominal pain.	No gender difference.	
James et al. (1991) n = 994f, 504m, ages 18–64 years, New Zealand.	Overall lifetime prevalence of abdominal pain.	25.9% ($P < 0.01$)	19.1%
	Lifetime of prevalence of abdominal pain with physical diagnosis.	18.2% (n.s)	12.8%
	Lifetime prevalence of abdominal pain attributed to psychological origins or without physical diagnosis.	7.7% (n.s)	6.3%
Larsson (1991) n = 269f, 270m, ages 13–18 years. Sweden.	Prevalence of abdominal pain. Frequency and intensity.	Girls reported more abdominal pain than boys ($P < 0.001$). Girls also reported more severe and frequent abdominal pain.	
Lester et al. (1994) n = 132f, 120m, ages 17–30 years, USA.	Frequency of pelvic pain.	Women reported significantly more pelvic pain than did men ($P < 0.0001$).	
Magni et al. (1992) n = 3,175f, 2323m, ages 20–74 years, USA.	Abdominal or lower chest pain present for at least 30 days in the past 12 months.	Women reported abdominal pain significantly more often than did men	
Oster (1972) n = 8,947f, 9,215m, ages 6–19 years, Denmark.	Prevalence of abdominal pain.	16.7%	12.1%
Ritchey et al. (1991) n = 28f, 72m, homeless persons, ages 20 + years, USA.	Prevalence of stomach cramps, sour stomach in past 30 days.	64% ($P < 0.001$)	20.8%
	Prevalence of gas pains in previous 30 days.	25%	15.3%
Taylor and Curran (1985) n = 625f, 629m, ages 18 + years, Nuprin Pain Report, USA.	Prevalence of stomach pain on 1 or more days in the past previous 12 months.	49%	45%
		17% of women and 10% of men reported 11 + days of stomach pain.	
Von Korff et al. (1988) n = 593f, 423m, ages 18–65 + years, USA.	Prevalence of abdominal pain in the previous 6 months.	20%	14%

Figure 2. Sex differences in various abdominal and visceral pain conditions. In conditions where sex differences were reported, females reported a higher prevalence of pain (Unruh, 1996).

Males experience abdominal pain very differently than females, with research demonstrating that abdominal pain in males is likely acute in nature and associated with injury or disease (Unruh, 1996). The hormonal makeup of biological males is rarely to blame for the incidence of abdominal pain, as there are not as drastic of fluctuations in hormonal levels. Males additionally do not experience as much referred pain as do females (Arendt-Nielsen et al., 2004). In general, males can withstand higher pain thresholds than females, although the duration and severity of the experienced pain is higher in females (Arendt-Nielsen et al., 2004).

Pain Treatment

This discussion would be incomplete without acknowledging the role that gender and the societal expectations of males and females plays in how pain is experienced and managed. In terms of seeking treatment for chronic pain, women are more likely to consult medical professionals to manage their pain (van Hecke et al., 2013). Not only do women seek medical help, but they additionally are more likely to seek more social support than men, and use a wider range of coping strategies. These include methods such as problem solving, positive self-statements and palliative behaviors (Greenspan et al., 2007). In other words, females often use emotion-focused coping strategies (Keogh & Eccleston, 2006). On the other hand, it has been found that males often resort to behavioral distraction and problem-focused strategies to moderate and cope with their pain, rather than seeking social support (Keogh & Eccleston, 2006). This brings into

question if males actually are experiencing more acute and chronic pain than what is reported in literature, as they are underrepresented in clinical pain treatment settings. Currently, research suggests that physical symptoms are typically reported at least 50% more often by women than men (Kroenke & Spitzer, 1998). Interestingly, a study that tried to implement emotion-focused coping strategies with males showed to be detrimental, in that such strategies correlated to greater pain in the subjects (Keogh & Eccleston, 2006). This suggests that their usual method of coping, where they focus on the pain rather than their emotional response, was more helpful in terms of reducing pain outcomes.

Psychophysical Processing

Chronic pain and its development is an extremely complex process that results from a variety of factors. In order to fully understand the onset of pain, we must look at how pain manifests in younger populations, and how the trajectories of pain differ between young males and young females. A 2000 Dutch study revealed that chronic pain is a common complaint in childhood and adolescence (Perquin et al., 2000). Specifically, the study showed that young males reach a plateau in their experience of chronic around 8 years of age, while young females continue to increase in the prevalence of chronic pain into their adolescent years (Perquin et al., 2000), as visualized in **Figure 3** below. As shown, females experienced the peak of their pain development around 12-14 years of age, likely due to the onset of menstruation.

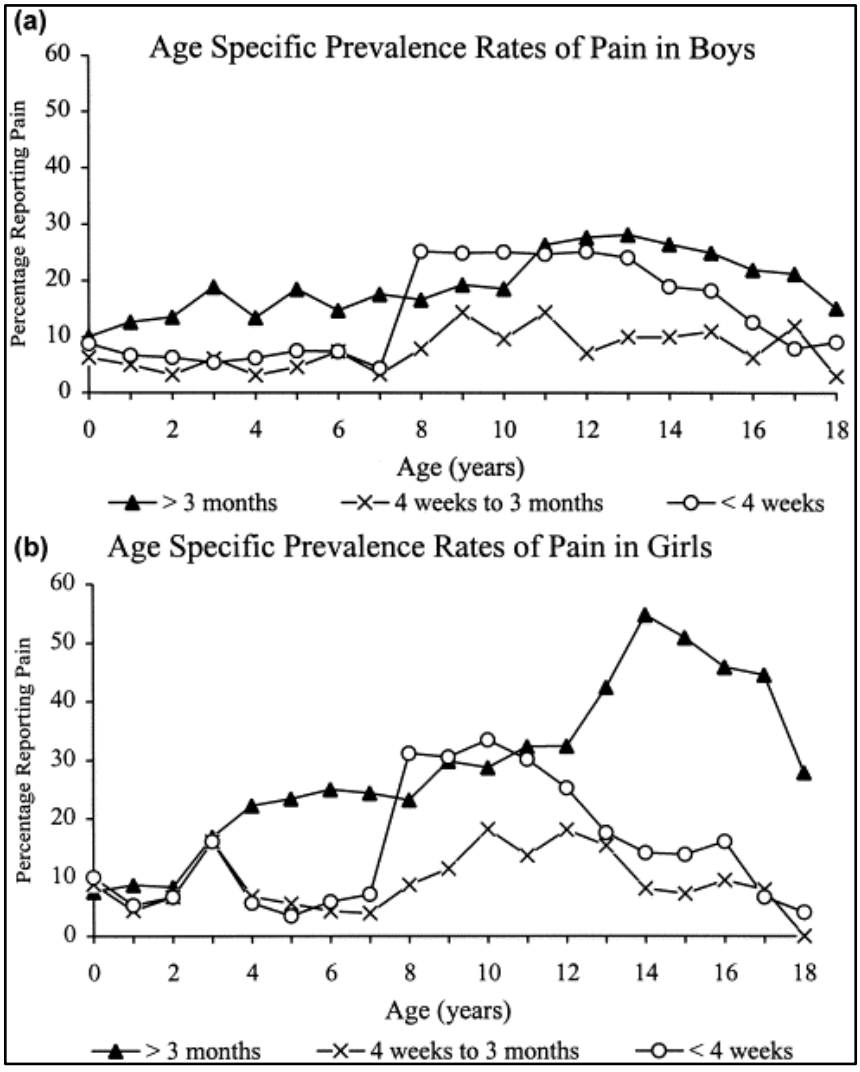

Figure 3. Trajectories of pain development between young males and females. Each line represents a different duration of pain. Chronic pain is defined as pain experienced for over 3 consecutive months (Perquin et al., 2000).

In addition to the timeline of pain development in adolescents, it is also important to note that young females reported a higher prevalence of chronic pain and were twice as likely to experience pain in more than one location than their male counterparts, specifically in

the head and abdomen (Perquin et al., 2000). Something that this study highlighted is the complexity of chronic pain, and how it develops in young people.

Given the complexity of chronic pain and its contributors (see **Figure 4**), and given that pain is entirely subjective and difficult to quantify, it is important that we explore sensory processing in a quantitative way.

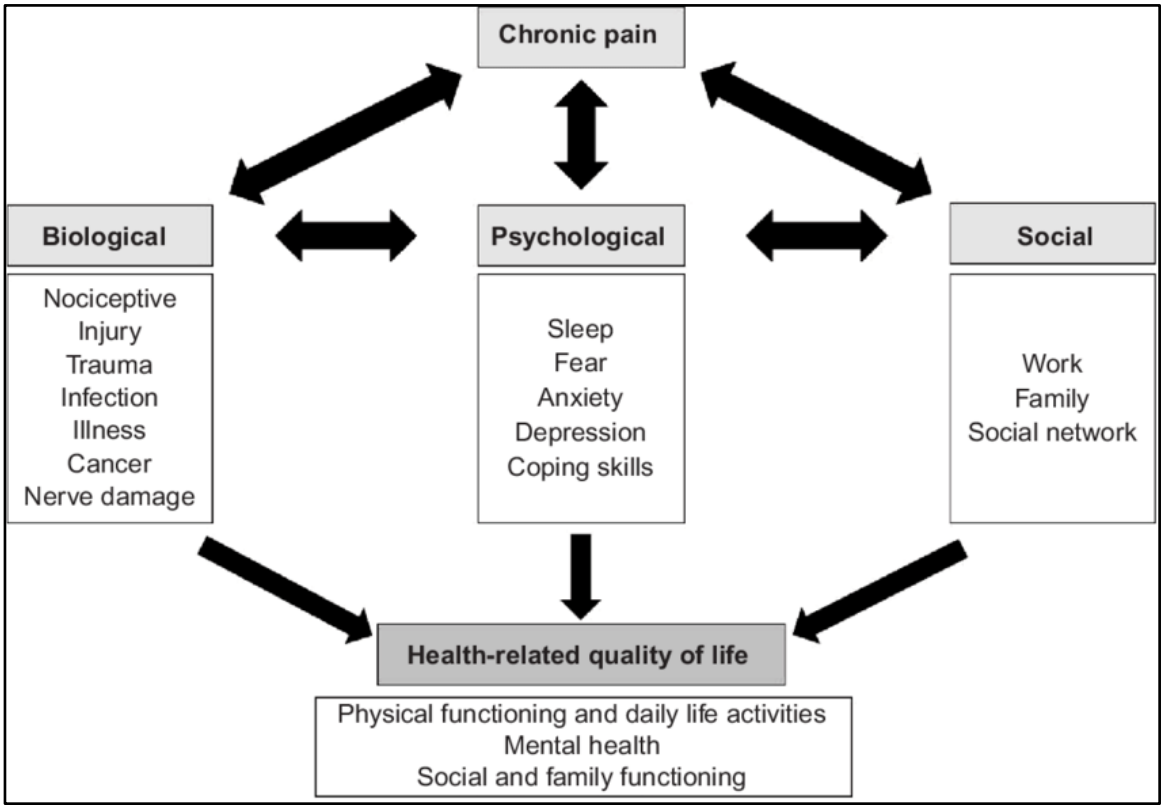

Figure 4. Biopsychosocial Model of Pain. An illustration of the multiple factors that contribute to the development of chronic pain. (Dueñas et al., 2016).

The German Research Network on Neuropathic Pain established and implemented a standardized quantitative sensory testing (QST) protocol to conduct on regions of the body (Rolke et al., 2006). The protocol was specifically conducted on the face, hand and

foot. In terms of sex differences and how males and females responded to the stimuli in these regions, it was concluded that females were more sensitive than males, especially with thermal stimuli (Rolke et al., 2006). These findings were consistent with other studies that conducted similar protocols, such as Dr. Rollman's. The purpose of that study was to prove that women are more prone to experience musculoskeletal pain than men (Rollman & Lautenbacher, 2001).

The German Research Network's protocol has been widely used since its inception, and its outcomes assess pain hypo/hyperalgesia and mechanical allodynia (Rolke et al., 2006). The main findings of the pilot study suggested that there are significant differences between males and females in how they process each type of stimuli, with females generally being more sensitive than males (Rolke et al., 2006).

A shortcoming of this protocol, however, is that it does not include abdominal testing, and therefore there are not published reference values for abdominal pain sensitivity. These researchers do, however, acknowledge that each body region needs its own QST reference data (Rolke et al., 2006).

Pain Catastrophizing and Emotional Functioning

In the field of pain research, an important conversation that is continuously had surrounds the idea of pain predictors and their modulation (Edwards et al., 2004). While it is clear that chronic pain can result from a culmination of various biopsychosocial factors (**Figure 4**), there is research to support that pain catastrophizing is the strongest

predictor of pain outcomes (Edwards et al., 2004). This additionally feeds into the larger aforementioned conversation about pain coping mechanisms and how individuals are encouraged to contextualize and respond to their pain.

In regards to pain catastrophizing and the role that it plays in the development and processing of pain, current literature widely supports that females are more likely to catastrophize pain than males (Paller et al., 2009). While most catastrophizing research is conducted in populations that are experiencing pain, it is still interesting to explore the differences between how males and females anticipate and emotionally process their pain, and additionally to explore catastrophizing specifically in the context of abdominal pain.

In an interdisciplinary pain management program with both male and female participants experiencing chronic pain, improvements in pain were achieved by both groups; however, pain improvements were experienced by females an average of 3 months after those by men. Additionally, the females reported higher catastrophizing scores than males (Bartley & Fillingim, 2013). Here, females both experienced both a longer duration of pain and a heightened catastrophizing response, which suggests that catastrophizing is associated with pain and pain-related disability.

Specifying this trend to those experiencing abdominal pain, there are a few studies that highlight the effects of specific abdominal conditions on catastrophizing. The first studied a group of females who were living with endometriosis (McPeak et al., 2018). Not only did these females report higher levels of catastrophizing, but they also reported more severe CPP, more severe dysmenorrhea and abdominal wall pain (McPeak

et al., 2018). Another was a study with a population of 100 adults, both male and female, that had IBS. Of these individual experiencing abdominal pain due to this condition, there were significant findings that those who endorsed high levels of catastrophizing also reported worse psychosocial and functional outcomes (Sherwin et al., 2017). This study had a disproportionately female population; although, there were male participants that demonstrated these outcomes as well (Sherwin et al., 2017). The overarching sentiment in the prevailing research surrounding pain catastrophizing is that in pain populations, there is a direct relationship between catastrophizing and experimental pain outcomes and it is one of the biggest predictors of pain outcomes (Trost et al., 2015).

SPECIFIC AIMS

Given the lack of existing literature examining pain sensitivity of the abdomen and how this may confer risk to diseases and conditions, which often have accompanying abdominal pain (e.g., IBS, Irritable Bowel Disease, endometriosis) the primary aim of the present study is to further explore this in a healthy population of adolescents, young adults, and adults. Additionally, we aim to examine potential sex differences and the role of pain catastrophizing in this relationship, which may elucidate the relationship between biological sex and abdominal pain and inform more personalized treatments. Based on the current literature, it is expected that the findings of this study will align with published findings, where females are more sensitive to pain stimuli than males. In terms of pain catastrophizing, it is difficult to predict what the findings of the analyses will bring to light, as very little literature examines pain catastrophizing in healthy, pain-free populations.

It is hoped that the findings from this study can be utilized in clinical settings. It is imperative that clinicians approach pain populations with the consideration that males and females respond to pain stimuli differently, which could have important clinical and treatment implications.

METHODS

Study Population and Eligibility

To analyze the relationships between sex and abdominal pain sensitivity, we used data collected from healthy controls from a study entitled "Examining Pain, Psychosocial, and Sensory Factors in Adolescents and Young Women with Endometriosis", conducted through the Biobehavioral Pediatric Pain Lab at Boston Children's Hospital (BCH). This study was approved by the BCH Institutional Review Board.

Participants for this study, ages 12-50 years, were recruited via the Adolescent Medicine Clinic at BCH as well as from community settings and social media. Once interest in the study was expressed, participants were screened via phone to ensure that they did not possess any comorbid conditions (e.g., a diagnosis of endometriosis or chronic pain) that would exclude them from participation. Additionally, in order to be eligible for the study, participants needed to speak sufficient English to complete questionnaire measures. A total of 186 individuals were eligible for and participated in the study. Once recruited, they were scheduled for a ninety-minute appointment at the Biobehavioral Pediatric Pain Lab, where they completed a series of measures and completed the sensory protocol in one session.

Study Visit and Sensory Protocol

Prior to beginning the sensory protocol, participants were asked to complete a series of measures. A **Health Screening Form** gathered general demographic details, health history and lifestyle information that allowed for the confirmation of the eligibility of the participant. A numeric 0-10 **pain scale** was provided to the participants to be referenced throughout the sensory protocol. At several points during the study, they were asked to rate the discomfort that the stimulus caused them, where a rating of 0 indicated "no pain at all" and a rating of 10 indicated "worst pain imaginable". Lastly, the **Pain Catastrophizing Scale** (PCS) is a 13-item, 5-point scale that assesses negative thinking associated with pain (Sullivan et al., 1995).

According to Dr. Sullivan, the developer of the PCS that was used in this study, there are three subcategories of catastrophizing: rumination, helplessness and magnification. Rumination is assessed by questions such as, "When I am in pain, I can't stop thinking about how much it hurts". Helplessness is assessed by questions such as, "When I'm in pain, it's awful and I feel that it overwhelms me". Magnification is assessed by questions such as, "When I'm in pain, I worry that something serious may happen" (Sullivan et al., 1995). Items that corresponded to each of these subcategories were summed and analyzed.

The protocol used in this study followed the Quantitative Sensory Test method validated by the German Research Network (Rolke et al., 2006). Each sensory test was conducted on the four quadrants of the abdomen; Upper Left (Q1), Upper Right (Q2), Lower left (Q3) and Lower Right (Q4) as well as on a control site (e.g, deltoid, nailbed of

finger, palm of hand). **Figure 5** below illustrates the exact regions of the abdomen where the QST protocol was conducted.

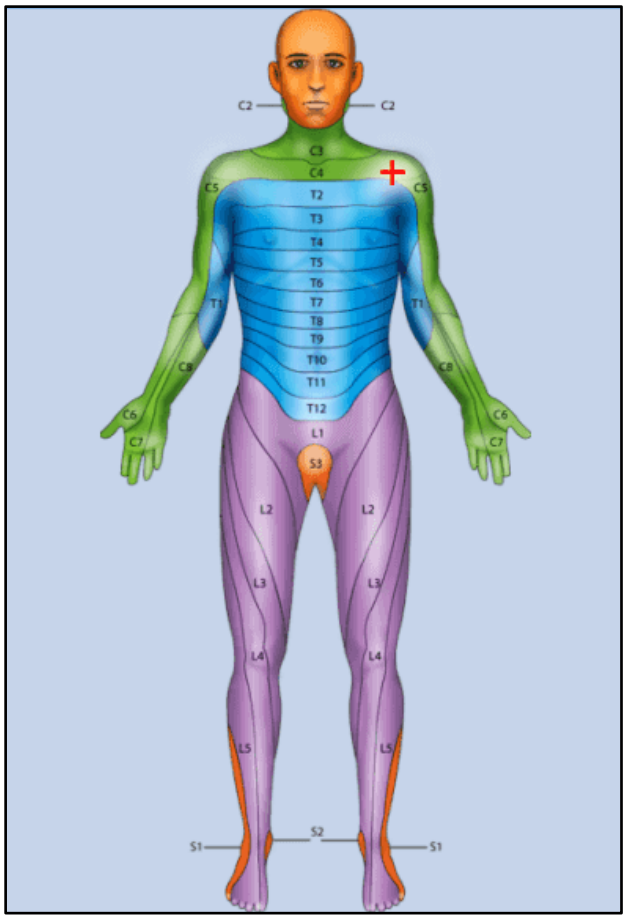

Figure 5. Body diagram. Each of the steps of the sensory protocol was conducted on the four quadrants of the abdomen. Q1 corresponded to section T10 on the left side of the midline. Q2 corresponded to section T10 on the right side of the midline. Q3 corresponded to section T11 on the left side of the midline. Q4 corresponded to section T11 on the right side of the midline. (Ofer, n.d.).

The sensory protocol was conducted as follows:

Light Touch Detection Threshold Test (LTDT)

Von Frey (VF) filaments of increasing size were applied three times to each quadrant of the abdomen until the participant reported that they sensed the filament two of three times.

Sharp Prick Detection Threshold Test (SPDT)

Starting at the touch threshold VF filament, VF filaments increased in size until the participant reported feeling a prick-like sensation on each quadrant of the abdomen two of three times. The participant was also asked to reference the pain scale to rate the pain of the stimulus on a scale of 0-10. The purpose of this test was to detect pinprick hypoalgesia (Rolke et al., 2006).

Sensation of Pressure and Pressure Pain Sensation Test (SPP)

Using an electronic pressure algometer, with a probe area of 1 cm^2, pressure was increasingly applied to each quadrant of the abdomen until the participant expressed pain or discomfort. This was conducted three times per quadrant and the mean of the three trials was recorded.

Thermal Sensory Detection (TSD)

A TSA-II Medoc thermode was held to each abdominal quadrant. The thermode rested at a baseline temperature of 30°C, with an upper limit to 50°C and a lower limit of 0°C, at which point the heating or cooling process would stop and the following test was run for each section-

- Four trials of cool detection threshold tests, where the thermode would cool down from the baseline temperature and the participant would press a button to stop the cooling and signify that they detected a change in temperature.
- Four trials of warm detection threshold tests, where the thermode would warm up from the baseline temperature and the participant would press a button to stop the warming and signify that they detected a change in temperature.
- Three trials of cold threshold tests, where the thermode would cool down from the baseline temperature until the participant pressed a button to stop the cooling and signify pain or discomfort. After each trial they were asked to reference the pain scale to rate the pain of the stimulus on a scale of 0-10.
- Three trials of hot threshold tests, where the thermode would warm up from the baseline temperature until the participant pressed a button to stop the warming and signify pain or discomfort. After each trial they were asked to reference the pain scale to rate the pain of the stimulus on a scale of 0-10.

Statistical Analysis

Following the administration of the sensory protocol, the data was compiled into SPSS Version 26 software. In order to assess if there were significant relationships between each of the sensory tests and biological sex, One-way ANOVA tests were run between sex and each of the tests. Rather than running these analyses on each quadrant, Q1 and Q2 were grouped as the "upper abdomen", and Q3 and Q4 were grouped as the "lower abdomen". A similar procedure was conducted to assess the relationship between sex and catastrophizing. The PCS was scored according to Dr. Michael Sullivan's manual (Sullivan et al., 1995), where the three subscales of catastrophizing- rumination, helplessness, and magnification were examined along with the total score. The means that were calculated were correlated to the percentiles outlined by Dr. Sullivan's manual. Each of the catastrophizing subscales were compared via one-way ANOVA between sexes. Statistical significance was classified if $p<0.05$.

RESULTS

Description of the Variables in the Study Population

The 186 participants of this study consisted of 123 cisgender females and 63 cisgender males between the ages of 12 and 50 years from the greater Boston area. With a mean age of 25 years, 70% of the participants were age 25 and younger and the remaining 39% of participants were age 26 or older. Among the study population, 85% identified as White, 32% identified as Black/African American, 30% identified as Asian/Pacific Islander, 28% identified as Spanish/Hispanic/Latinx, and 9% identified as Other. **Tables 1, 2 and 3** displays the descriptive data for the study variables.

Table 1: Age Distribution of Study Population. The majority of the study participants were aged 12-25.

Age	Frequency	Cumulative Percent
12 - 25	129	70.0
26 - 50	56	100.0
Total	185	
Missing	1	
Total	186	

Table 2: Sex Distributions of Study Population.

Sex	Frequency	Percent	Valid Percent	Cumulative Percent
Female	123	66.1	66.1	66.0
Male	63	33.9	33.9	100.0
Total	186	100.0	100.0	

Table 3: Race Distributions of Study Population.

Race	Frequency	Percent	Valid Percent	Cumulative Percent
White	85	45.7	46.2	46.0
Asian/PI	30	16.1	16.3	63.0
Spanish/Hispanic/Latina	28	15.1	15.2	78.0
Black/African American	32	17.2	17.4	95.0
Other	9	4.8	4.9	100.0
Total	184	98.9	100.0	
Missing	2	1.1		
Total	186	100.0		

Pain Catastrophizing

Of the study participants, 164 completed the PCS questionnaire to assess pain catastrophizing. The maximum possible score for the full PCS questionnaire is 52. The maximum possible score for the rumination subscale is 16, the maximum possible score for the magnification subscale is 12 and the maximum possible score for helplessness is 24. The mean total PCS score was 12 (SD=10.38), which corresponds to the 31st percentile as given by literature (Sullivan et al., 1995). The mean rumination score was 5.5 (SD=4.35), corresponding to the 35th percentile. The mean helplessness score was 4.19 (SD=4.67), corresponding to the 30th percentile, and the mean magnification score was 2.33 (SD=2.44), corresponding to the 45th percentile. However, as **Table 5** shows, despite mean scores in the non-clinical range, some participants did endorse clinically elevated symptoms of pain catastrophizing. **Table 4** displays the differences in means between males and females for total PCS score and its subscales.

For the total PCS score, ultimately there were no statistically significant differences in the catastrophizing responses between males and females, as determined by one-way ANOVA analysis ($F(1,162)=0.387$, $p=0.5$). For the rumination score, there was no statistically significant difference between males and females ($F(1,162)=0.362$, $p=0.5$). For the helplessness score, there was no statistically significant difference between males and females ($F(1,162)=0.306$, $p=0.6$). Finally, for the magnification score, there was no statistically significant difference between males and females ($F(1,162)=0.263$, $p=0.6$).

Although the means for the catastrophizing scores fell within normal ranges, there were participants that endorsed clinically elevated catastrophizing. This was classified by scores that were at or above the 75th percentile published in Dr. Sullivan's manual (Sullivan et al., 1995). The 75th percentile for the total PCS score was a score of 30 or above, for the rumination subcategory was 11 or above, for the magnification subcategory was 5 or above, and for helplessness was 13 or above. From the 164 participants that completed the PCS measure, 20 (12.19%) participants endorsed clinically elevated rumination scores, 24 (14.63%) participants endorsed clinically elevated magnification scores and 13 (7.93%) participants endorsed clinically elevated helplessness scores. In regards to the total PCS score, 11 (6.71%) participants endorsed clinically elevated catastrophizing overall. **Table 5** displays the number of participants who endorsed clinically elevated catastrophizing scores, as well as the distribution between the sexes.

Table 4: Pain Catastrophizing Scale Responses. The responses were compiled and analyzed alongside the published percentiles to which they correspond according to Dr. Sullivan's manual (Sullivan et al., 1995).

	N	Minimum	Maximum	Mean(SD)	Published Percentile
PCS total	164	.00	52.00	12.07(10.38)	31
Rumination	164	.00	16.00	5.54(4.35)	35
Magnification	164	.00	12.00	2.34(2.44)	45
Helplessness	164	.00	24.00	4.20(4.67)	30
Valid N	164				

Table 5: Clinically Elevated Catastrophizing. Despite clinically normal means from the catastrophizing scores, there was a subset of participants whose scores correlated to or above the 75th percentile published by Dr. Sullivan.

	Rumination	Magnification	Helplessness	PCS Total
Female	15	16	9	9
Male	5	8	4	2
Total N	20	24	13	11
Percent of 164 Participants	12	15	8	7

Sensory Processing

Table 6 displays each test, and the exact numerical values associated with the thresholds of the participants, as well as the degree of statistical significance. The LTDT test on the upper and lower quadrants, the SPDT test on the upper and lower quadrants, the cold threshold test on the upper and lower quadrants, and the hot threshold test on the upper quadrants showed no statistically significant difference between males and females. On the other hand, there were several tests that exhibited significant differences between males and females. For the SPP test on the upper quadrants, males exhibited a higher mean threshold for experiencing pressure-induced discomfort than the mean threshold for females ($F(1,182)=55.91$, $p<.001$). Males also showed a higher mean threshold compared to females for pressure-induced discomfort on the lower abdominal quadrants ($F(1,182)=52.03$, $p<.001$).

For the thermal tests in the sensory protocol, females detected the thermode as "cool" at a higher mean temperature compared to males on the upper ($F(1,176=24.15$, $p<.001$) and lower ($F(1,174)=20.49$, $p<.001$) quadrants, indicating that females were more sensitive to cool temperatures on their abdomen compared to males. Similarly, females additionally detected a "warm" temperature at a lower mean temperature compared to males on the upper ($F(1,174)=25.49$, $p<.001$) and lower ($F(1,174)=20.72$, $p<.001$)) quadrants, again indicating that females were more sensitive to warm temperatures compared to males. While the cold threshold tests on both upper and lower

quadrants, and heat threshold test on the upper quadrants displayed no statistically significant difference between males and females, males had a significantly higher temperature threshold compared to females on the lower quadrants when assessing heat pain thresholds ($F(1,173)=4.42$, $p<.05$), indicating that females were more sensitive to heat pain in the lower abdominal quadrants compared to males.

Table 6: Sensory Processing Protocol. Each step of the sensory protocol was analyzed via one-way ANOVA against sex. (*= p<0.5, **= p<0.05, ***= p<0.01)

	Male				Female					
Test	N	Mean(SD)	Minimum	Maximum	N	Mean(SD)	Minimum	Maximum	df	F
LTDT upper (g)	14	0.15(0.21)	0.02	0.80	87	0.48(1.42)	0.01	13.01	100	0.796
LTDT lower (g)	63	0.27(0.53)	0.01	4.00	123	2.82(27.02)	0.01	300.00	185	0.56
SPDT upper (g)	63	79.51(121.40)	0.12	300.00	123	89.17(125.91)	0.21	300.00	185	0.251
SPDT lower (g)	63	83.60(124.64)	0.06	300.00	123	91.80(126.94)	0.24	300.00	185	0.176
SPP upper (lbf)	61	35.94(18.71)	3.30	97.47	123	19.19(11.52)	2.28	90.00	183	55.91***
SPP lower (lbf)	61	35.72(18.66)	4.30	88.33	123	19.37(11.88)	1.93	90.00	183	52.03***
Cool detection upper (°C)	61	27.78(2.36)	20.04	31.18	117	29.38(1.90)	15.54	31.67	177	24.15***
Cool detection lower (°C)	61	27.30(2.61)	20.14	31.34	115	28.99(2.21)	20.51	31.25	175	20.49***
Warm detection upper (°C)	61	37.00(2.22)	33.94	43.09	117	35.60(1.47)	33.65	41.06	177	25.49***
Warm detection lower (°C)	61	37.21(2.57)	33.41	44.75	115	35.70(1.79)	33.39	44.34	175	20.72***
Cold threshold upper (°C)	61	16.46(9.66)	-0.02	28.02	117	24.26(76.38)	0.00	36.03	177	0.63
Cold threshold lower (°C)	61	16.90(9.55)	0.00	29.33	115	16.80(10.40)	0.00	31.03	175	0.00
Hot threshold upper (°C)	61	44.75(3.65)	35.87	54.00	117	44.31(8.04)	35.17	104.85	177	.17
Hot threshold lower (°C)	60	44.81(3.00)	38.23	51.00	115	43.62(3.84)	34.70	50.47	174	4.42*

DISCUSSION

The purpose of this study was to supplement the lack of literature on abdominally-specific pain sensitivity. As mentioned previously, there is a significant amount of literature on pain mechanisms and responses, especially in the context of chronic pain conditions. What the existing literature neglects, however, is the importance of examining the abdomen separately in pain research and practice. This study's use of the German Research Network's QST protocol on the abdomen satisfies its developer's call for more regionally-specific sensory testing. Ultimately, the findings of this study validated much of the predictions made in current literature about the increased likelihood of females being more sensitive to pain stimuli than males. However, these results revealed discrepancies in the types of stimuli to which females were more sensitive. Additionally, the results in catastrophizing countered the suggestions of the literature.

Catastrophizing

Based on the results from the scoring of the PCS responses, and the one-way ANOVA analyses as they correlate to sex, there was no significant relationship between sex and pain catastrophizing. This held true throughout each of the subscales related to pain catastrophizing- rumination, helplessness and magnification. The majority of research published has been on chronic pain samples, which has consistently found that

females are more likely to report elevated catastrophizing. As aforementioned, these higher levels of catastrophizing often lead to longer durations of chronic pain and a higher severity of pain (Trost et al., 2015).

Although a small subset of this sample, with more women than men, endorsed clinically elevated pain catastrophizing, it was only a small percentage and the mean scores for the total score as well as the subscales were all within a normal range. Having this result negates the generalization that has been made in prevailing literature that "women worry more about pain" and these results indicate that the sex differences found in abdominal pain sensitivity are likely not attributed to excessive worry or psychological distress. This contributes to a larger conversation about the way females have been treated in clinical settings. Female stereotypes generally contribute to the idea that a woman who presents with pain are wrote off as "hysterical" or "dramatic" (Micale, 1995). It is essential that the results of this study, one of only a few that measure catastrophizing in pain-free populations, are taken into consideration.

While the averaged results of the PCS scores did not represent clinically elevated catastrophizing in this population, it is important to note that there was a percentage of the participants who did endorse high levels of pain catastrophizing. Of the subset of participants who exhibited clinically elevated pain catastrophizing, the majority of them were female. It was a very small subset of the 164 participants who completed the catastrophizing measure; however, this was an unexpected result, as this study was conducted in a pain-free population. It would be interesting to look further into patterns

of catastrophizing in healthy populations, as much of the existing literature is exclusive to populations with either a history of chronic pain or those are currently experiencing pain.

Sensory Processing

The results of the sensory processing protocol were interesting, as certain tests indicated significant differences in the processing of pain stimuli between males and females, while others did not. Specifically, females were more sensitive in all abdominal quadrants to pressure pain, and cool and warm detection, and displayed more heat pain sensitivity in the lower abdominal quadrant compared to males. These could be possibly explained by the increased cutaneous nerve fiber density in females (Mowlavi et al., 2005). With a higher nerve density, it would make sense that female would be more sensitive to cutaneous stimuli. This does not explain, however, the lack of sex differences in mechanical touch stimuli. This would be an interesting area to explore in further research.

The minimum age of our participants was 12; thus, based on the trajectories of the development of chronic pain (**Figure 3**), the younger female participants of this study, although pain-free, were entering the stage of their development where the prevalence of chronic pain would peak. There could be a correlation between the young age of the participants and the sensitivity to abdominal stimuli, not only to the development of pain. It would be interesting to look further into the specific links between age and pain sensitivity.

Although it was not found that mechanical touch stimuli were processed differently between the sexes in this study, it was shown that males and females process thermal stimuli differently. A possible explanation of why females were more sensitive to the thermal sensory tests could be that a common treatment employed by females when experiencing menstrual pain is to use heat. In fact, warm compresses have been proven more effective than other methods, such as massage or aromatherapy, in reducing menstrual pain (Yunianingrum et al., 2018) (Almasith et al., 2017). The use of heat as a therapeutic measure decreases the likelihood of processing thermal stimuli as painful.

Strengths and Limitations

There were several strengths of this study. For one, this study supplements a significant gap in beginning to understand sex differences in abdominal pain sensitivity . As discussed, there is very little literature on abdominal QST, and as the German Research Network had suggested, it is important to conduct this protocol on all bodily regions, as each region processes pain stimuli differently (Rolke et al., 2006). Additionally, this study's participants represented an extremely diverse population, in several ways. Given the large sample size of 186 participants, there was a wide distribution of age and race, which is significantly more diverse than pain samples typically are (Tait & Chibnall, 2014). Another strength of this study is the consideration of the biopsychological factors contributing to pain. Given the psychological measures on

catastrophizing, we are able to get a more comprehensive idea of possible contributors to abdominal pain.

A possible limitation of this study is that we did not control for the day of the menstrual cycle on which females participated in the study. During the luteal phase of the menstrual cycle, females perceive more pain (Paller et al., 2009). Given that over 60% of this study's participants were biologically female, it is more than likely that a portion of the population was in this phase of their cycle. This could have posed a confounding factor affecting the results of the sensory processing procedure. It would be interesting to see how females respond to the stimuli during specific phases of their menstrual cycle. Additionally, although the QST protocol is, at its core, an objective procedure, we must consider the possible confounders posed by self-reporting. Our measures, although quantitative, are based on self-reported responses. There is no way to completely ensure accuracy in the responses.

Further Directions

This study provided preliminary data that could be analyzed to identify many relationships between biological sex and sensory processing. However, given the vast amount of demographic data that was collected, it would be interesting to examine how other demographic or lifestyle factors affect one's response to pain stimuli, such as race, substance use or BMI. Additionally, rather than only drawing conclusions about the thresholds of discomfort between males and females, we could look at the average pain

scores reported by the participants in response to each stimulus. In this way we could see if there was a significant difference in the intensity of discomfort experienced between males and females, although females exhibited lower thresholds for detection and discomfort.

As this study was conducted in a healthy population, we now have reference values for abdominal pain sensitivity. With this information, there is a breadth of possible comparisons to be drawn using this protocol. For example, we can now assess specific differences in pain processing between this healthy population and populations experiencing abdominal pain conditions such as IBS, functional abdominal pain and endometriosis. The QST protocol is an extremely helpful procedure, in that it allows us to quantitatively assess an individual's response to physical stimuli, rather than rely on subjective responses to pain.

Another interesting possibility for a future direction from this is in the field of transgender and nonbinary health. Our study's participants were all cisgender individuals. While we were focusing on biological links to differences in pain sensitivity and pain catastrophizing, it would be fascinating to see how transgender individuals who are possibly undergoing hormone treatments would respond to these sensory stimuli. It is clear that people who are transgender and nonbinary are greatly marginalized in current medical research, which neglects the world of discoveries to be made about the social and clinical treatment of this population.

Often times the conditions discussed in this paper, such as endometriosis and menstrual pain, are considered to be exclusive to one sex, and as a result there are often

life-threatening oversights in clinical settings. For example, as described in the New England Journal of Medicine, a 32-year-old transgender man arrived in the Emergency Department with severe abdominal pains, that would later be discovered as labor contractions. Because pregnancy is associated with females, this man did not have access to the necessary prenatal care, and unfortunately lost his child (Stroumsa et al., 2019). With the idea of "gendered diseases", we are limited in terms of the treatment of individuals who do not identify with the gender binary.

Clinical Implications

The implications of the results of this study could be important to the treatment and management of pain. These results reinforce the fact that extra consideration need to be taken when approaching a patient experiencing pain. Given the current climate surrounding opioid over-prescription and abuse, it is also an important consideration that clinicians should be wary of, especially given that males are consider more "at-risk" for opioid-related problems (Rogers et al., 2020). As males and females experience pain differently, so too should the management and treatment of the pain be different in clinical settings. Perhaps given the fact that females are more likely to seek non-medical treatment for pain (Greenspan et al., 2007), we should encourage males to follow suit rather than address their condition medicinally. When suggesting pain coping strategies to these patients, it should additionally be acknowledged that males and females resort to

different methods to moderate their pain, and that generalizing treatment for all patients may be detrimental to their pain outcomes (Keogh & Eccleston, 2006).

CONCLUSION

Hopefully, the results of this study will encourage clinicians to use a more individualized approach to their patients who are experiencing pain. There is a complex network of factors that contribute to one's development of chronic pain, which is subsequently manifested differently in every individual. Specifically for those patients experiencing abdominal pain, it should be acknowledged that biological males and females will respond to pain stimuli differently, as confirmed by this sensory protocol. With more inclusive research, we can hopefully gain a more comprehensive idea of how to better diagnose and treat abdominal pain.

REFERENCES

Almasith, Y. K., Yunita, F. A., & Yunita, A. E. N. (2017). The Difference of Menstural Pain Reduction between Warm Compress and Back Massage. *Journal of Health Science and Prevention*, *1*(2), 79–84. https://doi.org/10.29080/jhsp.v1i2.7

Arendt-Nielsen, L., Bajaj, P., & Drewes, A. M. (2004). Visceral pain: Gender differences in response to experimental and clinical pain. *European Journal of Pain*, *8*(5), 465–472. https://doi.org/10.1016/j.ejpain.2004.03.001

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: A brief review of clinical and experimental findings. *BJA: British Journal of Anaesthesia*, *111*(1), 52–58. https://doi.org/10.1093/bja/aet127

Chiantera, V., Abesadze, E., & Mechsner, S. (2017). How to Understand the Complexity of Endometriosis-Related Pain: *Journal of Endometriosis and Pelvic Pain Disorders*. https://doi.org/10.5301/je.5000271

de Leeuw, R., Albuquerque, R. J. C., Andersen, A. H., & Carlson, C. R. (2006). Influence of Estrogen on Brain Activation During Stimulation With Painful Heat. *Journal of Oral and Maxillofacial Surgery*, *64*(2), 158–166. https://doi.org/10.1016/j.joms.2005.10.006

Dueñas, M., Ojeda, B., Salazar, A., Mico, J. A., & Failde, I. (2016). A review of chronic pain impact on patients, their social environment and the health care system. *Journal of Pain Research*, *9*, 457–467. https://doi.org/10.2147/JPR.S105892

Edwards, R. R., Haythornthwaite, J. A., Sullivan, M. J., & Fillingim, R. B. (2004). Catastrophizing as a mediator of sex differences in pain: Differential effects for daily pain versus laboratory-induced pain. *Pain*, *111*(3), 335–341. https://doi.org/10.1016/j.pain.2004.07.012

Fuentes, I. M., & Christianson, J. A. (2018). The Influence of Early Life Experience on Visceral Pain. *Frontiers in Systems Neuroscience*, *12*. https://doi.org/10.3389/fnsys.2018.00002

Greenspan, J. D., Craft, R. M., LeResche, L., Arendt-Nielsen, L., Berkley, K. J., Fillingim, R. B., Gold, M. S., Holdcroft, A., Lautenbacher, S., Mayer, E. A., Mogil, J. S., Murphy, A. Z., & Traub, R. J. (2007). Studying sex and gender differences in pain and analgesia: A consensus report. *Pain*, *132*(Suppl 1), S26–S45. https://doi.org/10.1016/j.pain.2007.10.014

Keogh, E., & Eccleston, C. (2006). Sex differences in adolescent chronic pain and pain-related coping. *PAIN*, *123*(3), 275–284. https://doi.org/10.1016/j.pain.2006.03.004

Kroenke, K., & Spitzer, R. L. (1998). Gender Differences in the Reporting of Physical and Somatoform Symptoms. *Psychosomatic Medicine*, *60*(2), 150.

Leslie, K., & Kasza, J. (2020). Sex and gender inclusion, analysis, and reporting in anaesthesia research. *British Journal of Anaesthesia*. https://doi.org/10.1016/j.bja.2019.12.003

McPeak, A. E., Allaire, C., Williams, C., Albert, A., Lisonkova, S., & Yong, P. J. (2018). Pain Catastrophizing and Pain Health-Related Quality-of-Life in Endometriosis. *The Clinical Journal of Pain*, *34*(4), 349–356. https://doi.org/10.1097/AJP.0000000000000539

MICALE, M. S. (1995). A SHORT "HISTORY" OF HYSTERIA. In *Approaching Hysteria* (pp. 19–30). Princeton University Press; JSTOR. https://doi.org/10.2307/j.ctv8pzbz5.5

Mittuniversitetet. (n.d.). Retrieved April 6, 2020, from https://www.miun.se/

Mowlavi, A., Cooney, D., Febus, L., Khosraviani, A., Wilhelmi, B., & Akers, G. (2005). Increased Cutaneous Nerve Fibers in Female Specimens. *Plastic and Reconstructive Surgery*, *116*(5), 1407–1410. https://doi.org/10.1097/01.prs.0000182339.83156.06

Nunnink, S., & Meana, M. (2007). Remembering the pain: Accuracy of pain recall in endometriosis. *Journal of Psychosomatic Obstetrics and Gynaecology*, *28*(4), 201–208. https://doi.org/10.1080/01674820701388781

Ofer, G. (n.d.). *TSA-II Operating Manual*. 61.

Paller, C. J., Campbell, C. M., Edwards, R. R., & Dobs, A. S. (2009). Sex-Based Differences in Pain Perception and Treatment. *Pain Medicine (Malden, Mass.)*, *10*(2), 289–299. https://doi.org/10.1111/j.1526-4637.2008.00558.x

Perquin, C. W., Hazebroek-Kampschreur, A. A. J. M., Hunfeld, J. A. M., Bohnen, A. M., van Suijlekom-Smit, L. W. A., Passchier, J., & van der Wouden, J. C. (2000). Pain in children and adolescents: A common experience. *Pain*, *87*(1), 51–58. https://doi.org/10.1016/S0304-3959(00)00269-4

Rogers, A. H., Manning, K., Garey, L., Smit, T., & Zvolensky, M. J. (2020). Sex differences in the relationship between anxiety sensitivity and opioid misuse among adults with chronic pain. *Addictive Behaviors*, *102*, 106156. https://doi.org/10.1016/j.addbeh.2019.106156

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R.-D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Rolko, C., Schaub, C., … Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *PAIN*, *123*(3), 231–243. https://doi.org/10.1016/j.pain.2006.01.041

Rollman, G. B., & Lautenbacher, S. (2001). Sex Differences in Musculoskeletal Pain. *The Clinical Journal of Pain*, *17*(1), 20–24.

Sherwin, L. B., Leary, E., & Henderson, W. A. (2017). The association of catastrophizing with quality-of-life outcomes in patients with irritable bowel syndrome. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *26*(8), 2161–2170. https://doi.org/10.1007/s11136-017-1554-0

Stroumsa, D., Roberts, E. F. S., Kinnear, H., & Harris, L. H. (2019). The Power and Limits of Classification—A 32-Year-Old Man with Abdominal Pain. *New England Journal of Medicine*, *380*(20), 1885–1888. https://doi.org/10.1056/NEJMp1811491

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7*(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Suso-Ribera, C., García-Palacios, A., Botella, C., & Ribera-Canudas, M. V. (2017). Pain Catastrophizing and Its Relationship with Health Outcomes: Does Pain Intensity Matter? *Pain Research & Management*, *2017*. https://doi.org/10.1155/2017/9762864

Tait, R. C., & Chibnall, J. T. (2014). Racial/ethnic disparities in the assessment and treatment of pain: Psychosocial perspectives. *American Psychologist*, *69*(2), 131–141. https://doi.org/10.1037/a0035204

Thompson, W. G., Longstreth, G. F., Drossman, D. A., Heaton, K. W., Irvine, E. J., & Müller-Lissner, S. A. (1999). Functional bowel disorders and functional abdominal pain. *Gut*, *45*(suppl 2), II43–II47. https://doi.org/10.1136/gut.45.2008.ii43

Tolin, D. F., & Foa, E. B. (2008). Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychological Trauma: Theory, Research, Practice, and Policy*, *S*(1), 37–85. https://doi.org/10.1037/1942-9681.S.1.37

Traub, R. J., & Ji, Y. (2013). Sex differences and hormonal modulation of deep tissue pain. *Frontiers in Neuroendocrinology*, *34*(4), 350–366. https://doi.org/10.1016/j.yfrne.2013.07.002

Trost, Z., Strachan, E., Sullivan, M., Vervoort, T., Avery, A. R., & Afari, N. (2015). Heritability of pain catastrophizing and associations with experimental pain outcomes: A twin study. *Pain*, *156*(3), 514–520. https://doi.org/10.1097/01.j.pain.0000460326.02891.fc

Unruh, A. (1996). Gender variations in clinical pain experience. *Pain*, *65*(2–3), 123–167. https://doi.org/10.1016/0304-3959(95)00214-6

van Hecke, O., Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology – where do lifestyle factors fit in? *British Journal of Pain*, *7*(4), 209–217. https://doi.org/10.1177/2049463713493264

Yunianingrum, E., Widyastuti, Y., & Margono, M. (2018). The effect of warm compress and aromatherapy lavender to decreasing pain on primary dysmenorrhea. *Jurnal Kesehatan Ibu Dan Anak*, *12*(1), 40–49.

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