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Nature, Nurture, or Both? Study of sex and gender and their effects on pain

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Abstract

As a pain researcher, in order to have a better understanding of pain, we should adopt a multidimensional view, such as the biopsychosocial (BPS) model and consider physical, psychological, and social elements altogether. The studies in this dissertation are part of the bigger project of SYMBIOME in which the aim is to help to create and develop a prognostic clinical phenotype in people post musculoskeletal (MSK) trauma. Chapter 2 presents a Confirmatory Factor Analysis (CFA) in order to assess the structural validity of the first section of the new Gender Pain and Expectation Scale (GPES). Our analysis indicated a 3-factor structure "Relationship-oriented," "Emotive" and "Goal-oriented". Its construct validity was also assessed. The subsequent study, chapter 3, explores the roles of sex-at-birth, GPES subscales and their interactions in explaining the variability of Brief Pain Inventory (BPI) Severity and Interference scores. It showed no sex differences in scores of BPI Pain Severity and BPI Pain Interference. GPES Relationship-oriented had a significant association with BPI pain severity (r=0.20) while GPES Emotive had a significant correlation with BPI Interference (r=0.24). Also, hierarchical multivariate linear regression suggested that GPES Emotive could partially explain the variances in pain-related interference. Chapter 4 presents correlations between sex-at-birth, hormones (Progesterone, DHEA-S, Estradiol, and Testosterone), GPES subscales and BPI scores. Also, as our second goal of this chapter, potential pathways between these variables have been tested through structural equation modelling. It has been shown that GPES Relationship-oriented had a significant correlation with progesterone (r=-0.21) and DHEA-S (r=-0.33), and GPES Emotive had a significant correlation with the DHEA-S (r=-0.20). The GPES Goal-oriented had a significant association with estradiol (r=-0.20). Our findings suggest that gender-related interpersonal-expressive characteristics could have mediator roles in relationships between sex-at-birth and pain, and also between the hormones and BPI pain ratings.

Keywords

Pain, Musculoskeletal, Trauma, Sex, Gender, Hormones.

Summary for Lay Audience

Pain is a message, a beautifully designed communication between our cells and our brains. Pain is also a unique feeling influenced by different factors. Accordingly, meeting the needs of people suffering from pain requires access to different types of pain management that come with a profound social and financial burden. The most common treatment for pain in the world and especially in North America has been opioid prescription. Canada is the world's 2nd-highest per capita user of opioids. It is currently estimated that pain costs Canadians annually about 60 billion dollars. Gender bias is one of the pathways by which inequalities in pain management adversely affect men's and women's health. To study pain effectively, we must consider psychosocial, biological and cultural factors. One area that remains understudied is the differences in pain experience and reporting between men and women. A better understanding of the effects of sex and gender on pain reporting and recovery is a critical step in this direction, but the mechanisms to explain this difference remain unknown. Are women more culturally conditioned to report pain while men are conditioned to suppress it? Or are there biological differences that influence the way pain is experienced? While sex-based research has recently increased especially in animals, the topic of socially constructed gender roles and how they interact with biological sex differences in humans remains underexplored. I am proposing a new model to look at both gender and biological variables together. I will look at the links between sex, hormones, gender-related characteristics, and pain reports. I expect these results will lead to encouraging further investigating for better and more approaches to sex-and gender-based pain research and management. This comprehensive approach could represent a new direction in the field of pain and recovery that could change the way that pain is managed and help curb the opioid crisis.

Co-Authorship Statement

The three studies included in this dissertation were co-designed, co-conceptualized, analyzed, co-interpreted, and written by Maryam Ghodrati. Dr. David Walton had provided a precious and invaluable collaboration and guidance for this dissertation. Dr. Joy MacDermid made a substantial contribution in study design, planning, data collection and provided valuable feedback on interpretation of results and critically reviewed the manuscripts. Dr. Paul Tremblay had a valuable contribution and provided pivotal feedback regarding the study design, structural equation modelling, interpretation of results and review and revision of the manuscript of Chapter 4 and critically reviewed provided valuable feedback on the other chapters. Dr. Joshua Lee was provided guidance for hormone analysis, and Shannon Seney has done the hormone assessment. The different datasets that were used in this study were collected by Dr. Joshua Lee, Paul Phares, and Ryan Power, and with help of Helen Phan; Mike Lukacs; and Dr. Joy MacDermid.

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Dedication

To my loving parents, I cannot thank you both enough for your constant love, sacrifices, the strength you gave me to chase my dreams and your encouragement to constantly seek to challenge myself and make a better version of myself each and every day.

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Chapter 1

1 General introduction and thesis outline

1.1. Preamble

The focus of this dissertation is to explore the biopsychosocial variables that could explain the complexities and variabilities of individuals in experiencing and/or expressing pain after a non-catastrophic musculoskeletal (MSK) trauma. We planned to concurrently evaluate a range of psychosocial and biological factors in a series of three studies. These exploratory studies lay a foundation for researchers and clinicians to consider both sex- and gender-based variables when dealing with patients' pain while leading to more informed research questions and designs. In the following, the necessary background information for a better understanding of the subsequent chapters is provided.

1.2. Pain definition

The phenomenon of pain is complex and multidimensional. Although it is now well recognized that particular pain receptors exist in different tissues, along with the specific anatomical pathways for pain, evidence from functional magnetic resonance imaging show that, during the transition phase of acute pain to a chronic state, the somatosensory neural circuitry shifts to the more emotional circuitry and becomes more centralized.[1] Thus, does pain only have a sensation base, or does it also have an emotion base in the brain? A possible answer could be found in the recently revised definition of pain by the International Association for the Study of Pain (IASP), "pain is 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' that people learn through life experiences."[2]

Pain represents a significant universal health concern with a considerable personal, emotional, societal, and economic burden.[3–6] The challenges of pain are evident in two

competing public health crises in Canada: an epidemic of chronic pain affecting an estimated 1 in 5 adults,[7] and a crisis of opioid addiction driven largely by a desire to help those who are suffering from pain.[8]

1.3. A Biopsychosocial approach

Historically, scholars, philosophers, and empiricists have discussed and debated the nature of pain and different definitions and explanations have been given as to what the nature of pain is, and based on these definitions, pain has been dealt with in various ways.[9–12] It was not until the 20th century when an integrative model, the Gate Control theory of pain was proposed,[12–14] and that has enjoyed widespread acceptance as a unifying theory of pain. The Gate Control theory of pain recognized the integration of the critical role of psychological factors and cognitive processes within the nervous system in the pain experience. As suggested in this model, other stimuli (other nerve fibres' feedback) could modify messages like pain and affect their interpretation in the brain as the gate intensifies, reduces, or blocks them and the modifiers that open and close the gate are introduced as negative and positive thoughts or emotions, respectively.[15]

The gate control theory is consistent with Engel's integrated conceptual framework of the biopsychosocial (BPS) model.[16] According to the BPS model, multiple intra- and inter-individual variabilities sculpt the experience of pain. These include biological, psychological, and social factors that interact with each other to greater or lesser extents to shape experiences and reports of pain.[17,18] Accordingly, it has been proposed that pain experience and reporting may be influenced by genetics, prior life experiences, socioeconomic status, or other biopsychosocial influences.[19,20] In this light, some research on sex-related differences in pain has been generated in recent decades.[21–25]

Empirical evidence exists to suggest that biological factors, including hormones, genetics, blood pressure, brain structure and function, and pain-relevant peripheral neuroanatomy,[23,26–28] likely contribute to explaining sex differences in pain (perception, reporting, coping and treatment).[29–32] For example, it has been found that average nerve fibre density is double in

women compared to men.[33,34] Also, some evidence has reported differences in pain sensitivity in women across different stages of the menstrual cycle.[35,36] However, due to variations in research methodologies, the observed differences are varied and inconclusive.

1.4.   Sex and Gender in pain research

To date, the focus of much of the research on sex-related differences in pain has been devoted to discovering biological determinants. Whereas the psychosocial domains of the BPS model of pain have received less attention in the existing literature. Social agents should receive more attention, since there is a discourse of social impacts on different pain experiences, consciously or unconsciously.[37] Accordingly, past history of pain, early-life exposure to stressful environments, gender-specific expectations, and socio-cultural norms, appear to be a significant source of pain-related variability between the sexes.[21,25,38–41]

For example, regarding sociocultural models, Robinson and colleagues investigated the Gender Role Expectations of Pain questionnaire (GREP) and found that both men and women tended to indicate a belief that men were less likely to report pain compared to women.[42] However, in another study, less willingness to report pain was reported by both men and women regarding the viewpoints of their own sex category.[39] Also, the different social milieus for individuals in research and clinical settings likely impact men and women differently. For instance, studies suggesting that manipulations of gender-related expectations could influence the reporting of sex differences in pain responses, including the rating, tolerance, and threshold.[31,32,43] As mentioned by biologist Anne Fausto-Sterling, "Our bodies physically imbibe culture"(p. 1495).[44]

Culture-based norms limit perception of human capabilities,[45] affect health care delivery and are reflected in research, patients and clinicians.[46] However, much current knowledge tends to stop there. Considerable research indicates women and men are treated differently and that a gender bias appears to exist, but what aspects of gender have the greatest influence on care and outcomes is essentially unknown.[47–50] As gender equality in health care is coming to bear

on people in pain, it is far past due that we reassess the way gender as a socially-constructed trait is conceptualized from a healthcare perspective.

Accordingly, there has been a lack of attention to 'gender' as a health determinant. However, gender could influence how health is produced and maintained (e.g. illness vulnerabilities and quality of care).[51,52] In this line, some government and health granting agencies (e.g. the Canadian Institutes of Health Research (CIHR)) now require the inclusion of sex and gender variables and analysis in research.[53] Despite this, not all researchers in the field acknowledge the importance of gender as a key health determinant.[51] The complexities of gender studies in pain research partly stem from the misunderstandings of the underlying principles of this field. Blurred vision in distinguishing between the two terms "sex" and "gender" has led to interchangeable use in different contexts, especially in research, but they do not share the same meaning. However, it should be considered that some languages might not even have separate terms for sex and gender.

The term "gender" has not always been available. While sex was assigned to explaining biological differences, the term gender evolved in research in the late 1970s as a way to avoid overgeneralizing men and women merely based on their sex.[54–56] The CIHR Institute of Gender and Health describes gender as "*the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it.*"[57] Accordingly, most current conceptualizations of gender describe the concept as a continuum on which a person could fall somewhere between exclusively "feminine" or exclusively "masculine" characteristics as prescribed by society.[48,55] In many cultures, feminine traits include more social bonding and communication, while stoicism and suppression of distress have traditionally been viewed as masculine traits.[58–60] These traditional views of femininity/masculinity may at least partly explain the consistent findings of differences in pain expression in both lab-based and clinical pain research.[61]

Bernardes et al., 2008, described how gender could be conceptualized in the pain field based on Doise's framework.[62] In this sense, we could view and probably analyze gender at different levels (Intra-personal, Situational, Positional, Ideological).In another study, Boerner et al., 2018, illustrated some gender-related dimensions of pain research, which include gender identity, gender expression, gender role orientation, gender ideology, and gender bias.[63] Such theories considering various levels of analysis, or dimensions of the gender concept in pain can be reflected in the emphasis on the complex construct of gender and the importance of a more manageable approach for its measurements, especially in the pain field. Despite the changes in gender roles, norms, and beliefs and the variety of them in different cultures, there is no advancement in related measurements.

Work in this field has been hampered by limited options for measurement of traditionally genderized traits and tools of questionable psychometric properties, also it has been argued that even some studies wrongly use "sex" as a proxy for determining gender.[46,64] While not all things that can be measured are important and not all things that are important can be measured, for those attempting to explore these phenomena through quantitative means, adequately valid and reliable measurement tools are needed.

1.5. Sex, gender and hormones roles in pain experiences

From a biological standpoint, one of the more recognizable yet under-studied differences between males and females are differences in relative contributions of key sex hormones (testosterone, progesterone, DHEA-S and estradiol) in pain experiences and/or expressions. The mechanisms to explain the effects of these differences on pain are unclear,[65] though they may function at either or both of the transcription level or in cellular signalling and propagation pathways that, collectively, influence the affinity of receptors, or sensitivity to noxious stimuli.[23] Sex hormones have shown some association with clinical and experimental pain in both human and animal studies.[48,66] Several studies support the involvement of estrogen and progesterone in the sensitivity threshold of women and these hormones appear to lower the pain threshold in animals.[67–70] Conversely, there is some evidence for the role of testosterone in pain modulation such as increased pain tolerance.[71–73]

In humans, some have pointed to the chronology of between-sex differences in pain sensitivity that tend to manifest around puberty as evidence that sex hormones are important influencers of pain.[74] However, the majority of existing studies of sex differences in pain have used the menstrual phase in women as a proxy for relative sex hormone concentration rather than measuring them directly.[28,36] Findings of the relationship between sex hormones and pain are not consistent and this does not only reflect the complex effect of hormones, but also methodologic variability.[75–79]

There is controversy about a hypothesis that individual differences in central pain modulation might be a sensitive index of future risk for chronic pain.[80–83] Thus, examining the possible involvement of sex hormones as one of the important biomarkers of chronic pain, and pain perception is helpful for a deeper understanding of pain while potentially pointing to novel sex-specific treatments.[73,84] Overall, we need to maintain this perspective that the complex phenomenon of pain exists in an equally complex individual, living in, again, a complex environment. Despite this, integration of sex and hormones as biological variables and gender as a social construct has been under-explored in explanatory models of pain and to date, and there have been very few attempts to explore these constructs in the same pain-focused research program.

1.6.   Thesis outline

In this dissertation, the initial findings of our three exploratory observational cross-sectional studies to investigate the role of sex and traditionally genderized traits on pain experience and expression are presented. While sex- or gender-based differences in pain expression have been documented, exploration of traditionally genderized traits on pain has been hampered by the lack of strong measurement tools. Thus, the aim of chapter 2 is to evaluate the structural validity of a 16-item 'Gender personality traits' subscale of a recently developed Gender Pain and Expectation Scale (GPES). In this chapter, ML(maximum likelihood)-based Confirmatory Factor Analysis (CFA) is carried out while considering the conceptual meaningfulness of subscales to evaluate the factor structure identified by these traits. Construct validity is explored using a *priori* hypotheses regarding anticipated mean

differences in scores between biological males and females. The aim of chapter 3 is to examine the role of self-reported sex-at-birth and self-rated interpersonal-expressive traits that might reflect gendered role expectations (captured by GPES), and their interactions in explaining the variability of pain ratings in people with acute MSK injuries. In this chapter, the associations between Brief Pain Inventory (BPI) and GPES subscale scores explored by Pearson correlations for the overall sample and also for the sample when disaggregated by sex. Also, a multiple linear regression was outlined to investigate the interaction of sex and gender traits in explaining the BPI scores. The aims of chapter 4 are: First, to explore potential correlations between steroid hormones (Progesterone, Estrogen, Estradiol, and DHEA-S), BPI pain scores, and GPES subscale scores post MSK trauma. The second aim is to explore the potential pathways among these and the mediator effects of gender-related interpersonal-expressive traits on the potential relationships of sex and hormones with BPI pain reports.

The overall aim of these studies is to provide a unique theoretical contribution to sex-gender pain theory by advancing understanding of the processes through which biopsychosocial meta-variables interact to affect the pain experience.

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Chapter 2

2 Exploring the domains of gender as measured by a new Gender, Pain and Expectations scale

(A version of this chapter has been published.[1])

2.1. Introduction

The phenomenon of pain is multidimensional and complex, representing an almost universal experience with a high personal, societal, and global burden.[2–5] Like any sensory and emotional experience, the experience and/or expression of pain is highly subjective and influenced by multiple interacting factors. To better understand it, exploration of the experience of pain requires consideration of psychological, biological and cultural variables.[6–8] There is a growing push for deep phenotyping of people in pain that will lead to more personalized treatment approaches when multiple aspects of the person are considered concurrently.[9]

One arguably under-studied phenomenon in both clinical and experimental pain research on humans is growing evidence of differences in the experience or expression of pain between men and women.[7,10–14] Where differences have been identified, many hypotheses have been proposed, ranging from cellular mechanisms that affect nociceptive processing[15] to culture-specific genderized social norms and roles such as stoicism and expressiveness.[15,16] Often aligned with traditional views of masculinity or femininity, dominant cultural roles have been proposed as at least partial explanations for the findings of differences in pain expression.[7,16–22]

Sex and gender are commonly but erroneously used interchangeably in much of pain research.[23] Sex assigned at birth does not infer gender; sex is defined as the physiological and biological characteristics of males and females such as differences in the genetic complement of chromosomes, hormones and sex organs.[24,25] While sex has been traditionally considered,

perhaps over-simplistically, as a binary factor (male/female), gender is a more complex construct that refers to the traits and qualities of a person in relation to culturally-determined norms including characteristic roles, interpersonal relationships, and expressive behaviours that can be conceptualized along a continuum.[24,26,27] The interpretation of gender in pain research should be considered an amalgam of social norms and individual values and preferences.[24] While gender is commonly described in terms of feminine and masculine traits, such conceptualizations seem too reductionistic. Feminist and queer scholars, in particular, acknowledge the non-binary nature of sex and gender[28,29] and encourage researchers to consider both sex and gender as fluid concepts rather than rigid dichotomies.[30] Butler (1999) and West & Zimmerman (2009) are amongst those who encourage a reconceptualization of gender not as a stable adjective but as a verb of "doing" and ways of behaving or becoming.[31,32]

Consideration of sex and gender in health research is increasingly acknowledged as important, evidenced partly by the Sex and Gender Equity in Research (SAGER) guidelines.[33,34] A critical issue that has burdened research in quantitative pain science is a lack of sound measurement tools for assessing traditionally genderized traits.[25] While different scales intended to 'measure gender' have been developed such as the non-pain-specific Bem Sex Role Inventory (BSRI),[35] we are aware of very few examples of its use in pain research.[36,37] At 60 items the BSRI is long, and not all traits appear to be relevant to pain research.[37] Designed four decades ago, the items on the BSRI are rooted in the genderized beliefs, values, and roles of the 1970s' America that may hold less relevance in the 2020s. The more recent Gender Role and Expectations of Pain (GREP) scale is intended as a more pain-oriented gender scale[38] designed to capture self-assessment of role expectations and attributions of pain (sensitivity, endurance and willingness to report) in relation to how respondents think of 'typical' male or female behaviours. This requires respondents to have a reasonably accurate representation of how other people experience or react to pain, and also a fairly accurate understanding of how they themselves react in comparison. The psychometric properties of both BSRI and GREP scales have not been rigorously evaluated by current

measurement standards, and uptake in pain research appears to have been very limited to date.

In the interest of reducing the burden of capturing gender in pain research, the Gender, Pain and Expectations Scale (GPES) was developed to capture constructs included on both the BSRI and GREP.[39] Using a selected subset of items from both those existing scales, the GPES is a multi-section tool wherein each section is to be interpreted separately and has its own distinct measurement properties. "Genderized personality traits" is the first section of this scale and consists of 16 items drawn from the BSRI by researchers experienced in sex- and gender-based pain research. These were chosen for their expected alignment with more contemporary conceptualizations of genderized traits, in particular related to expressiveness and inter-personal behaviours. As it is intended to provide summative subscale scores, there are measurement properties (e.g. structural validity) that must be established before it can be endorsed as a sound alternative to the existing scales.

The purpose of this observational cross-sectional study was to explore the structure (factors) definable by a list of "traditionally genderized traits" under consideration for adoption as section one of the new GPES. Results were interpreted through a lens of genderized traits and qualities as the authors understood them with a particular focus on their use in pain research. Structural (factorial) validity was the priority, with concurrent known-groups validity used as a supporting evaluation.

2.2. Methods

2.2.1. Participants

Secondary data collected from a sample of participants in related prior studies were collapsed into a single database for this psychometric analysis. The data were drawn from studies which had institutional REB approval: the 'Systematic Merging of Biology, Mental Health and Environment' (SYMBIOME) study (clinicaltrials.gov ID number NCT02711085) comprised of working-age adults recently involved in non-catastrophic musculoskeletal

(MSK) traumas (e.g. falls, work, sports, or related injuries), and an independent existing database from healthy university-aged adults or practicing healthcare clinicians. Eligible participants in all studies were at least 18 years or older, did not have cancer, serious neuromuscular or other significant systemic diseases, and could read and understand (Grade 6) English. Among other study-specific questionnaires, consistent to both databases were participants completing the GPES and providing demographics including sex-at-birth (male, female, or other) and age. Forms were completed once by each participant.

2.2.2. GPES

The first section of the prototype GPES under study included 16 trait items that aligned with genderized roles or expectations drawn from the gendered traits literature.[39] These included 7 directly from the BSRI ("Independent", "Aggressive", "Gentle", "Leader", "Competitive", "Sensitive", "Decisive",) and 9 added by the tool designer as being aligned with both potentially genderized traits and ways of experiencing or behaving in the face of pain ("Emotional", "Confident", "Weak", "Tough", "Giving", "Accepting", "Determined", "Nurturing", "Patient").

Respondents ranked the degree to which each of the 16 traits represents how they see themselves using a 5-point magnitude-based scale: (1) "not at all like me", (2) "very little", (3) "somewhat", (4) "A lot", or (5) "Extremely like me". Additional data tools were collected but not used for the purposes of this analysis.

2.3. Analysis

2.3.1. Preliminary analysis: Data fidelity

We first identified missing data by separating the 16 items into two broad subscales based on their theoretical assignment towards either feminine or masculine traits (8 items per scale). Those with a single missing response per scale had that response replaced with the mean of the other 7 items.[40–42] Those with 2 or more missing responses (≥25% missing) had that subscale, for that respondent, removed from the analysis.

Floor or ceiling effects (>30% of the sample choosing either 'not at all' or 'extremely')[43] or those items with *any* response option selected by <10% of respondents, were identified and flagged. Decisions on how best to address these were made on an item-by-item basis.

Descriptive analyses (frequencies, means, skewness and kurtosis) were calculated for the demographic characteristics and GPES item response frequencies. Data were explored for normality using the Kolmogorov-Smirnov test, and skewness and kurtosis to inform the appropriate statistical test.

2.3.2. Construct validity: Confirmatory Factor Analysis

2.3.2.1. First Model: First-order measurement model

As the items under consideration were based on a traditionally genderized dichotomy of 'masculine' and 'feminine' traits, we started with a hypothesis that all 16 items would load on one of two latent constructs, 8 on each. To test this hypothesis a Confirmatory Factor Analysis (CFA) was conducted with a base model on which the 16 items were assigned to one of the two first-order latent variables (Factor 1: "Gentle," "Sensitive," "Emotional," "Weak," "Giving," "Accepting," "Nurturing," "Patient"; Factor 2: "Independent," "Aggressive," "Leader," "Competitive," "Decisive," "Confident," "Tough," "Determined"). Model fit of the ML(maximum likelihood)-based Confirmatory Factor Analysis (CFA) was evaluated using standard goodness-of-fit criteria including a non-significant chi-square test,[44,45] normed chi-square ($\chi 2/df$) less than 3,[46] and the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) as incremental fit indices where values above 0.90 were desirable.[4.]Root mean square error of approximation (RMSEA) was evaluated with values less than 0.08 indicating acceptable fit.[47–49] If the model fit was poor, communalities, residual (error) and modification indices were evaluated to identify items that were problematic (not fitting the constructs) or should have error terms correlated (indicating non-random error) and the models re-tested. This initial model was intended to provide an omnibus test of the degree to which all 16 traits could be adequately explained by two latent constructs and identify where shared variance may exist, but was not intended to be the final structure.

From here, an iterative process of item removal and model refinement was undertaken. This process was informed by both statistical (residuals, path coefficients, and communalities) and theoretical (consideration of alternative ways to conceptualize the items as interpersonal qualities) considerations through consensus between the co-authors (two females, one male (who consider themselves as cisgender) with different ethnocultural backgrounds). Different factorial structures were explored that included a four-factor first-order structure (relationship-oriented, emotive, goal-oriented, and confident), a four-factor second-order structure in which the 4 factors from the prior model were loaded onto two second-order constructs (masculinity, femininity), and finally a 3-factor first-order model in which the 'confident' construct was removed owing to poor statistical and conceptual fit (on further critical interpretation, confidence did not easily fit the intention of the tool). At each step, fit indicators, residuals, and communalities/covariance were explored with the intention of identifying the model that balanced statistical and conceptual meaningfulness for the intended purpose of use in pain research with parsimony to minimize respondent burden.

2.3.3. Validation step

After settling on the most appropriate factor structure, we explored construct validity of the new subscales by first creating *a priori* hypotheses based on the factors identified. As the original intent of both the GPES and the two prior subscales from which items were adapted was to explore traditionally genderized traits, self-reported sex-at-birth was used as a criterion standard against which to compare differences in subscale means. Mean scores on the new subscales were compared for differences between two levels of respondent sex-at-birth (male vs female) using an independent *t*-test or Mann Whitney U-test depending on the nature of the data. We hypothesized that self-identified males would score higher on any subscales indicating more aggressive or goal-oriented traits and females would score higher on those containing more expressive or relationship-oriented traits.

As the final model was unknown, the sample size was estimated for models of 2, 3, or 4 latent variables and 12 to 16 observed variables. Assuming a moderate effect size (r=0.3) and desiring 80% power to detect it, a sample of 200 participants was considered the minimum

acceptable.[50–52] Data analysis was carried out using the IBM® Statistical Package for Social Sciences (SPSS)® software, version 26.0 and IBM SPSS AMOS® Version 25 software (SPSS, Inc., Chicago, IL).

2.4. Results

2.4.1. Preliminary analysis: Data fidelity

After removing participants with >25% missing responses (n=12), the entire database consisted of 248 eligible participants (15 participants per item). **Table 1** provides the sample characteristics.

Frequencies of response options for each GPES trait are presented in **Table 2.** The lowest value ("not at all") option was selected <10% of the time in 14 of the 16 items and not selected at all in 3 items. On the other extreme, the highest value ("extremely") was selected by <10% of respondents on 7 of the 16 items. Factor analysis is impaired if not impossible when one response option has a frequency of zero, hence a decision needed to be made. Through team discussion informed by data and theory, the two lower options ("not at all" and "very little") were combined into 'very little' and the two higher options ("a lot" and "extremely") were combined to "a lot." Therefore, the response structure became 3 options for each item: 1= "very little", 2= "somewhat", and 3= "a lot" like me. This meant that the traits of 'aggressive' and 'weak' showed strong floor effects, but that effect was present even prior to collapsing the two lower response options. The traits of 'independent', 'accepting', 'giving' and 'determined' showed potential ceiling effects though less severe than those with floor effects. Consistent with the purpose of the tool and the researchers' positions on the value of such items, *aggressive* and *weak* were flagged for removal as, upon reflection and data distribution, both were deemed to be burdened by negative cultural stigma. All remaining items showed no strong evidence of skewness (non-significant Kolmogorov-Smirnov test) after collapsing response options. The correlation matrix of the 16 items is shown in **Table 3**.

2.4.2. Construct validity: Confirmatory Factor Analysis

The path diagram for the base model is shown in **Figure 1**. As expected, fit indicators suggested poor model fit to the data and therefore the model was rejected ($\chi 2$/df= 43.560/ 103; CFI=0.57; TLI=0.50; RMSEA=0.09).

Each of 'aggressive', 'weak', 'independent', 'accepting', and 'patient' showed either very large residuals, non-significant path coefficients with their assigned construct, or strong floor/ceiling effects. These were removed and the model retested, resulting in moderate fit improvement but still below acceptable thresholds.

The 4-factor first-order model showed an acceptable fit to the data, but the 4-factor second-order model did not (**Table 4**). In both models, the trait 'decisive' showed consistently high residuals and very low path coefficients (standardized β<0.30) regardless of the factor to which it was assigned. Again turning to theory, while 'decisive' and 'confident' appeared to both be informed by a latent construct of *confidence in decisions*, we could not achieve an acceptable model fit while loading those two items onto a single construct. The 'confident' item also loaded strongly onto one of the other latent constructs, hence through deliberation we removed 'decisive' and loaded the remaining 10 items onto 3 latent constructs that were subsequently termed 'Relationship-oriented' (nurturing, giving, and gentle), 'Emotive' (sensitive, emotional), and 'Goal-oriented' (determined, leader, competitive, tough, and confident). This model (shown in **Figure 2**) revealed good fit to the data ($\chi 2$/df=1.77; CFI=0.93; TLI=0.90; RMSEA=0.05, **Table 4**). Variance in the 'sensitive' item was fixed to zero to achieve adequate convergence with no substantive effect on any other path coefficient. The *Emotive* factor had a positive significant correlation with the *Relationship Oriented* factor (p<0.01), and a negative significant correlation with the *Goal-oriented* factor (p<0.01), supporting concurrent validity. The *Relationship-oriented* factor had no significant correlation with the *Goal-oriented* factor. This 10-item, 3-factor structure was deemed optimal in both statistical and theoretical terms and carried forward to the subsequent validation step.

2.4.3. Validation step

The sample was comprised of 85 self-identified biological males and 163 biological females. No participants reported a non-binary sexual identity. The data were adequately normal and of equal variance per Levene's test in both groups. An independent sample t-test revealed that mean scores on all subscales were statistically significant in the direction supported by theory. Results revealed that males scored significantly higher on the G*oal-oriented* subscale (t (246)=-3.05, P<0.01) while females scored significantly higher on the *Emotive* subscale (t (246)=4.74, P<0.01) and the R*elationship-oriented* subscale (t (246)=2.31, P=0.02) (**Table 5**). The clustered bar charts are presented in **Figure 3**.

2.5. Discussion

While the volume of sex-based research has increased, driven notably by recent advances in lab-based animal research, the socially constructed phenomena of gender roles or identities remain under-explored in pain research. While many authors have reported differences in pain expression between the sexes, other authors have reported conflicting evidence for a between-sex difference in pain sensitivity, pain endurance or threshold.[21,53–59] It is therefore unclear what mechanisms may be driving between-sex differences, what proportion of those differences are related more to gender than sex, and how, if at all, such findings should influence clinical decisions.

This study describes a rigorous analysis of 16 traits that have been traditionally associated with gender role expectations for use in a new Gender, Pain and Expectations Scale intended to facilitate research in this area. While all 16 traits may be of value, our analyses have revealed three subscales informed by 10 of those traits with factor structures that are in keeping with our theoretical understanding. We intentionally termed the two subscales *Traditionally* Feminine or Masculine as we align with other gender scholars who endorse a position that these constructs are not dichotomous, and may be unintentionally harmful. Indeed, other authors have found that traditionally "masculine" and "feminine" traits might be quite similar between men and women.[60] This may be due to a lack of sound assessment

tools for gender traits, or it may be the result of a shift in how gender has been conceived and defined over recent decades.[61] The shifting roles of women in North American society is arguably most noticeable, with epidemiological data showing clear upward trends in the numbers of women who work outside of the home, hold leadership positions, and delay childbearing until later in life.[62–64] Accordingly, some scholars have endorsed alternative nomenclature to unlink sex from gender, towards traits such as "Interpersonal Sensitivity", "Communion", "Expressiveness" or "Instrumentality" rather than *feminine* or *masculine*.[65–69]

The three subscales of 'Emotive', 'Relationship-oriented' and 'Goal-oriented' appear to congruent with the arguments of those more contemporary scholars, and hold theoretical value for exploring pain experience or expressiveness. We have intentionally used the phrase 'experience or expressiveness', as it is widely recognized that, as outside observers, it is impossible to separate the experience of the person in pain from their expressions of that pain.[70] As such, the evaluation of another person's pain is necessarily dependent on their willingness to express (or their emotiveness), their sense of connection (or relationship) with the observer, and their drive to overcome the experience of pain to achieve certain goals. The subscales of 'Emotive', 'Relationship-oriented' and 'Goal-oriented' should therefore hold meaning for those conducting sex- and gender-based pain research.

The "*Goal-oriented*" subscale includes tough, competitive, leader, confident and determined, traits that are likely associated with goal-oriented people that could be used to motivate others to action regardless of biological sex. "*Emotive*" includes sensitive and emotional, and "*Relationship-oriented*" includes nurturing, giving, and gentle, all of which are expected to be associated more with prosaically bonding with and supporting others. While this approach is supported by our independent samples t-tests that revealed statistically significant sex differences on the subscales, the absolute mean differences between sexes were small. Costa et al.[71] found that women were perceived as more nurturing than men and men more assertive, supporting this as a reasonable approach to 'known-groups' construct validity, but is admittedly an elementary one. By moving beyond conceptualizations of traits as either rigidly 'masculine' or 'feminine,' this framework allows a person to be *goal-oriented*, *emotive* and *relationship-oriented* all at the same time, and not inherently defined by sex.

While we believe this approach to be more rooted in current cultural values, it will likely also add complexity to sex- and gender-based pain research, though also add rigour as traditional dichotomies may be overly-reductionistic.

Many existing gender-based scales, whether for pain research or otherwise, have been adapted from Bem's study in 1974.[35] These include the Personal Attributes Questionnaire (PAQ)[72], Appropriate Pain Behaviour Questionnaire (APBQ)[73], GREP[38], Traditional Masculinity-Femininity Scale (TMF)[61], masculinity and femininity Adjective Checklist scales (ACL)[74], and PRF (Personality Research Form) ANDRO scale.[75] For example, Myers et al.[37] used the BSRI in an investigation of the influence of gender in interpreting the correlation of experimental pain and sex, and showed an association between noxious cold responses and masculinity-femininity but they opined that future work needed to build better explanations regarding sex- and gender-based pain perception, which would be very difficult with the original BSRI. Nayak et al. developed two distinct versions of the APBQ to find that, in U.S. and Indian cultures, expressing pain was considered more acceptable for women than for men.[73] Pool and colleagues used the Gender Group Identification Questionnaire and Gender Norms for Pain Tolerance Questionnaire to explore differences in pain tolerance between men and women and how those were explained by self-perceptions of gender.[76] They found higher pain tolerance in high-identifying men than high-identifying women and low-identifying men; they highlighted the role of social norms in pain reporting.[76] As a more pain-centric tool, Robinson and colleagues developed and tested the GREP scale. The GREP has been used in a number of studies in different cultures, and commonly reveals a relationship with experimental pain across multiple stimulus modalities[7,17–19,77] though evidence of its use in clinical pain samples is more difficult to find. We hope that the GPES, as a tool that combines self-perceived traits with beliefs and expectations of pain sensitivity, will offer a brief yet robust approach to capturing these important person- and social-level constructs.

Our findings revealed that several of the items, themselves a carefully chosen subset of the original BSRI traits, could not be reliably or confidently assigned to any single meaningful factor. Interestingly, it seems the field has seen this several times prior when using the BSRI;

a summary of findings from 23 factor analysis studies showed that the structure of the masculine and feminine subscales was not adequate to capture the complexity of these constructs.[78] Rose and colleagues suggested that the inherent meaning of the BSRI items is questionable, and may be better defined as instrumentality and expressiveness rather than the masculinity and femininity.[79] Frable[80], and Holt & Ellis[81] have both opined that the BSRI has been used widely without considering the appropriation of its conceptual framework for the hypotheses being studied. Others have suggested that masculinity and femininity are not simple constructs that can be conceptualized as ends of a single continuum but potentially interact in complex ways and are better suited to dedicated subscales.[82–84] The GPES seems to be a tool that could allow such complex interactions to be explored in new ways. This position will be strengthened as we explore associations between the subscales identified herein and clinical indicators of pain severity or interference. These are planned analyses for subsequent studies.

Limitations of the study include a smaller representation of males than females in our combined databases, and an inability to retest the revised scoring of the tool in an independent cohort. The homogeneous sampling design was not adopted in this study. While perhaps adding some statistical noise, a heterogeneous sample allows capture across a wide range of perspectives, and the arrival at a theoretically- and statistically-acceptable model despite the noise suggests our fit indicators are likely more conservative than would have been seen in a more homogenous sample. The over-representation of females is consistent with what is known both about the population of people reporting pain after trauma, and the composition of rehabilitation training programs at our university from which the second (non-clinical) cohort was largely drawn. Testing of the revised scoring of the tool in more diverse cultural groups and tests of measurement invariance across genders are logical next steps.

In light of the results of our study, the new GPES appears to be a promising general measure of personal traits that may be related to traditionally genderized factors. While the factor structure was supported with only 10 of the 16 items, we are not yet endorsing the removal of all other items because structural validity should not be conflated with importance, which has

yet to be fully explored. If the reliability and validity of the GPES hold up in future studies, it could be used as part of a comprehensive exploration of sex- and gender-based differences in clinical and experimental pain research in humans. However, through discussion, we have also highlighted that the traditional conceptualization of common traits as 'masculine' and 'feminine' is likely overly-simplistic and that researchers are encouraged to consider what the important domains of these constructs are that may influence things like pain experience, reporting, or endurance.

2.6.   References

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Table 1: Characteristics of the samples

	Healthy database (N= 136)	MSK trauma database (N= 112)	Total database
Sex (%Female)	66.9%	64.3%	65.7%
Mean age (SD)	30.6 (12.9)	43.7 (14.8)	35.5 (14.8)

Table 2: Descriptive Statistics for the items in the GPES

Items	Response options percent					Mean	Skewness	Kurtosis	Floor/ Ceiling effect
	Not at all	Very little	Somewhat	A lot	Extremely				
Independent	0.0	0.8	11.3	46.6	41.3	4.3	-0.6	-0.2	✗
Emotional	2.4	19.0	42.9	26.7	8.9	3.2	0.1	-0.3	
Aggressive	17.1	50.4	26.8	4.5	1.2	2.2	0.6	0.6	✗
Gentle	1.2	8.5	43.7	39.7	6.9	3.4	-0.2	0.2	
Confident	1.6	6.5	35.6	47.8	8.5	3.5	-0.5	0.6	
Weak	27.4	50.0	19.4	2.8	0.4	2.0	0.6	0.3	✗
Tough	2.0	13.4	43.5	32.5	8.5	3.3	-0.1	-0.1	
Leader	1.2	10.9	33.9	41.5	12.5	3.5	-0.3	-0.2	
Competitive	3.6	14.2	23.9	36.4	21.9	3.6	-0.5	-0.5	
Nurturing	0.4	9.7	32.3	37.9	19.8	3.6	-0.2	-0.6	
Accepting	0.0	4.0	26.6	48.8	20.6	3.8	-0.2	-0.4	✗
Giving	0.0	2.0	25.4	54.0	18.5	3.9	-0.2	-0.3	✗
Determined	0.4	1.2	15.3	52.4	30.6	4.1	-0.6	0.7	✗
Sensitive	1.2	9.8	35.8	39.4	13.8	3.6	-0.2	-0.2	
Decisive	5.3	19.4	40.5	29.1	5.7	3.1	-0.2	-0.3	
Patient	4.4	16.1	35.9	33.1	10.5	3.3	-0.2	-0.3	

Table 3: Pearson correlation matrix of the 16 items

	Independent	Emotional	Aggressive	Gentle	Confident	Weak	Tough	Giving	Accepting	Leader	Competitive	Determined	Nurturing	Sensitive	Decisive	Patient
Independent	1															
Emotional	-.17**	1														
Aggressive	-.07	.19**	1													
Gentle	.08	.15*	-.21**	1												
Confident	.05	-.18**	.07	-.11	1											
Weak	-.17**	.08	-.01	-.03	-.27**	1										
Tough	.11	-.07	.11	.04	.18**	-.09	1									
Giving	.14*	.13*	-.07	.33**	.05	-.16*	.12	1								
Accepting	.03	-.08	-.19**	.17**	.00	-.11	.08	.33**	1							
Leader	.18**	-.00	.15*	-.06	.26**	-.09	.22**	.05	.06	1						
Competitive	.042	-.05	.11	.05	.07	-.02	.19**	-.01	-.01	.32**	1					
Determined	.13*	-.01	.00	.05	.22**	-.26**	.25**	.12	.03	.24**	.28**	1				
Nurturing	.05	.24**	-.19**	.44**	-.07	-.06	-.02	.32**	.20**	-.01	-.11	.15*	1			
Sensitive	-.20**	.52**	-.02	.26**	-.15*	.00	-.11	.24**	.09	-.12	-.16**	-.08	.47**	1		
Decisive	.19**	-.13*	-.00	-.07	.19**	-.09	.08	.01	-.04	.07	-.04	.14*	.00	-.09	1	
Patient	.06	-.10	-.27**	.35**	-.01	-.09	-.03	.16**	.25**	-.03	.01	.01	.23**	.10	.22**	1

Table 4: Summary of fit indices for models of the GPES derived from confirmatory factor analysis

Model	$X^2(p)$	df	X^2/df	CFI	TLI	RMSEA
Model 1 (Two first-order factors)	343.56 (0.00)	103	3.33	0.57	0.50	0.09
Model 2 (Four first-order factors)	63.08 (0.00)	38	1.66	0.93	0.90	0.05
Model 3 (Four first-order factors, two second order factors)	123.79 (0.00)	43	2.87	0.78	0.71	0.08
Model 4 (Three first-order factors)	56.85 (0.00)	32	1.77	0.93	0.90	0.05

Table 5: Independent sample t-test for Model 4

		Sex	N	Mean	SD	t (df)	P-value
Model 4	Relationship-Oriented subscale	Female	163	7.69	1.41	2.31 (246)	0.02
		Male	85	7.27	1.33		
	Emotive subscale	Female	163	4.82	1.14	4.74 (246)	<0.01
		Male	85	4.07	1.28		
	Goal-Oriented subscale	Female	163	12.09	2.08	-3.05 (246)	<0.01
		Male	85	12.90	1.74		
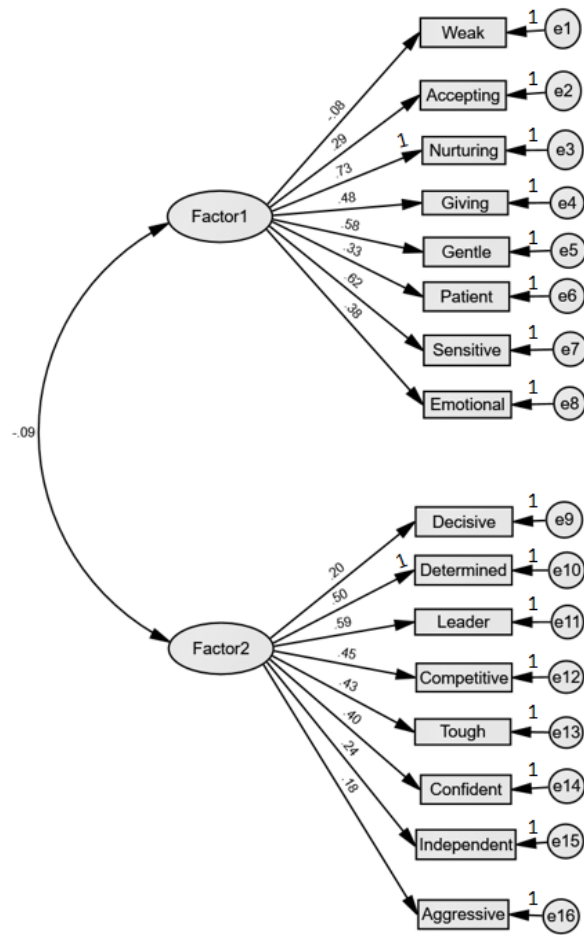
Figure 1. Model 1: Two first-order factors

Path diagram for the confirmatory factor analysis of Model 1 (Two first-order factors). Values are standardized path coefficients for items. The loading for each item is shown above the arrow. e = error
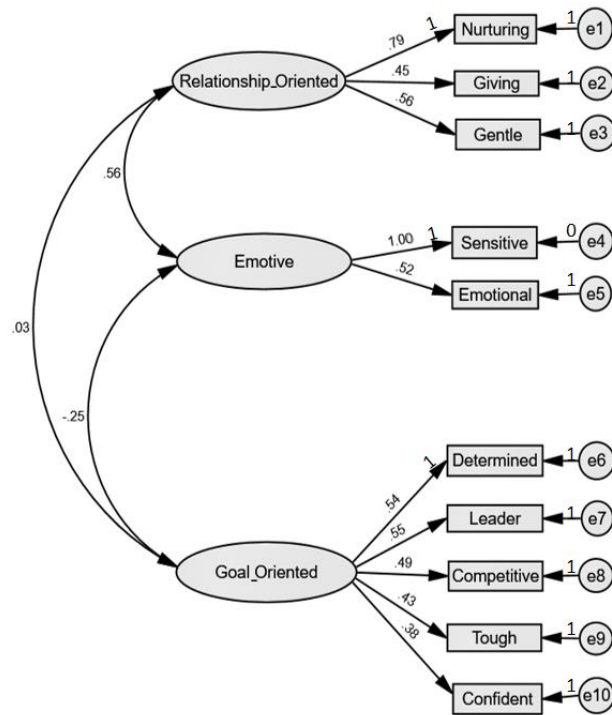
Figure 2. Model 4: Three first-order factors

Path diagram for the confirmatory factor analysis of Model 4 (Three first-order factors). Values are standardized path coefficients for items. The loading for each item is shown above the arrow. e = error
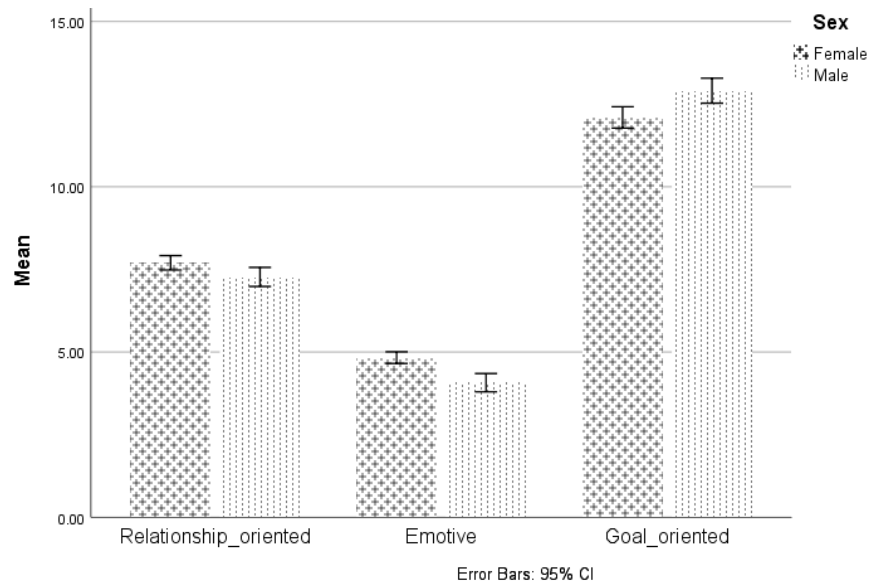
Figure 3. Compare mean scores of subscales in Male and Female

Compare mean scores of subscales (Relationship-oriented, Emotive, Goal-oriented) in Male and Female. Sex-based differences are significant ($p \leq 0.02$) for all 3 subscales. Error Bars: 95% Confidence Interval (CI).

Chapter 3

3 Exploring the contributions of sex and traditionally genderized interpersonal-expressive traits to variability in post-trauma pain ratings

3.1. Introduction

Sex-based differences have been studied in pain for several decades. For example, prior epidemiological research suggests that women are over-represented compared to men across most musculoskeletal (MSK) pain disorders.[1–4] Similarly, a large volume of laboratory and clinical research reports that females tend to report or exhibit higher pain sensitivity, intensity, and lower pain tolerance than males when exposed to similar pain stimuli.[5–8] Despite the evidence of sex-based differences in pain reporting or experience, there are enough inconsistent findings (e.g.[9,10]) to suggest that ascribing those differences to a simple dichotomy of biological sex is missing a larger biopsychosocial picture. Various factors from multiple domains of study likely have an interdependent influence on pain.[11] For example, from a biological perspective, empirical evidence exists to suggest the differences between males and females may be due to differences in how nociceptive signals are generated or transmitted. These could be functions of genotypes,[12–14] or the sensitivity of nociceptive/pain pathways due to relative sex hormone concentration.[7,15–17] However, even here, the differences have not been fully or consistently explained based on biology alone.

In human research, pain can only be known as far as individuals are willing and able to express it, thus it is filtered through cognitive and interpersonal states, experiences and values. Less explored are the potential gender-based psychological and social influences on pain experience or reporting. Per the recent revision of the definition of pain and accompanying notes, people learn the concept of pain through life experiences,[18] and those experiences appear to interact with personality factors.[19] Accordingly, it has been suggested

that person-level characteristics such as introversion or stoicism could act as vulnerability or resilience factors for pain.[19,20] For example, emotional vulnerability as measured by the Personal Attribute Questionnaire (PAQ) Scale,[21] explained sex differences in pain better than catastrophizing, and higher pain reporting/lower pain tolerance in women could be partly explained by differences in emotional vulnerability.[22]

Pain reports and behaviours are best conceptualized as communicative tools intended to translate personal experiences into interpersonal messages.[23] As with any behaviour, pain ratings might be shaped by social pressures regarding what is normal and acceptable for a given context or gender. While the traditional concepts of gender-based norms are being rapidly challenged and transformed in North America, there remain certain interpersonal qualities that are more common to one sex. For example, despite an increase in women in the workforce over the past 50 years, goal-directed leadership qualities are still more commonly ascribed to males.[24–27] Similarly, despite the increasing involvement of males in caregiver roles, interpersonal nurturing and emotive qualities remain more commonly ascribed to females.[24,28] Whether these traditionally genderized qualities can also explain some of the interindividual variances in pain and disability ratings is an area demanding further study. However, one of the major challenges in quantitative gender-based investigations of pain is the lack of clear consensus on gender constructs and appropriate tools to measure them. The Gender, Pain, and Expectations Scale (GPES) was designed to capture self-rated traditionally genderized traits and to assess gender-based perceptions of personal pain behaviours (pain sensitivity, endurance, reporting). A structural analysis of the genderized traits section of this scale led to the identification of three main subfactors: Relationship-oriented, Emotive, and Goal-oriented which represent areas where society has traditionally placed gendered expectations on women and men.[29]

We propose that the interaction between biological sex-at-birth and socially-constructed 'traditionally genderized traits' will predict the variance in pain ratings following recent MSK trauma more than either variable in isolation. As such, the aims of this observational cross-sectional study were to explore the extent that sex-at-birth and three traditionally

genderized traits of Relationship-oriented, Emotive, and Goal-oriented explain variance in pain ratings after acute MSK trauma, both in isolation and as an interaction effect.

3.2. Methods

3.2.1. Participants

Data were drawn from a prospective observational study of recovery following acute non-catastrophic MSK injury (the 'Systematic Merging of Biology, Mental Health and Environment' (SYMBIOME) study, clinicaltrials.gov ID number NCT02711085). Methods of screening and recruitment have been described previously.[30] In short, eligible participants were at least 18 years or older, presented to a local urgent care centre for reasons of pain or functional interference following MSK trauma within the prior 3 weeks, did not require inpatient admission or surgery, could read and understand conversational French or English, and did not have a systemic or chronic condition that would be expected to delay recovery such as cancer, neuromuscular disorders (e.g. stroke) or other significant systemic diseases.

At inception (<3 weeks from injury), all participants completed a set of questionnaires that included the Brief Pain Inventory (BPI), the GPES, and a study-specific demographics form including age and sex-at-birth (male, female, or other). Participants were followed for up to 12 months post-injury to establish recovery outcomes, though only the baseline data have been used for this analysis. The protocol was approved by the local institutional review board prior to initiating data collection.

3.2.2. Study tools

The BPI is an 11-item self-administered questionnaire with subscales to assess Pain Severity and Pain Interference with daily activity.[31] Each of the 11 items is scored on a 10 point numeric rating scale where 0=no interference/pain and 10=severe or complete interference/pain. A combination of 4 items form a *pain severity* subscale (worst, least, average, and current pain, mean /10), and 7 items form a *pain interference* subscale (general activity, normal work, walking ability, mood, sleep, relationships, and enjoyment of life,

sum/70). Higher scores on the pain severity subscale and pain interference subscale indicate worse pain and more significant functional interference, respectively. The BPI is one of the most widely used pain-related self-reported outcomes tools and has shown acceptable psychometric properties in a variety of conditions, including MSK disorders.[32,33]

The GPES was recently developed by our group as a new gender-focused pain-related expectations and beliefs scale. The first section of the GPES was used in this study; this section includes 16 items that were partly adapted from the Bem Sex Role Inventory (BSRI)[34] considered as traditionally genderized personality characteristics.[35] Participants rate themselves on each item according to how well that trait describes them ("1=not at all like me," "2=somewhat like me," and "3=extremely like me"). In a prior analysis of 198 responses to this section, three factors emerged: Relationship-oriented (nurturing, giving, and gentle, scored out of 9), Emotive (sensitive and emotional scored out of 6), and Goal-oriented (determined, leader, competitive, tough, and confident scored out of 15).[29] The GPES also includes a second independent section in which respondents rate their sensitivity to, endurance for, and willingness to report pain in comparison to others of their same sex, but only the genderized traits section of the tool has been used here.

3.3. Analysis

3.3.1. Pre-Analysis: descriptives and bivariate association

Participants' characteristics were evaluated descriptively (mean ± SD and range/proportion as appropriate). The assumptions of data normality were then examined prior to the association analysis, and the homogeneity of variances was assessed via Levene's test.[36] As the database represented a mix of extremities (arms or legs) and spinal (neck, upper, or low back) injuries, we first classed all participants according to the primary region of injury (extremity or spinal) and conducted independent t-tests for each of the primary variables to identify any systematic bias in scores. If a significant difference was found, the type of injury was retained in subsequent analyses. In the base analyses, the dependent variables (mean BPI Pain Severity and Interference scores) were evaluated for differences between sex-at-birth

(male vs. female) through independent samples t-test or Mann-Whitney U-test, dependent on data distribution. The associations between each of the three GPES subscales and the two dependent variables (BPI Pain Severity and Interference) were evaluated using Pearson's r. This analysis was also repeated for the sample when disaggregated by sex. As an exploratory analysis intended to inform and help interpret the subsequent multivariate analyses, no a *priori* hypotheses were posed and no adjustment of p-values was done.

3.3.2. Hierarchical multiple linear regression

Stepwise hierarchical multiple linear regression was used to explore the role of each of the three GPES subscales and sex-at-birth in predicting significant unique variance in BPI Pain Severity and BPI Pain Interference scores. Assumptions of regression (normality, multicollinearity, and homoscedasticity) were first evaluated. Normality was tested through the evaluation of histograms, skewness and kurtosis statistics. Multicollinearity was assessed through a correlation matrix (flagging any inter-item correlations>0.85) and the variance inflation factor (VIF) (flagging VIF>3.3).[37–39] Homoscedasticity was evaluated through inspection of a plot of predicted to residual estimates to ensure no systematic bias or pattern of residuals existed.[40,41]

Three models were created for each of the BPI Pain Severity and BPI Pain Interference scores by forcing all variables into the equation, meaning six total models: Model 1=Sex, Relationship-oriented score, Model 2=Sex, Goal-oriented score, and Model 3=Sex, Emotive score. The final model fit was explored through R2, adjusted R2 and P-value analysis. Finally, the hypothesis of sex ✕ GPES interaction effects was tested for each of the six models established in the previous step by adding the interaction term after including the two independent variables separately. The final model fit was explored through R^2, adjusted R^2 and P-value analysis.

3.3.3. Sample size

Sample size was estimated using the algorithms of Soper,[42] with 3 predictors and medium effect size ($f^2=0.15$) while accepting 5% alpha error and 20% beta error ($p<0.05$ and 80% power, respectively) the minimum sample was estimated at a minimum of 76 participants.

3.4. Results

3.4.1. Participant characteristics

A total of 130 participants were recruited in this cohort, of which 113 provided complete data for all of the studied variables. The characteristics of this sample are presented in **Table 6**. The sample was 60.2% female, with a mean age of 43.2 years. Average pain severity and interference ratings were 4.3/10 (SD=2.0) and 26.9/70 (SD=16.7), respectively.

3.4.2. Pre-Analysis

No significant differences in pain severity or interference were found between the two types of injury (spinal vs. extremity, $p>0.07$). Data were adequately normal with equal variances in pain between the sex groups. There were 45 males and 68 females, and an independent sample t-test revealed no differences in BPI Pain Severity or Interference between the sexes (**Table 7**).

3.4.3. Bivariate correlations

Table 8 contains correlations between GPES subscales and the BPI subscales, both as an overall sample and when stratified by sex. Significant associations were found between the GPES subscale 'Relationship-oriented' and BPI Pain Severity ($r=0.20$, $p<0.05$), and between GPES 'Emotive' subscale and BPI Pain Interference ($r=0.24$, $p<0.01$). In the sex-disaggregated analysis, both the GPES Relationship-oriented and GPES Emotive subscales showed a significant association, respectively, with BPI Pain Severity ($r=0.27$, $p<0.05$) and BPI Pain Interference ($r=0.33$, $p<0.01$) scores only in female participants. The GPES Goal-

oriented subscale was not associated with either BPI subscales, either as an aggregate sample or when disaggregated by sex. **Figure 4** and **Figure 5** provides a graphical representation of the associations between each of BPI Pain Severity and BPI Pain Interference with the independent variables for both males and females, respectively.

3.4.4.   Hierarchical multiple linear regression

Assumptions of regression (normality, linearity, homoscedasticity and outliers) were satisfied. No standardized residuals were beyond +/- 3.0 SD from the mean and VIF values were all<3.3. **Table 9** and **Table 10** provide the regression results. After partialling out the effects of sex-at-birth, only the GPES Emotive subscale significantly (P=0.01) predicted BPI Pain Interference, explaining a unique 5.9% of score variance. There were no significant sex ✖ GPES interactions found in any model tested.

3.5.   Discussion

The purpose of this study was to determine whether sex-at-birth and traditionally genderized traits as measured through self-ratings on the GPES subscales could significantly explain variance in scores on the popular BPI questionnaire in people with acute MSK injuries. Findings from this study are in accordance with current conceptualizations of the complexity of pain, however, our results indicated that only the Emotive subscale had a role in predicting the pain interference.

Prior studies have shown some consistencies with part of our results regarding no significant sex differences in either pain severity or pain interference.[43–45] Zhao and colleagues found no differences in BPI pain severity or interference between sexes in a sample of 377 participants with cancer-related pain.[43] Similarly, Chung and colleagues used a case-control design and found no significant sex differences in BPI Pain Severity, Interference and total scores from a survey of 2021 construction workers in different trades.[44] Also a systematic review by Racine et al., 2012, showed that most of the included studies that measured pain unpleasantness and intensity found no sex differences in many pain modalities.[10]

However, other studies have found higher scores in the BPI Pain Severity and BPI Pain Interference in women compared to men.[1,46] Several factors may account for this inconsistency, the most important ones could be the different populations studied, causes of pain, their dominant culture, and the measurement tools used. For instance, in comparison to our study of people with acute MSK injuries, in the study by Stubbs et al. (2010), primary care patients were enrolled who had chronic MSK pain (low back, hip, and knee pain) while half of them had clinical depression as well.[1] Ours is also a rare study in this field that focuses on a clinical sample with acute pain, while much of the work in this field has used either clinical samples with chronic pain or healthy samples and experimental pain protocols. It is possible that differences between the sexes in clinical samples manifest more clearly as pain persists.

Robinson et al. highlighted the critical role of gender-specific expectations in explaining sex differences in pain outcomes.[47] In their study, prior to performing the cold pressor task, pain-related gender-role expectations were manipulated by assigning participants to three groups with different instructional sets including no expectation, 30-second gender expectation ("The typical *man/woman* lasts 30 seconds in this task."), and 90-second gender expectation ("The typical *man/woman* lasts one minute and thirty seconds in this task."). They showed that sex differences in pain threshold, tolerance and ratings could be altered by manipulating the gender-specific tolerance expectations.[47]

The role of psychological and social factors in pain experiences has received considerable attention among pain researchers.[19,48,49] There is convincing evidence that both psychological and social factors such as cognitions and emotions, personality traits,[22,50] coping styles,[51–53] social, and gender-related norms should be taken into account in pain research. These factors have functioned as both predictors and mediators of pain-related variables.[54–57] In this field, gender has often been conflated with sex, though gender is a complex multidimensional construct. Theories from behavioural psychology, such as Social Learning Theory[58] and Cognitive-Developmental Theory[59] suggest that pain perception and expression could be at least partly influenced by gender socialization.[60] For instance, considering Social Learning Theory, some pain models shape at an early age by observing others' responses to pain, and

this could have an important role in understanding the complex pain behaviour patterns in adults.[61]

According to our results, participants who rated themselves higher on the GPES Relationship-oriented subscale (the combination of nurturing, giving, and gentle items) also reported greater pain severity. Participants who considered themselves more Emotive (the combination of sensitive and emotional items) reported greater pain-related interference. In sex-disaggregated analyses, the effect was only present in female participants. While mechanisms to explain these findings are purely speculative, it makes intuitive sense that those who see themselves as more emotive and relationship-oriented are also more likely to disclose their experiences of distress, and some research has also suggested that to be more emotionally vulnerable could also be associated with reporting higher pain levels and lower pain tolerance.[22,62] We found that emotive men were not as likely to report pain as emotive women in our study. A possible linkage could be that women are more likely to experience interpersonal adverse life events, that could manifest as greater emotional vulnerability. Another possible explanation could be that men also experience vulnerability, pain and distress but sometimes is combined with an unwillingness to talk about it or report it. For example, in a study by Thorn et al., (2004), the effects of personality and pain catastrophizing on pain tolerance and pain ratings were examined in 219 students by using the PAQ.[22] According to their results, the tendency to be described as emotionally vulnerable partially accounted for the sex-related differences recorded in pain responsivity and pain catastrophizing (women's scores were higher on both pain catastrophizing scale and cold pressor task VAS ratings).[22] However, another explanation for this finding could be the possibility that GPES alone is not able to account for the nuances of genderized interpersonal-expressive traits.

In the present study, we found no significant relationship between GPES Goal-oriented score (determined, leader, competitive, tough, and confident) and either of the BPI Pain Severity or Interference. To the best of our knowledge, there is no other research that has assessed the relationship between the personality characteristics that has been described in GPES Goal-oriented and pain reports. It is possible that the absence of a relationship between the GPES

Goal-oriented subscale and the BPI subscales is simply the presence of a social desirability bias (that people are more likely to rate themselves as goal-oriented), but if that was the case, we would expect such a bias to also mean lower pain severity ratings (people are less likely to complain of pain to others), and therefore a negative correlation should be present. We would also expect that if the phenomenon was social desirability, the results of the Relationship-oriented and Emotive analysis would also have yielded similar non-significant results. Given the current data, all we can say with confidence is that scores on the 5-item Goal-oriented subscale were not associated with pain severity or interference after MSK trauma in our sample. Further investigation is encouraged.

Counter to our a *priori* assumption that GPES subscales and sex variables would explain differences in BPI Pain Severity and Interference ratings, in the regression analyses, only the Emotive subscale was retained in predicting the pain interference. This was supported by our results of the correlations, as it showed the Emotive trait was positively associated with BPI Pain Interference following an acute MSK trauma. Although the results of the regression analyses were non-significant for other models, the results were suggestive of the potential prognostic factor of Relationship-oriented for pain severity (F Change=3.58, p=0.06), and considering the significant correlation between the Relationship-oriented scores and pain severity, it could be implying that this needs more exploration in the future and may be a function of low statistical power. Also, the differential effects of emotiveness between the sexes on pain reports from the disaggregated analyses could indicate a potential interaction effect despite the non-significant findings of regression analysis. Furthermore, as indicated by our results and given the complexity of psychosocial variables and pain experiences, we should not expect that only sex assigned at birth or GPES subscales would completely explain the variances in pain responsivity.

We acknowledge critiques of gender measurement scales such as the BSRI,[63–66] and this is why we have used the GPES scale because it does not rely on gendered norms. However, prior studies have used such scales with their traditional underlying assumptions and explored gender roles in pain. In a study examining the mediator roles of pain appraisal and gender role, assessed by the Extended Personal Attributes Questionnaire (EPAQ), 145

participants completed a cold pressor task.[57] Sanford et al. found only the femininity scale had a significant relationship with sex and pain tolerance time, but it was not a significant moderator of the relation between sex and pain tolerance. These authors also found that the interaction effect was not significant through simultaneously entering sex, femininity, and sex by feminine interaction as predictors in a similar approach to what we have used here. Their results suggested that psychosocial variables, including a combination of positive feminine gender roles (such as awareness of feelings and warmth) and threat appraisals of pain, play an important but complex role in partially mediating the sex and pain relationship.[57] Their results regarding masculinity are similar to what we found in the current study, in which the GPES Goal-oriented subscale (traditionally assumed as a masculine trait) was not significantly related to pain-related outcomes and did not function as a significant moderator contrary to the GPES Emotive. This might be due to the more pronounced relationship between the items of GPES Emotive subscale including sensitive and emotional with a higher tendency to report pain.

Another study assessed the effects of gender-role socialization indicated by BSRI and systolic blood pressure (SBP) of 104 participants in explaining the relationship between sex and pain reports from a cold pressor task.[17] Using a similar hierarchical regression, gender-role socialization was only a significant predictor of pain tolerance, while neither SBP nor gender explained sex differences in pain reports.[17] Differences in methodologies between our study and the aforementioned studies[17,57] may explain our different results. For instance, BSRI,[17] EPAQ,[57] or Gender Role Expectations of Pain (GREP)[67,68] scales were used to a set of regression analyses in the prior studies to explore the relationship of the sex, gender and pain outcomes, however, we used the GPES subscales. Besides using different pain and gender measurement tools, we used a sample drawn from a clinical post-trauma population, whereas most prior studies have used experimental pain stimuli (e.g. cold pressor task) in otherwise healthy participants.

Some limitations to the present study will be addressed here. This study investigated a unique, but narrow, aspect of personal characteristics for gender differences. There is a large array of gender-related traits or personality characteristics that were not investigated. The

concepts of goal-oriented, emotive or relationship-oriented can be difficult to define and may be gendered in a way that could manifest differently for men and women. Gendered expectations of these characteristics can also evolve in societies over time. All of these issues complicate explanatory modelling and we see results such as those presented here as steps towards a broader conceptualization of sex, gender, culture, and other socially-constructed phenomena in pain research. A larger sample size should be recruited for future studies. Also, other potential predictors should include in future research in order to have a clearer picture of the pain outcomes.

In conclusion, results from the current study highlight that variances in pain outcomes such as pain severity and interference might be explained by considering some of the gender-related personality characteristics as it was shown for self-perceptions of 'Emotive' qualities. From a broader perspective, the variances in pain outcomes could explained better with considering sex and gender along with the other important dimensions such as socioeconomic status, age, culture, race, and family's role for a better understanding of people's differences in pain responding.

3.6. References

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Table 6: Characteristics of the study sample

N = 113	
Sex (% female)	60.2%
Age (y), $\overline{x} \pm$ SD (min-max) (N = 93)	43.2 ± 14.8 (18-66)
Medicolegal involvement	
None	89.4%
Active insurance claim[1]	10.6%
Region affected	
Axial (neck or back)	26.5%
Peripheral (upper or lower extremities)	73.5%
BPI[2] subscales, $\overline{x} \pm$ SD (min-max) , skewness and kurtosis	
Severity (/10)	4.3 ± 2.0 (0-8) , -0.07 and -0.89
Interference (/70)	26.9 ± 16.7 (0-67) , 0.43 and -0.73

[1] Includes auto insurance, worker's compensation, or personal injury claim

[2] BPI (short form): Brief Pain Inventory

Table 7: Independent sample t-test

	Male		Female		P-value	95% Confidence Interval of the Difference (LLCI, ULCI)
	N	Mean (SD)	N	Mean (SD)		
BPI Pain Severity[1]	45	4.0 (2.1)	68	4.5 (2.0)	0.2	-1.3 , 0.2
BPI Pain Interference[1]	45	26.4 (16.0)	68	26.8 (17.3)	0.8	-6.8 , 5.9

[1]: BPI (short form): Brief Pain Inventory

Table 8: Simple bivariate associations between GPES subscales and pain variables in the acute stage of injury

*:

	Relationship-oriented	Goal-oriented	Emotive
BPI Pain Severity subscale[1]			
Full sample	**0.20***	0.15	0.06
Male (n = 45)	0.05	0.16	-0.13
Female (n = 68)	**0.27***	0.16	0.15
BPI Pain Interference subscale[1]			
Full sample	0.16	0.05	**0.24****
Male (n = 45)	0.10	-0.04	0.10
Female (n = 68)	0.21	0.10	**0.33****

Correlation is significant at the $p < 0.05$ level

**: Correlation is significant at the $p < 0.01$ level

[1] BPI (short form): Brief Pain Inventory

Table 9: Summary of regression analysis for predicting pain severity by sex and GPES subscales variables

	β(ß)	Δr^2	ΔF (p)
Model 1: Relationship-oriented			
Constant	3.51**		
Sex	0.50 (0.12)	0.01	1.62 (0.20)
Constant	1.88		
Relationship-oriented	0.25 (0.18)	0.03	3.58 (0.06)
Constant	5.52		
Sex x Relationship-oriented	0.31 (0.74)	0.01	1.38 (0.24)
Model 2: Goal-orientated			
Constant	3.51**		
Sex	0.50 (0.12)	0.01	1.62 (0.20)
Constant	1.52		
Goal-oriented	0.15 (0.16)	0.02	3.13 (0.07)
Constant	1.04		
Sex x Goal-oriented	-0.02 (-0.07)	0.00	0.01 (0.89)
Model 3: Emotive			
Constant	3.51**		
Sex	0.50 (0.12)	0.01	1.62 (0.20)
Constant	3.31**		
Emotive	0.06 (0.03)	0.00	0.14 (0.70)
Constant	6.57**		
Sex x Emotive	0.49 (0.79)	0.02	2.37 (0.12)

*: Correlation is significant at the $p < 0.05$ level

**: Correlation is significant at the $p < 0.01$ level

Table 10: Summary of regression analysis for predicting pain interference by sex and GPES subscales variables

	β(ß)	Δr^2	ΔF (p)
Model 1: Relationship-oriented			
Constant	25.96**		
Sex	0.46 (0.01)	0.00	0.02 (0.88)
Constant	13.34		
Relationship-oriented	1.95 (0.17)	0.02	3.17 (0.07)
Constant	31.13		
Sex x Relationship-oriented	1.55 (0.44)	0.00	0.49 (0.48)
Model 2: Goal-orientated			
Constant	25.96**		
Sex	0.46 (0.01)	0.00	0.02 (0.88)
Constant	21.01*		
Goal-oriented	0.38 (0.05)	0.00	0.28 (0.59)
Constant	42.37		
Sex x Goal-oriented	1.05 (0.42)	0.00	0.48 (0.48)
Model 3: Emotive			
Constant	25.96**		
Sex	0.46 (0.01)	0.00	0.02 (0.88)
Constant	15.09*		
Emotive	3.30 (0.25)*	0.06	**6.89 (0.01)**
Constant	37.49*		
Sex x Emotive	3.40 (0.67)	0.01	1.79 (0.18)

*: Correlation is significant at the $p < 0.05$ level

**: Correlation is significant at the $p < 0.01$ level

Figure 4: Scatter plot of the relationship between BPI Pain Severity and Relationship-oriented, Emotive, and Goal-oriented subscales in males and females.

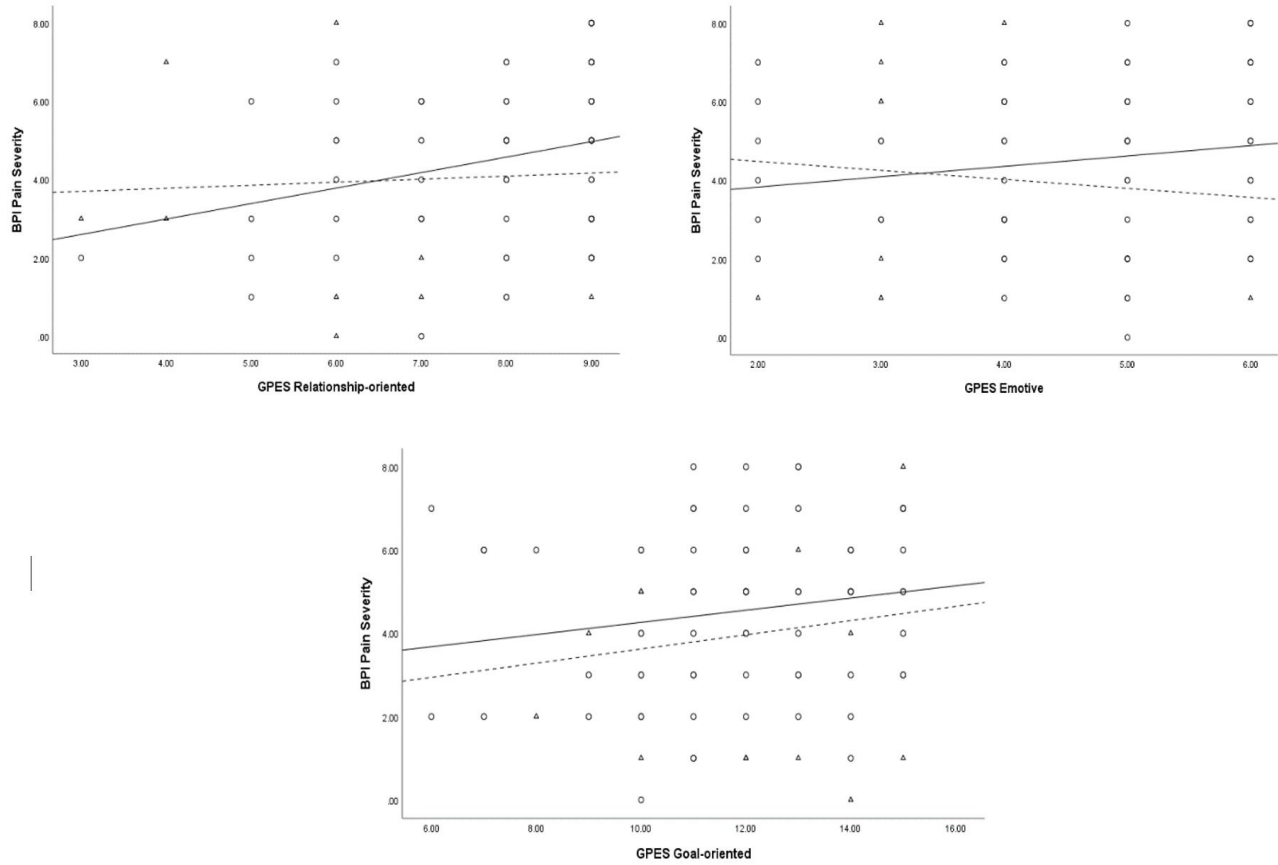(○) and (—) represent Females; (△) and (--) represent Males.
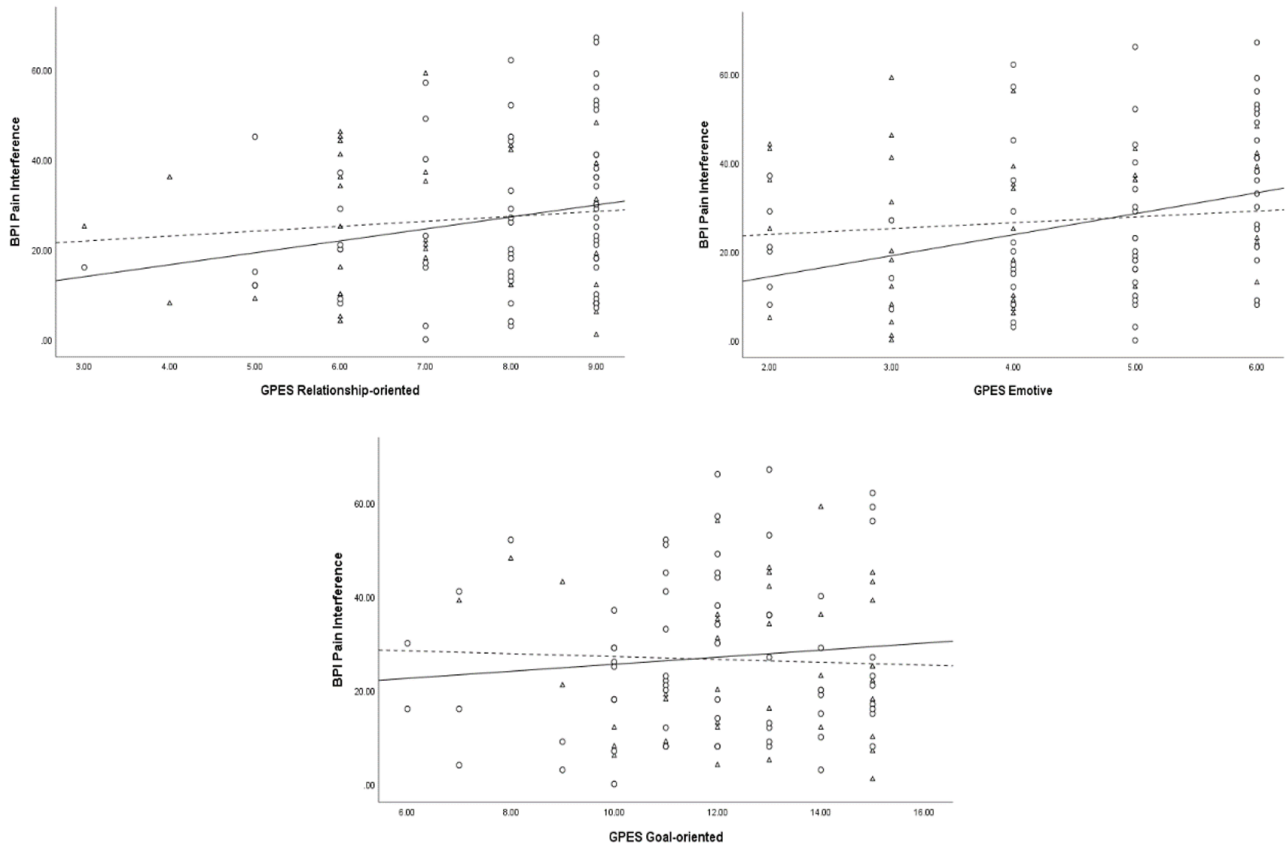
Figure 5: Scatter plot of the relationship between BPI Pain Interference and Relationship-oriented, Emotive, and Goal-oriented subscales in males and females.

(○) and (—) represent Females; (△) and (--) represent Males

Chapter 4

4   Exploring the role of sex hormones and traditionally genderized interpersonal-expressive traits in predicting pain in people with acute musculoskeletal trauma

4.1.   Introduction

It has been shown in various experiments that despite the same stimulus, the pain experience or at least the report of that experience, can be different between people.[1–3] Based on the interactions of multiple individual factors, each individual experiences, reports, and copes with pain uniquely. Despite the growing evidence of individual differences in pain experience and expression, the mechanisms to explain these differences are largely unknown. For example, it has been proposed that pain experience and reporting may be influenced by hormones, prior life experiences, socioeconomic status, or other biopsychosocial influences, all of which may contribute to an individual's different responses to interventions.[2,4] Therefore, it would be important to investigate if these factors interact in specific ways.

Over the last few decades, increasing attention has been paid to exploring the associations between health and personality characteristics, specifically in the pain field.[5–8] Based on the reviewed literature, personality characteristics, either assumed as sex- and gender-related or as general characteristics,[9] are expected to influence the differences in the pain experience.[10–12] As patterns of emotions, thoughts, and behaviours, personality traits can be conceptualized as characteristic ways of interpreting and responding to events that are unique to the person.[13] These are thought to be established through a combination of nature (biological influences) and nurture (social or life experiences; for instance, under the substantial influence of gender role socialization),[14–19] and tend to become more stable from childhood through to adulthood.[20] Personality traits, as individual characteristics, could be learned and determined through life experiences, for instance, under the substantial influence of gender role socialization.[18,19]

Traditionally, some personality characteristics or behaviours have been ascribed more to one sex,[21,22] and these have generally become accepted as 'cis', or normative, for that sex in a specific society. In many Western cultures, 'cis' traits for males have been stoicism and emotional suppression while traits for females have been more relational and expressive.[23,24] There are consistent differences in pain reports between males and females, and some have hypothesized that such differences may be the effect of these traditionally genderized traits.[23]

As it is described by Bernardes et al. (2008), one of the levels that gender could be conceptualized in pain research is the 'intra-individual' level which is defined as what people are and how they describe themselves.[25] For instance, to explore the role of the gender-related personality traits in experimental and clinical pain experiences, self-report measurements such as the Personal Attributes Questionnaire (PAQ)[21] and the Bem Sex Role Inventory (BSRI)[22] have been used in numerous studies.[26–30] Despite some inconsistencies in results and magnitude of effects of such studies, they collectively indicated that genderized personality traits and gender norms could have a relationship with experimental and clinical pain and need further assessments.[25] The Gender, Pain, and Expectations Scale (GPES) is a newly designed scale to capture self-rated traditionally genderized traits and also assess gender-based perceptions of personal pain behaviours in relation to others of the same sex. Our previous structural analysis of the first section of this scale (genderized traits) led to the identification of three main sub-factors including Relationship-oriented, Emotive and Goal-oriented, reflecting traditionally gendered norms by Western standards that may have an effect on pain experience or expression.[31]

Empirical research has also shown that the influence of sex hormones on personality traits should be considered and studied more.[32–34] One of the most abundant hormones in human peripheral circulation is Dehydroepiandrosterone-sulphate (DHEA-S). DHEA-S is primarily produced in the adrenal glands[35] and is considered a prohormone that can be metabolized into estrogen and testosterone.[33,36] DHEA-S levels are usually higher in males and decrease with age in both sexes.[37] A relationship between DHEA-S and stress, depression, mood, and certain behavioural states has been suggested in several studies.[33,38] It has been shown that

DHEA-S decreases the neural activity in regions related to negative emotions and increases activity in areas of regulatory control of emotion [39]. For instance, some studies have found that DHEA-S levels have been inversely correlated with expansive personality ratings (as assessed by scale 9 of the Minnesota Multiphasic Personality Inventory (an abbreviated version)), and with Type A behaviour (personalities like competitive, highly organized, and aggressive).[40–44]

Another sex hormone is estradiol. It is the most active form of estrogen,[45] present in higher abundance in females.[33] Evidence has shown that estradiol has an impact on emotions and is associated with sensation-seeking and relationship-relevant personality constructs.[46,47] It has also been suggested that estrogen can change the intensity of emotional experience through neuropsychological factors.[48]

Progesterone and testosterone (a common type of androgen) are the other well-known sex hormones that have been shown to be associated with mood regulation, sensation-seeking and femininity-masculinity characteristics.[49–53] Contrary to progesterone, testosterone usually has a lower concentration in women than in men[54] and a number of studies have documented a positive association between testosterone and aggression and dominance-related personality characteristics[55,56] while a negative correlation has been shown with maternal personality as assessed through the BSRI.[56]

DHEA-S, estradiol, progesterone, and testosterone have each been linked to acute pain and chronic pain disorders by both clinical and preclinical research over the past few decades.[57–59] The complex underlying mechanisms (molecular and anatomical) of these relationships have garnered more recent attention[57,58] and it has been demonstrated that these hormones influence both the peripheral and central nervous system.[57] For instance, estrogens showed exacerbation and attenuation of pain while testosterone and progesterone presented protective effects against pain by influence on nociceptive pathways.[57,58] Thus, considering both sex and hormonal status has been endorsed as a priority focus in pain research by prior authors.[60]

Given the highlighted discussions around the relationship between sex hormones, gender and pain ratings, in this observational cross-sectional study, our first goal was to explore potential correlations between sex hormones, gender-related interpersonal-expressive traits and Brief Pain Inventory (BPI) Severity and Interference scores following recent musculoskeletal (MSK) trauma and explore their differences between males and females. Our second goal was to explore the potential pathways that link sex-at-birth, hormones, gender-related traits, and pain scores and also the potential mediator effect of gender-related interpersonal-expressive traits on the relationships of biological sex indicators and pain ratings.

4.2. Methods

4.2.1. Participants

Data were drawn from the prospective acute trauma SYMBIOME (Systematic Merging of Biology, Mental Health and Environment) cohort database (clinicaltrials.gov registration number NCT02711085). The study protocol was approved by the local institutional review board. All consecutive participants were at least 18 years or over, presented to a local hospital Urgent Care Centre seeking care for non-catastrophic MSK injury. Eligible participants could read and understand conversational English and did not have systemic comorbidities or chronic conditions such as neuromuscular disorders, cancer, or uncontrolled mental health disorder. Participants who indicated that were on hormone replacements or birth control were not included in this study. The baseline data were collected by several questionnaires and study-specific tools. The participants' demographic data in this study included age, sex-at-birth (male, female, or other), Body Mass Index (BMI), and region affected (extremity or spinal).

The standardized tools for this analysis are as follows:

1- BPI – short form: The BPI is a widely used pain-related 11-item self-administered questionnaire with the quantifiable subscales of Pain Severity and Pain Interference.[61] It shows acceptable psychometric properties with adequate reliability in MSK disorders.[62,63] The

Pain Severity subscale is the mean of 4 items (worst, least, average, and current pain), with each scored from 0 (no pain) to 10 (pain as bad as you can imagine). The Pain Interference subscale is the sum of 7 items (general activity, normal work, walking ability, mood, sleep, relationships, and enjoyment of life), with each rated from 0 (does not interfere) through 10 (interferes completely). Higher scores on the pain severity subscale and pain interference subscale indicate severe pain and more significant functional interference, respectively.

2- GPES: The GPES is a new gender-focused pain-related expectations and beliefs scale developed by our group. The first section of this scale was used in this study.[31] The original section includes 16 items that were partly adapted from the BSRI[22] and considered as traditionally genderized personality characteristics.[64] Participants rate themselves on each trait from "1=not at all like me" to "3=extremely like me. In our prior analysis of this section, three factors emerged: Relationship-oriented (nurturing, giving, and gentle, scored out of 9), Emotive (sensitive and emotional scored out of 6), and Goal-oriented (determined, leader, competitive, tough, and confident scored out of 15).[31]

4.2.2. Capture and analysis of hormones

All consenting participants provided blood samples prior to leaving the hospital. Two samples of antecubital blood were drawn into 4mL K2 EDTA BD vacutainer tubes and transported on ice to a -80C freezer at an immunity and proteomics lab.[65] Bloods were drawn again 3, 6, and 12 months post-injury, but only the baseline blood samples were analyzed for this study. Progesterone, DHEA-S, estradiol, and testosterone were assayed using industry-standard approaches with Enzyme-Linked Immunosorbent assay (ELISA) kits (Human Progesterone ELISA Kit, Abcam, ab108670; DHEA sulfate ELISA Kit, ab108669; Estradiol Parameter Assay Kit, R&D Systems Company, KGE014; Testosterone Parameter Assay Kit, R&D Systems Company, KGE010). Assay range for each hormone (the assay range of the kit multiplied by the dilution factor) included: Progesterone: 0.2–40 ng/mL; DHEA-S: 5.0–500 ug/mL; Estradiol: 19.7–4800 pg/mL; Testosterone: 0.4–100 ng/mL. All hormone levels were within the expected range for the age range of our participants.

4.3. Analysis

4.3.1. Preliminary analysis

Characteristics of participants are reported descriptively (mean, SD, range/ frequencies). The normality of data was statistically tested through the Kolmogorov-Smirnov tests, the skewness and kurtosis values, and data were log-transformed where necessary to achieve adequate normality.[66,67] Independent samples t-test was used to evaluate the differences in mean hormone concentrations, GPES subscales and BPI subscale scores between the two levels of sex-at-birth (male vs. female). While presented as an option, no respondent indicated 'other' sex.

4.3.2. First Goal: Bivariate association

As the first goal of this paper and a first-pass analysis to facilitate interpretation of subsequent steps, we explored simple bivariate associations between the 4 hormone levels and scores on the GPES subscales and BPI Pain subscales using Pearson's r or Spearman's rho depending on the distribution of data. Also, as differences by sex-at-birth were expected in pain experience and hormone levels, a sex-disaggregated analysis was done for each of the correlations.

4.3.3. Second Goal: Hypothetical Models testing

Based on both theory and results from the prior steps, two *a priori* structural equation models (SEM) were created, one for BPI pain Severity and one for BPI Interference (**Figure 6** and **Figure 7**, respectively). These were evaluated through path analysis. GPES Goal-oriented was not included in our hypothesized models as it showed no significant correlation with pain ratings in this dataset (chapter 3). The hypothetical models were created for the hormones which presented significant correlations with GPES subscales. In our model 1 (**Figure 6**), we assessed our full SEM model while also tested the three mediational analyses

for BPI Pain Severity, including the Sex -> Relationship-oriented -> BPI Pain Severity pathway, Progesterone -> Relationship-oriented -> BPI Pain Severity pathway, DHEA-S -> Relationship-oriented -> BPI Pain Severity pathway. In Model 2 (**Figure 7**), we analyzed the full SEM model and conducted two mediational analyses for BPI Pain Interference including Sex -> Emotive -> BPI Pain Interference, and DHEA-S -> Emotive -> BPI Pain Interference. Standardized and unstandardized total, direct, and indirect effects were evaluated through AMOS 24 for IBM Statistics SPSS and P-values and bootstrapped 95% confidence intervals were used for assessing the significance of the effects through *the PROCESS macro* for SPSS.[68] Where the confidence intervals did not include zero, the pathway was considered significant. According to the classification of mediation by Zhao et al. (2010), when an indirect (mediated effect) exists but no direct effect, indirect-only mediation was present.[69] Also, when an indirect (mediated effect) does not exist, but the direct effect exists, it is called direct-only (Non-Mediation).[69]

In the path analysis, for evaluating model fit, multiple tests are examined, including: Chi-square, where smaller values indicate better fit; Comparative Fit Index (CFI)>0.95; Tucker Lewis Index (TLI)>0.95; Normed-fit index (NFI)>0.95; Root Mean Squared Error of Approximation (RMSEA) ≤ 0.05.

4.3.4. Sample size

Using the algorithms of Soper[70] for estimating the sample size with an anticipated effect size of 0.1 and accepting 5% alpha error and 20% beta error (80% power), the minimum sample size was estimated at a minimum of 87 participants.

4.4. Results

4.4.1. Preliminary Analyses

From the SYMBIOME databank (N=130), a total of 94 participants provided blood samples with adequate data for this analysis. As preliminary analyses revealed that hormone levels

were positively skewed, progesterone, testosterone, estradiol, and DHEA-S were log-transformed for all analyses.

The baseline characteristics and descriptive data of our study population are provided in **Table 11**. The sample was 59.6% female, and 74.5% presented with upper or lower extremity injuries. Their rating of BPI Pain Severity (4.5/10) and Interference (28.3/70) were moderate.

In the base analyses (**Table 12**), the independent t-test indicated that the testosterone level (P<0.01, 95%CI: 0.3 to 0.6), and DHEA-S level (P=0.01, 95%CI: 0.0 to 0.3) were significantly higher in males, while no significant differences found in progesterone and estradiol. **Table 12 also** presents an independent t-test for GPES subscales and BPI Pain subscales which revealed that women described themselves as more Relationship-oriented (P = 0.04) and Emotive (P<0.01) than men. No significant differences were found between sexes in GPES Goal-oriented and BPI Pain scores in our sample.

4.4.2. First Goal: Bivariate association

Table 13 presents the simple Pearson bivariate correlation coefficients between the 4 hormones and other study variables. Relationship-oriented subscale showed a significant negative correlation with progesterone (r=-0.21, P=0.04) and DHEA-S (r=-0.33, P<0.01). The Emotive subscale had a significant negative association only with the DHEA-S (r=-0.20, P=0.04) while the Goal-oriented subscale showed a negative correlation only with estradiol (r=-0.20, P=0.04). None of the hormones on their own demonstrated a significant correlation with either BPI Pain Severity or Interference. Sex disaggregated analysis revealed a significant negative association between DHEA-S and GPES-Relationship oriented only in women (r=-0.28) and a significant positive correlation between DHEA-S and Goal-oriented only in men (r=0.39).

4.4.3. Second Goal: Hypothetical Models testing

4.4.3.1. SEM for Pain Severity

The *a-priori* proposed statistical model for BPI Pain Severity (**Figure 6)** was fully saturated (χ^2=0.00 (df=0, p<0.001) which indicates that the model replicates the data perfectly and as such is irrelevant, and therefore needs the focus to be on the magnitude of the hypothesized regression coefficients and their tests of significance. The coefficients for two of the hypothesized paths were significant, the path from DHEA-S to Relationship-oriented (β=-0.26, P=0.01) and Relationship-oriented to BPI Pain Severity (β=0.28, P<0.001). The results of three mediation analyses are presented in **Table 14**. The mediation analysis revealed that only the indirect effect of DHEA-S -> Relationship-oriented -> BPI Pain Severity pathway was significant (Standardized indirect effect=-0.07, Unstandardized indirect effect=-0.52, (SE=0.24) 95% CI=-1.0 to -0.1). The standardized total effect of DHEA-S on BPI Pain Severity was -0.02 and non-significant.

4.4.3.2. SEM for Pain Interference

The resulting path coefficients of the hypothesized model of the BPI Pain Interference are presented in **Figure 7**. A saturated model was again indicated (χ2=0.00 (df =0, p<0.001)) with two significant paths, the path from sex to Emotive (β=0.25, P=0.01) and Emotive to BPI Pain Interference (β=0.21, P<0.05). Two mediation pathways were tested (**Table 14**) and indicated an indirect-only mediation for the Sex -> Emotive -> BPI Pain Interference path (Standardized indirect effect=0.05, Unstandardized indirect effect=2.10, (SE=1.10), 95% CI=0.2 to 4.5). The standardized total effect of Sex on BPI Pain Interference was 0.00 and non-significant.

4.5. Discussion

The focus of the current study was on exploring the relationships and pathways between sex hormones, self-reported traditionally genderized personality characteristics and the ratings of the BPI Pain Severity and Interference. According to our findings, those who had a lower

level of DHEA-S described themselves more as Relationship-oriented and Emotive typed persons who reported higher pain severity and interference, respectively. The following discussion clarifies the major findings and offers hypotheses concerning the relationships among the factors.

Our preliminary analysis showed that women in this study had significantly lower levels of DHEA-S and testosterone, as was expected, and also were significantly higher on Relationship-oriented and Emotive subscales. The reason for a non-significant difference in the Goal-oriented subscale in men and women is likely shifting of cultural norms, for instance, women having higher education and taking up more challenging roles in society and Politics and men taking on more caregiving , family responsibilities.[71,72] Also, it is possible that the scale is not sensitive enough to indicate these levels of differences or there is another intrinsic flaw related to this GPES subscale.

Sex hormones can act through many processes (cellular and molecular) to alter neural systems' structure and function and therefore influence behaviours.[73,74] Although the mechanism of the bidirectional relationship of hormones and behaviours and personality[75] is still unclear and inconsistency exists in findings of studies, it is noteworthy to mention that according to behavioural endocrinology, it has been suggested that there is not a causal relationship between hormones and behaviour rather hormones affect behaviour's likelihood of occurring[76] and predispose individuals to different behaviours that societal factors might have a role in activating.[77]

The results of our study demonstrated a negative significant correlation between serum progesterone and GPES Relationship-oriented. In other words, those who had a lower level of progesterone considered themselves more relationship-oriented which included nurturing, giving, and gentle characteristics. Despite the lack of studies on the relationship between progesterone and personality in humans, in a study by Al-Ayadhi, 2004, the relationship of professional status, personality characteristics and the levels of the sex hormones were assessed and it is indicated that the level of progesterone and estradiol did not correlate with personality characteristics.[34] In another study, Pletzer et al. (2015) found that being a female

with higher progesterone and/or estrogen level will favour higher scores in femininity assessed by a six-item sex-role scale.[78] These studies' results[34,78] are different from ours; however, as highlighted here, the study designs and methods are different as well. As another finding of our study, the level of serum testosterone did not correlate with GPES subscales either in men or women. However, in other studies, higher testosterone levels are usually considered to be contributed to a higher level of masculine characteristics.[78,79] On the other hand, it has been indicated that people with lower levels of testosterone possessed a high level of traditionally feminine characteristics and somewhat being more sensitive, possessing a caring attitude.[78] In the study of Pletzer et al., 2015, an interplay of societal factors like culture, and the levels of sex hormones (progesterone, 17β-Estradiol, and testosterone) in an individual's sex-role identity were explored.[78] They found that both sex hormones and culture interactively affect participant's sex-role orientation.[78] Regardless of the different factorial structure of sex-role that they found in their two different Northern American and middle European participants, they indicated that having the male sex with a higher testosterone level, favour higher masculinity ratings.[78]

Similar to testosterone, higher levels of estradiol in males seem to be positively associated with trait aggression while presenting either an unrelated or negative correlation in women.[80,81] In a study of 49 undergraduate and graduate women by Stanton and Schultheiss, (2007), no relationship was found between estradiol and self-reported dominance while correlated negatively with self-reported aggression.[82] According to our results, we found that individuals who rated themselves as more Goal-oriented, (including the determined, leader, competitive, tough and confident items) had a lower level of estradiol.

DHEA-S was one of the only hormones that showed negative significant associations with both GPES Relationship-oriented and GPES-Emotive in reference to the entire population, and positive significant correlation with GPES Goal-oriented in reference to men. Given the inconclusive results of the relationship of DHEA-S and personality, Do Vale and et al.,(2011), found that DHEA-S was significantly and directly related to the type A personality assessed by Minnesota Multiphasic Personality Inventory (MMPI). Those who manifest this personality pattern are usually Goal-oriented and show competitiveness.[83] On

the contrary, a study by Fava et al., (1988), confirmed a hypothesis that there is an inverse correlation between the degree of Type A behaviour pattern and DHEA-S level.[41]

In line with this scarcity of studies, there are not enough supportive findings for the directions of hormonal influences on different personality characteristics and behaviours. Although some of the correlations found in the current study were contrary to our expectations and previous findings in some studies, our findings may also be interpreted in the light of the fact that the relationship of sex hormones with personality and behaviour may depend upon some other factors like other hormones, cultural factors, professional and societal status, and current health status. Furthermore, this inconsistency could be explained regarding our sample which was drawn from a clinical post-trauma population.

Although the precise roles of sex hormones in pain are not well understood, a converging line of evidence suggested that these hormones could have effects on the developmental organization of the nervous system and modulating neurotransmission.[84,85] Several studies have been done on assessing the hormone's relationship with pain[86–88] and the results were inconsistent. For instance, while DHEA-S levels did not correlate with pain intensity in one study,[87] in another study, DHEA-S levels showed a negative correlation with pain intensity.[89] As another example, progesterone and testosterone, but not estradiol, showed an inverse correlation with changes in pain severity[88] In this study, we tested if progesterone, DHEA-S, estradiol, and testosterone are associated with BPI Pain Severity and BPI Pain Interference and no significant association was found. This inconsistent result rises this argument that an individual's current state and the situation might influence the complex relationship of hormones and pain experiences.

We have tested our hypothesized models for each BPI Pain Severity and Interference. One model hypothesized for the links between sex, DHEA-S and progesterone with BPI Pain Severity through the Relationship-oriented characteristic as a mediator for these links. Also, one model hypothesized for the paths between sex and DHEA-S through Emotive to BPI Pain interference. Regarding our hypotheses that the gender-related interpersonal-expressive traits could act as mediators of the relationships between sex and pain, and between steroid

hormones and pain. Our results indicated that indirect-only mediations (Mediated effect exists, but no direct effect) existed for two pathways of DHEA-S -> Relationship-oriented -> BPI Pain Severity, and Sex -> Emotive -> BPI Pain Interference. Our findings indicated that the level of DHEA-S may affect the likelihood of individuals characterizing themselves as more nurturing, giving, and gentle which we have labelled as Relationship-oriented and this positively predicts the severity of the pain reported by participants after a non-catastrophic MSK trauma. Likewise, according to our findings, sex-at-birth could play a role in the likelihood of possession and expression of sensitive and emotional traits (which are labelled as Emotive) by individuals and that would influence the magnitude of the reported pain-related interference.

A few limitations need to be taken into consideration. Although path analysis is a well-known mean of exploring hypothetical associations between variables and theoretical constructs, its interpretation requires caution as sometimes SEM has been referred to as causal modelling while indicating causation requires more evidence and a longitudinal dataset. We should also consider errors inherent to self-report measures, as such external bias like social desirability could affect the individual's responses. Another limitation of our study was that, regardless of the time of day, blood was drawn when participants presented in the urgent care center. And there are potential confounders for hormone levels, such as differences by sex, diurnal fluctuations, and menstrual cycle/pregnancy/post-menopausal status, and many of these factors were not captured on an individual participant basis.

Additionally, considering there is an expansive range of personality traits for gender differences, in this study, we capture a narrow aspect of gender-related personality characteristics. In order to better understand pain and inform pain management, other potential biopsychosocial variables and a larger and more socio-cultural diverse data set should be considered in future research.

In conclusion, the findings of our study suggest that the prediction of pain severity and interference in humans will require more complex interactions of biology, psychology, and social factors rather than just exploring individually that have traditionally been explored.

Considering the substantial individual differences in genetics, hormonal profiles, pain circuitry pathways, psychosocial and gender-related behaviours and characteristics, clearly, making studying the individual differences in pain perception more complex. The sex hormones will not on their own explain the differences in pain perception, but according to our findings, sex and DHEA-S as an anabolic protective pro-hormone could be a significant contributor in a hypothesis pathway through the Emotive and Relationship-oriented traits that lead to predicting the ratings on BPI Pain Interference and Severity, respectively. Overall, this study was conducted upon the assumption that a better understanding of the underlying variables that affect pain reports, could help and lead to more personalized pain management. We encourage further exploring hormones' role along with gender-related characteristics in pain studies.

4.6.   References

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Table 11: Participant demographics

Sex (% female) (N=94)	59.6%
Age (mean, SD, range) (N=75)	44.7 years (14.1, 18 to 66)
BMI (mean, SD, range) (N=91)	26.4 kg/m^2 (6.0, 14.3 to 51.5)
Region affected (N=94)	
Axial (neck or back)	25.5%
Peripheral (upper or lower extremities)	74.5%
BPI* Pain Severity /10 (mean, SD, range) (N=93)	4.5 (1.9, 0 to 8)
BPI* Pain Interference /70 (mean, SD, range) (N=94)	28.3 (16.8, 0 to 67)

* BPI = Brief Pain Inventory

Table 12: Independent sample t-test

	Male		Female		P-value	95% Confidence Interval of the Difference (lower , upper)
	N	Mean (SD)	N	Mean (SD)		
Progesterone* (ng/mL)	38	-0.0 (0.5)	52	-0.1 (0.8)	0.55	-0.2 , 0.3
DHEA-S* (ug/mL)	38	1.9 (0.3)	56	1.8 (0.3)	**0.01**	0.0 , 0.3
Estradiol* (pg/mL)	38	2.0 (0.1)	56	2.0 (0.1)	0.92	-0.0 , 0.0
Testosterone* (ng/mL)	38	0.9 (0.3)	56	0.4 (0.4)	**<0.01**	0.3, 0.6
Relationship-oriented	38	7.1 (1.6)	56	7.8 (1.4)	**0.04**	-1.2 , -0.0
Emotive	38	3.9 (1.2)	56	4.7 (1.2)	**<0.01**	-1.2 , -0.2
Goal-oriented	38	12.4 (2.1)	56	11.9 (2.4)	0.27	-0.4 , 1.5
BPI Pain Severity	37	4.2 (1.8)	56	4.7 (1.9)	0.19	-1.3 , 0.2
BPI Pain Interference	37	28.5 (15.4)	56	28.8 (17.6)	0.77	-8.0 , 6.0

* : Log-transformed data

** : BPI = Brief Pain Inventory

Table 13: Pearson's r correlations of hormones with the studied variables

	Progesterone	DHEA-S	Estradiol	Testosterone
GPES Relationship-oriented	**-0.21***	**-0.33****	0.14	-0.11
Male (N=38)	-0.14	-0.30	0.24	-0.24
Female (N=56)	-0.24	**-0.28***	0.08	0.12
GPES Emotive	-0.11	**-0.20***	0.12	-0.12
Male (N=38)	0.06	-0.03	0.16	-0.17
Female (N=56)	-0.18	-0.21	0.11	0.12
GPES Goal-oriented	-0.00	0.13	**-0.20***	0.13
Male (N=38)	0.12	**0.39***	-0.24	0.01
Female (N=56)	-0.08	-0.06	**-**0.19	0.11
BPI[1] Pain severity	0.13	-0.00	0.01	0.03
Male (N=38)	0.14	0.04	-0.08	0.18
Female (N=56)	0.14	0.01	0.02	0.10
BPI[1] Pain Interference	0.04	-0.10	0.13	0.03
Male (N=38)	0.02	-0.04	0.20	-0.14
Female (N=56)	0.05	-0.13	0.09	0.16

*: $p < 0.05$ level

**: $p < 0.01$ level

[1]: BPI = Brief Pain Inventory

Table 14: Total, Direct, and Indirect Effects for Mediator models

Path	Standardized Effect[1]	Unstandardized Effect (SE) , (95% LLCI, ULCI)[2]
Sex -> Relationship-oriented -> BPI Pain Severity	Total effect = 0.14	Total effect = 0.54 (0.41) , P=0.19 (-0.2, 1.3)
	Direct effect = 0.10	Direct effect = 0.34 (0.41) , P=0.41 (-0.4, 1.1)
	Indirect effect = 0.04	Indirect effect = 0.20 (0.12) , (-0.0, 0.4)
Progesterone -> Relationship-oriented -> BPI Pain Severity	Total effect = 0.14	Total effect = 0.36 (0.29) , P=0.20 (-0.2, 0.9)
	Direct effect = 0.18	Direct effect = 0.54 (0.28) , P= 0.06 (-0.0, 1.1)
	Indirect effect = -0.03	Indirect effect = -0.16 (0.11) , (-0.4, 0.0)
DHEA-S -> Relationship-oriented -> BPI Pain Severity	Total effect = -0.02	Total effect = -0.03 (0.60) , P=0.95 (-1.2, 1.1)
	Direct effect = 0.04	Direct effect = 0.48 (0.62) , P=0.43 (-0.7, 1.7)
	Indirect effect = **-0.07***	Indirect effect = **-0.52* (0.24) , (-1.0, -0.1)**
Sex -> Emotive -> BPI Pain Interference	Total effect = 0.00	Total effect = 1.01 (3.56) , P=0.77 (-6.0, 8.0)
	Direct effect = -0.04	Direct effect = -1.08 (3.65) , P=0.76 (-8.3, 6.1)
	Indirect effect = **0.05***	Indirect effect = **2.10* (1.10) , (0.2, 4.5)**
DHEA-S -> Emotive -> BPI Pain Interference	Total effect = -0.10	Total effect = -5.31 (5.22) , P=0.31 (-15.6, 5.0)
	Direct effect = -0.07	Direct effect = -3.31 (5.27) , P=0.53 (-13.7, 7.1)
	Indirect effect = -0.02	Indirect effect = -2.00 (1.42) , (-5.3, 0.2)

[1]: Standardized Effect values were assessed in AMOS 24 for IBM Statistics SPSS

[2]: The significance level was indicated through unstandardized effects which were conducted in PROCESS macro for SPSS.

Figure 6: A priori hypothetical model of BPI Pain Severity. $\chi2$ (0.00) =, p < 0.001, CFI = 1.00.

* indicates p < 0.05, ** indicates < 0.01. Path loadings are standardized coefficients. Covariation is presented as a curved arrow. e = error
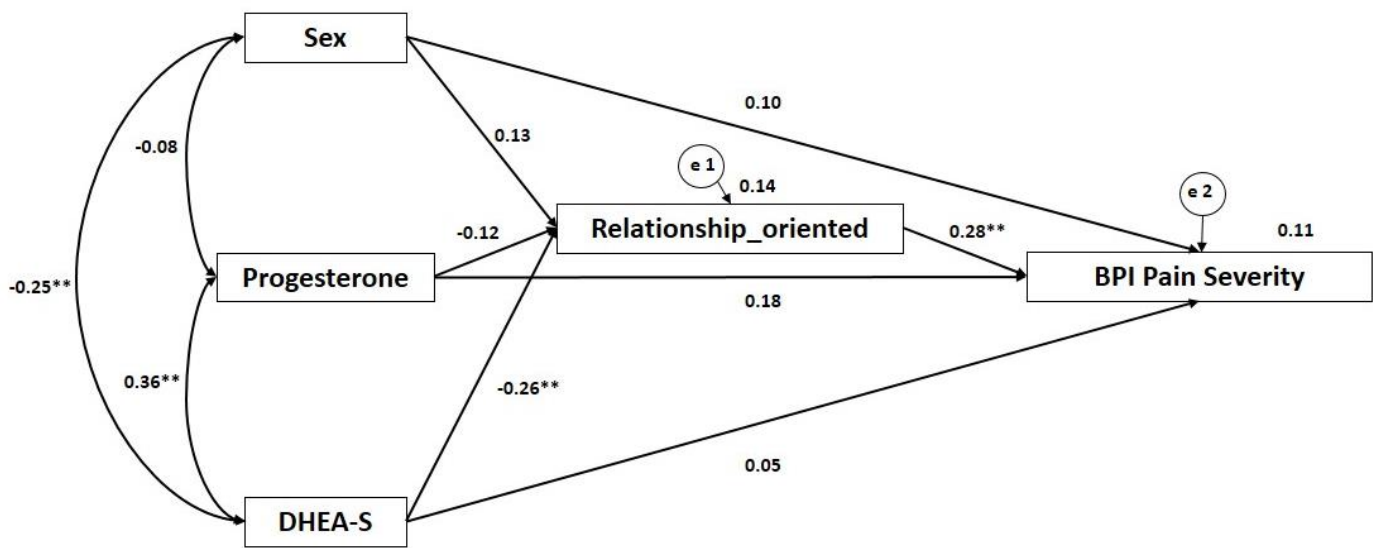
Figure 7: A priori hypothetical model of BPI Pain Interference. χ2 (0.00) =, p < 0.001, CFI = 1.00.

* indicates p < 0.05, ** indicates < 0.01. Path loadings are standardized coefficients. Covariation is presented as a curved arrow. e = error
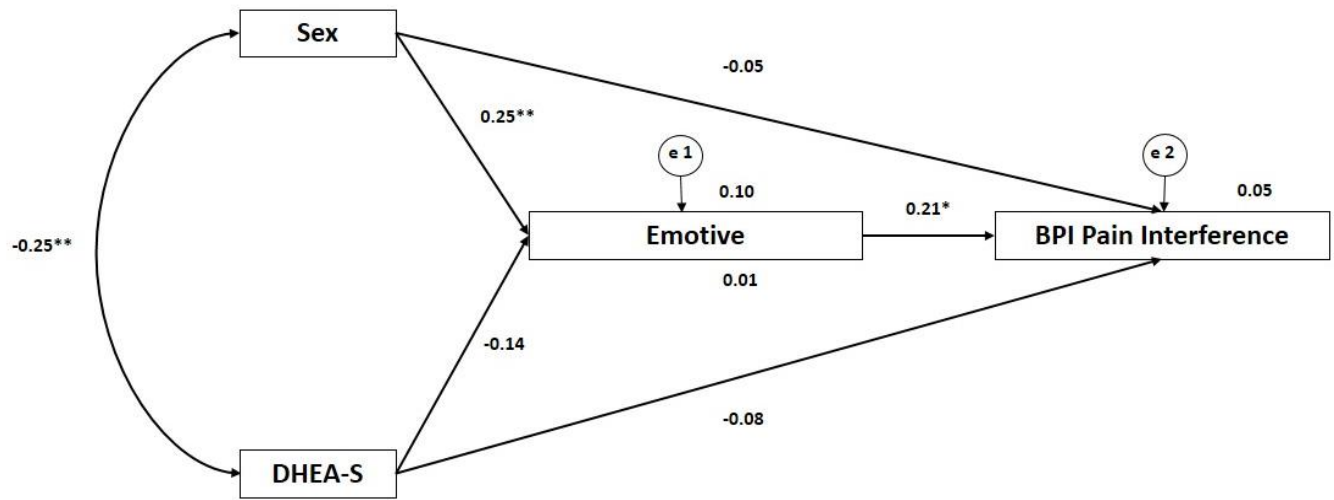
Chapter 5

5 Summary

5.1. General Discussion

The purpose of this dissertation was to present the initial findings of our effort to reconcile biological and psychosocial factors in pain experiences and/or expressions with a specific focus on utility in pain research.

To date, there has been a general confusion and a lack of clarity and about the conceptualization and approach to gender, especially in the pain field.[1,2] One point that should be considered is to be aware and sensitive to how gender is conceptualized and the very notions that there are a "masculine" and "feminine". Non-critical conceptualizations risk propagating and reinforcing structures that create inequities in society including healthcare for pain. Thus, we must be open to alternative explanations and approaches and view gender as a more fluid construct, which may be unfixed due to various factors such as changes in social roles and expectations. Moreover, since the interaction of words forms a screen through which we see the world, the words with a negative load towards sex and gender bias should be abandoned from our measurements. Language is a powerful tool that constructs our realities, but it is open to revision; it can and does change over time.[3,4]

One debate about the gender scales is the fact that as the self-report methods, a participant could give socially desirable answers in order to avoid being judged by others. Also, as a pain researcher and a clinician, I argue that what we really capture as 'pain experience' should not be considered an objective, unbiased indicator of the true experience, and it could be a degree of pain that the person is willing to report. In this line, in a literature review, I found a pattern of gendered norms described for women and men in pain literature, in which women were presented as being more willing to report pain whereas men were described as being stoic and denying pain.[5–8] This could raise the argument that as pain researchers, we should be cautious of what we really seek to quantify in gender-related pain research. As a

suggestion, if stoicism is thought to be part of being traditional masculine, and expressiveness is part of being traditional feminine, then a better way could be measuring stoicism and expressiveness rather than assuming that all masculine people are stoic and all feminine people are expressive. Similar arguments could be laid out for other traditionally masculine and feminine traits such as sensitiveness, extroversion, or gentleness.

Accordingly, chapter 2 demonstrates the evaluation of the structural validity of a 16-item 'Gender personality traits' subscale of a recently developed Gender Pain and Expectation Scale (GPES). While taking conceptual meaningfulness of subscales into consideration, Maximum likelihood (ML)-based Confirmatory Factor Analysis (CFA) identified a 3-factor structure informed by 10 items that satisfied acceptable fit criteria. Review of the items in the three factors led us to endorse a move away from naming these 'masculine' and 'feminine,' and focus rather on the nature of the traits: "Relationship-oriented," "Emotive" and "Goal-oriented." Evidence of construct validity was supported through significant sex-based differences ($p \leq 0.02$) in the expected directions for all 3 subscales. The self-perceived traits of the GPES seem to allow gender to be explored in new ways in pain research and to explore this more, the subsequent study was designed to explore the associations between these subscales and pain severity and interference.

Chapter 3 demonstrated the results of multiple linear regression in investigating the interaction of sex and these traditionally genderized interpersonal-expressive traits in explaining the Brief Pain Inventory (BPI) scores. The findings suggest that variances in pain-related interference are partially explained by scores on the GPES scale that measures self-perceptions of Emotive qualities. Sex-at-birth was not predictive of either pain outcome in both bivariate and multivariate analyses. An implication of this work is that it advocates for considering both sex- and gender-based variables when interpreting patient pain reports.

Chapter 4 integrated biological and traditionally-genderized traits and demonstrated the results of bivariate association analysis and the Structural Equation Modelling (SEM) in exploring the role of sex-at-birth, hormones, and genderized interpersonal-expressive traits scores in predicting pain reports. Our findings indicated that DHEA-S, a key gonadal

hormone that is higher in males, has significant negative correlations with GPES Relationship-oriented and Emotive. Progesterone and estradiol showed negative associations with GPES Relationship-oriented and Goal-oriented, respectively. Furthermore, the findings illustrated that lower DHEA-S level had a role in the higher likelihood of individuals reporting higher scores in GPES Relationship-oriented and these individuals reporting higher BPI Pain Severity. Likewise, a mediated effect of GPES Emotive was found for the pathway of Sex -> Emotive -> BPI Pain Interference. The interpretation of this study requires caution as SEM has been often referred to as causal modelling, as proving causality needs more investigation. One recommended guideline for assessing the strength of the future observational studies' results (causal inference) is Bradford Hill criteria which consider (1) Strength of Association, (2) Consistency, (3) Specificity, (4) Temporality, (5) Biological Gradient, (6) Plausibility, (7) Experimental evidence, (8) Analogy, and (9) Coherence.[9] An implication of this work is that it advocates and encourage for considering and exploring steroid hormones' role along with the other variables in pain studies.

This dissertation's results support the claim that a broader perspective is needed for a better understanding of people's differences in pain experiences and pain expressions, and researchers and clinicians are encouraged to consider biological parameters such as hormones along with the other important dimensions such as age, gender, culture, race, socioeconomic status and family's role when exploring influences on the experience or reporting of pain. This dissertation represents our endeavour to lay the groundwork for deep phenotyping of people in pain and encouraging the subsequent creation of clinical processes that allow for more personalized treatment approaches. We expect these studies, and their results will be encouraging further investigating in the sex-and gender-based pain research. Moreover, our efforts were in line with the shift from the traditional binary categorization of gender to a subjective expression of gender identity. As a pain researcher, if we adopt a multidimensional view, such as the BPS model, in order to have a better understanding of pain we should consider physical, psychological, and social elements.

5.2. Future Directions

In future studies, we should be aware of the limitations of generalizing our assumptions to all men and women of the world just based on the specified items. There are often more considerable differences within the sexes compared with those between. Another point that is noteworthy to mention is that by emphasizing the men's and women's differences, the wide range of similarities among individuals and the existence of transgender and intersex are understudied.

Moreover, future studies besides recruiting a larger and statistically powered sample size should also aim to further assess the reliability and validity of the GPES scale. Additionally, the intersectionality approach should gain more attention in future studies. Its idea of the multiplicative nature of identity highlights that for instance gender is not only learned or performed through interactions, rather gender is interdependently done with other intersecting identities and has an inextricable link with other components of a person's identity, such as age, sexual orientation, race, ethnicity, nationality, religion, and social/work status.[10] All of these facets of identity are interlocking parts of a whole that collectively impact our choices in behaviours and attitudes as well.[11]

Gender-specific pain behaviours not only affect the choice and interpretation of pain assessment but also influence the diagnosis and treatment offered.[12] Gender bias as a complex healthcare phenomenon is a pathway by which inequalities in pain management adversely affect health. Several studies have found women are at higher risk for under-treatment of their pain, alternatively at higher risk of polypharmacy and opioid overdose.[13–16] Although the conversation is beginning to change the problematic notion of normality, gender stigmas remain as significant barriers to effective health care.

The recognized disparities in pain reporting and management could be explained by hegemonic masculinity, and andronormativity in health care and research.[5] Andronormativity refers to the state in which male values are taken as normal.[17] From a sociological perspective, hegemonic masculinity express the stereotypic notion of a "real

man" in society, with a desire to suppress expression of emotions and weakness and reject many of what are considered more feminine attributes.[18] However, the traditional concept of masculinity has been recently criticized because of its counterfactual vision of men.[19]

Gender is just one way of framing pain experiences, while itself as a process is shaped by multiple perspectives, and we could not capture it as a singular construct. Thus, if we want to keep considering gender in pain research, there is a strong need for pain context-specific measures of different aspects of gender (which is meaningful for the research question) in a particular culture and society. One of the manageable ways to approach gender in pain research might be separately focusing on specific dimensions of gender (that are important to research question), while adopting the intersectionality and mixed methods approach, and using higher quality measurements (maybe employing more qualitative methods and critical social analyses along with the quantitative studies) in both experimental and clinical settings. Overall, there is a call for "change," but for finding the ideal way to study gender in pain research, further exploration is needed by an interdisciplinary expert panel.

Altogether, a holistic approach should be taken to understand people's experiences of pain because pain is the complex personal construction of the intersection of mind, body, and culture. No single lens gives us a comprehensive view, several lenses at once are needed.

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Appendices

Appendix 1: Ethics approval for the SYMBIOME project

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Dave Walton
Department & Institution: Health Sciences\Physical Therapy, Western University

Review Type: Expedited
HSREB File Number: 106140
Study Title: Modeling post-traumatic pain and recovery: The SYMBIOME longitudinal cohort study
Sponsor: Canadian Institutes of Health Research

HSREB Initial Approval Date: November 17, 2015
HSREB Expiry Date: November 17, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	Instructional pamphlet for biomarker collection	2014/11/28
Instruments	Intake questionnaires package	2014/12/05
Instruments	Follow-up questionnaires package	2014/12/05
Instruments	Intake questionnaire package	2015/10/29
Instruments	Screening form	2015/10/29
Instruments	Follow-up forms	2015/10/06
Advertisement	flyer	2015/11/02
Other	Crisis management protocol (received for information only)	2015/10/29
Recruitment Items	consent to contact form	2015/05/29
Western University Protocol		2015/11/15
Letter of Information & Consent		2015/11/15

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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Appendix 2: Letter of Information

Western
HealthSciences

version: March 2018

Principal Investigator: Dr. David Walton

Funding source: Western internal funding, CIHR bridge grant, Canadian Pain Society

Letter of Information

Modeling recovery after traumatic injuries: A Longitudinal Databanking project

Dear Sir/Madam,

Thank you for your time in reviewing this letter of information and for considering participation in our study. Please be sure to read this letter in its entirety and have any questions you may have answered to your satisfaction before consenting to participate.

Why am I being invited to participate?

You are being invited to participate because you have indicated that you are a male/female at least 18 years old and are seeking care from emergency, medical or rehabilitation services for a recent accident or injury to your muscles, bones or ligaments, or because you have responded to one of the posted advertisements for this study.

You are not eligible for this study if any of the following apply to you. Please tell the research coordinator if any of these apply:

1. Severe gingivitis, periodontal disease, active dental caries (tooth decay), or any other active oral condition

2. Actively undergoing cancer treatment
3. You have a neuromuscular disorder (e.g. stroke, multiple sclerosis, ALS or 'Lou Gehrig's Disease')
4. You have an autoimmune disorder (e.g. rheumatoid or psoriatic arthritis, scleroderma, lupus)
5. You have severe heart, lung, kidney or liver disease that affects your ability to function in every day life
6. You currently have stomach ulcers, Celiac or Inflammatory Bowel Disease (Ulcerative colitis or Crohn's Disease)

What is this study about?

We are trying to understand the process of recovery over the 12 months following a traumatic injury, and to identify things (factors) that may explain why people differ in how they recover after these events. We will be collecting information including the nature of your injury, your biology, psychology, and past experiences all in the same period. Our goal is to not only improve understanding of *how* people recover following different types of injuries, but what factors influence that recovery. By identifying important factors we will start to work on developing new ways to treat those factors and eventually improve the likelihood of successful recovery for people injured in the future.

What will I be asked to do?

If you agree to participate, you will be provided with a package that includes almost all of the data collection instruments that you will be asked to complete on your own at home starting at least 48 hours after your injury. The procedures include questionnaires for you to complete and different vials into which you will provide saliva and a stool sample. Once collected, the samples can be stored in your home freezer until a member of the research team comes to pick them up. The questionnaires will be repeated 1, 2, 3, 6 and 12 months after you enter the study and the biological sampling will be repeated after 3 and 6, and 12 months. After the 12th month, your participation in the study will be complete. Below you will find more detailed information on the types of data instruments in this study.

1. **A set of questionnaires** that will ask you about a variety of different things. These include: i) your age, sex, work and educational status, ii) the nature of your injury

(type of injury, when it occurred, how long ago it occurred, a brief description of the injury itself), iii) your medical and legal involvement (if any), iv) experiences from your childhood, including bullying and home environment, v) recent stressors you may have experienced, vi) the stress you have experienced as a result of your injury, vii) the type and amount of symptoms and interference you have experienced as a result of your injury. You will have the choice of completing the questionnaires in either paper copy or online using a secured personalized and de-identified email link.

2. **Drool/Saliva (part 1)** – You will receive 3 specialized test tubes with sterile cotton swabs in each. You will start on a day that is convenient to you within 5 days of completing your questionnaires. A pamphlet explaining all procedures is included with the instruments. This pamphlet should be read in its entirety. The tubes with the cotton swabs are to be used 3 times during the same day – once immediately upon waking, again 20-30 minutes after waking, and again mid-afternoon between 2pm and 4pm. This will require you to chew the cotton swab for about 10 seconds before returning it to the test tube, sealing it and placing it in your freezer.

3. **Drool/Saliva (part 2):** You will receive a specialized test tube into which you will spit or drool a small amount of saliva BEFORE your nightly (bedtime) routine, before brushing but at least 2 hours after eating. Once completed, this and the other samples can be stored in your residential freezer until retrieved by a member of the research team.

4. **Serum:** A trained phlebotomist will draw 2 vials of blood from the vein on the front of your elbow or forearm.

The following two components are optional.

5. **Stool**: This is an optional part of the study. You will provide a sample of stool using a specialized, sterile tube with a Q-tip type cotton swab. This will simply require you to twirl the end of the swab in a piece of used bathroom tissue, sealing it in the test tube and placing in your freezer. Only a small sample is required, and this can be collected at any time of day.

6. **Hair:** This is an optional part of the study for which you will be compensated if you choose to participate. As long as you have at least 3cm of hair on your head, we will cut approximately 100 hairs from the back of your scalp in a manner that minimizes any obvious physical change in your hair style using sterile scissors. This will be done by a member of the research team, and will be repeated with saliva and blood collection.

We are collecting saliva samples in order to analyze the levels of specific proteins, which we are calling "biomarkers", that are typically present in the body and that may change during

times of stress. Specifically, these are classed broadly as the stress hormone *cortisol*, the gonadal hormone *testosterone*, and immune or inflammatory markers that are referred to as '*cytokines*'. Stool samples, on the other hand, will provide us with specific information regarding the different bacterial populations that inhabit your intestines. The types of bacteria in your intestines may be influenced as a result of significant stressors, such as trauma or injury. We will be looking to see if any major shifts in the types of bacteria occur in your system as you are recovering. There is some research that suggests certain genes play a role in the speed and effectiveness of recovery from an injury. The blood will allow us to look at very specific genes to help us understand what is driving different recovery trajectories. At this stage we are planning to target specific genes and explore them only for their potential role in your pain and recovery. None of these analyses will indicate the current existence or future potential of any disease states. However, your data will be included as part of 'databank' for ongoing research by our or other researchers for currently unplanned research questions. These may involve sequencing your entire genome. Finally, from your hair we will be able to determine the presence of different hormones that have been stored in your hair from the time before your injury.

It is important to understand that everyone's body is different and it's currently difficult to say what is 'good' or 'bad' in these analyses. For that reason, these tests should not be considered diagnostic of any specific diseases or conditions.

Once all samples have been collected, contact the research team at Western University. These samples will then be retrieved from you by a member of the research team at a day, time and location that is convenient for you. A subset of the questionnaires will be completed again at 1, 2, 3, 6 and 12 months after you enter the study (approximately 10 minutes to complete). The biological samples (saliva, blood, stool) will be collected at 3, 6 and 12 months. After the 12th month, your participation in the study is complete.

What are the risks and benefits of participating?

There are no immediate anticipated benefits to you from participating in this study. However, if our predictions are correct and we are able to identify dysfunction in key systems that can explain at least part of the pain experience, this may open new avenues to treatment that may have benefit to you or others in the future.

All participants may receive a final report of the study in which the results (using only group data) will be presented. If you wish to receive this report, you will need to indicate this on the consent form and include contact information to which the report should be sent. Those participants who wish to receive their own individual results will be required to contact the Lead Researcher Dr. David Walton directly to make that request. His contact information can be found at the end of this letter. Keep in mind that the data associated with this study is not a medical record and should not be used as such. We will keep the Master List that links your name with your ID number for 6 months after your completion of the study after which it will be shredded for confidentiality and privacy protection reasons. This means that we will not be able to provide your individual results beyond 1 year from your injury.

The risks to participation are minimal and are largely inconveniences due to time. The salivette (saliva collection tube with cotton swab) samples must be performed at three separate times throughout a single day which may be a mild disruption to your daily routine for that day. Improper collection and handling of stool samples MAY pose a risk of bacterial contamination/infection, however, if carefully performed (including washing your hands afterwards), this risk is quite minimal. The blood will be drawn using a standard protocol by a trained phlebotomist that you have likely experienced before in a doctor's office or the Red Cross. Completion of the questionnaires may lead to some people experiencing emotional distress, especially those that ask you to recall and reflect upon childhood experiences if yours were not positive. We have provided suggestions for managing emotional distress, should you experience it, at the end of this letter and in the forms package itself.

We will do everything in our power to ensure your data are kept secure and confidential. However, we cannot guarantee against a data breach regardless of how good our physical and virtual security is. Your data will be stored on the REDCap (Research Electronics Data

Capture) online database management system. This system, created by researchers at Vanderbilt University, stores all data in fully encrypted format with HIPAA-compliant protections in place for both physical and electronic data security. The servers themselves are located at and managed by the London Hospitals Network Data Centre in London, Ontario Canada. When data are downloaded for analysis they will be stored on the dedicated networked drive of the Pain and Quality of Life Integrative Research Lab, the servers for which are also located on Western's campus. Your biological samples will be stored in research-specific secured scientific freezers located either on Western's campus or at St. Joseph's hospital in London. Your samples will be marked only with a study-specific unique ID number when stored, no personally identifiable information will be stored with the samples and only the lead researcher and a PhD student on the study will have access to the master list that connects your name with your ID number. Despite these protections, the risk of data breach or loss is possible and we want to ensure you're aware of this. Should this happen you will be quickly informed.

Will I be compensated for my participation?

You have different options for the degree to which you wish to participate in this study. The minimum level of participation is to complete the paper or electronic forms, saliva, and blood draw. This would be done once when you enter the study, then at 1, 2, 3, 6 and 12 months later. Each follow-up will likely take about 45 minutes of your time, and you will receive $30 total for participating in this level of the study. The hair and stool are optional components, and for each one you will receive an additional $15 ($30 for both). We recognize that collecting these samples is no small commitment, but can be completed in its entirety in a single day and a total anticipated time commitment of approximately 1 hour at each collection period. Out of respect for your time, you will be reimbursed a minimum of $180 total for participating in each phase of this study (intake and 1, 2, 3, 6, and 12 months). If you complete the two additional components you are eligible for an additional $30 per session, up to an additional $120 for the entire study ($300 total reimbursement).

Who will have access to my information?

A unique randomly-generated 4-digit ID number will appear on all forms belonging to you for the sole purpose of keeping your data de-identified while allowing the team to connect the data you provide for analysis. Once entered, all survey data are stored on the secure, encrypted REDCap server of the London Hospitals Network Data Centre and the paper forms are shredded. Your biological samples (blood, hair, saliva, stool if applicable) are stored using separate barcodes in a secured scientific freezer that is physically located inside Victoria Hospital (London Health Sciences Centre) that is only accessible by approved people. Western University's REB and representatives from Lawson's Quality Assurance and Education Program will have access to participant's data to ensure that it is following the proper laws and regulations. Outside of these groups, your specific information will not be shared with anyone without your express written consent to do so.

Note some of the tools to be completed are meant to measure severity of symptoms related to depression or anxiety. *IF* your responses lead to a score that is suggestive of either significant depression or anxiety, your family doctor will be contacted to inform him/her of the results of the scale and what they may mean. It will ultimately be up to your family physician to decide how and when he/she should follow up with you if at all.
Data will be retained in anonymous form indefinitely as an ongoing database, but your contact information will be uncoupled from your data 6 months after you complete the final data collection and stored in a separate database for 15 years. This means that there may be additional research conducted in the future about which we do not currently know that may use some or all of your data and for which you may not be able to be contacted for consent. If you should wish to have your data *removed* from the database, you will need to contact the lead researcher Dr. David Walton whose contact information can be found below and request it. You will *not* be required to provide an explanation.

Voluntary participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time. If you choose to withdraw from the study, you may request to have your contributions to that point removed, at any time up until 6 months after you are done the study. Withdrawal from the study or refusal to participate is your decision, and may be done without the requirement of explanation on your part. Withdrawal will in no way affect your current or future relationship with any of the research team or clinicians associated with the study.

What if I want more information?

You may contact the lead researcher, Dr. David Walton, at Western University (London, Canada) if you require any further clarification. His contact information can be found below. If you have any questions about your rights as a research participant or the conduct of the study you may contact the Office of Research Ethics. You are encouraged to keep this letter of information for your own records.

If you wish to receive a summarized copy of the results of this study and/or your individual results, you may leave your email address on a separate sheet. This sheet will be held by the research coordinator and the email addresses only used to provide results. If you choose to have electronic surveys emailed to you, your email address will be retained separately.

We thank you in advance for considering participation in this study. *You do not waive any legal rights by signing this consent form*.

Sincerely,

David Walton BScPT, PhD

Lead Researcher

Co-researchers:
Ruth Lanius MD PhD
Stan Van Uum MD, PhD
Greg Gloor PhD
Walter Siqueira DDS, PhD
Eric Wong MD
Doug Fraser MD, PhD
Melanie Colombus
Kristine Van Aarsen
Marnin Heisel MD, PhD
Joshua Lee PhD (c)
Sadia Siraj MSc (c)
Gordon Good
Joy MacDermid PT PhD
Lynn Cooper
Jordan Miller PT PhD (c)
Siobhan Schabrun PT PhD
James Elliott PT PhD
Paul Phares
Ryan Power

Consent form

Modeling recovery from traumatic injuries

Principal Investigator: Dr. David M. Walton PT PhD

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I also consent to being contacted by the Lead Researcher in the case any of my scale scores suggest possible problems with depression or anxiety.

Please indicate the level of study participation to which you are consenting by placing a check in the appropriate circle:

◯ Paper forms, saliva and blood only (paper forms at 1, 2, 3, 6, and 12 months, approximately 20 minutes each, saliva and blood at 3, 6, and 12 months. $30 compensation per period, max $180)

◯ (Optional): Provide stool at intake, and 3, 6, and 12 months (additional $15 per period, max $60)

◯ (Optional): Hair provided at intake, and 3, 6, and 12 months (additional $15 per period, max $60)

Please indicate how you would like to receive questionnaires (both collect the same information):

◯ Paper form (conventional mail)

◯ Electronic form (email)

_____

Participant name (print)

_____

_____

Participant signature   Date

_____

Person obtaining consent (print)

_____

_____

Signature of person obtaining consent   Date

Appendix 3: Ethics approval for the SYMBIOME project

HiREB

Hamilton Integrated Research Ethics Board

Hamilton Integrated Research Ethics Board
AMENDMENT REQUEST

REB Project #: 14-138

Principal Investigator: Dr. Joy MacDermid

Project Title: The Development and Validation of the Pain GRADE Survey

Document(s) Amended with version # and date:

> Protocol - Version: 4.0 Dated; 10 February, 2017
> Consent Form - Version: 3.0 Dated: 09 February, 2017
> Survey - Demographics for PT Trainees Version: 1.0 Dated; 10 February, 2017
> Recruitment Ad - Pain GRADE Survey Study Version: 1.0 Dated: 10 February, 2017
> Administrative Change - Add Student Investigator Joseph Chuang
> Administrative Change - Add Student Investigator Allyssa Kaplan
> Administrative Change - Add Student Investigator Stephanie Lupton
> Administrative Change - Add Student Investigator Deidra McDermid

[X] **Amendment approved as submitted**

[ ] **Amendment approved conditional on changes noted in "Conditions" section below**

[ ] **New enrolment suspended**

[ ] **Study suspended pending further review**

Level of Review:
 [ ] Full Research Ethics Board
 [X] Research Ethics Board Executive

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; For studies conducted at St. Joseph's Hospital, HIREB complies with the health ethics guide of the Catholic Alliance of Canada

<u>2/16/2017</u>
Date

x Mark Inman, MD, PhD, Chair

All Correspondence should be addressed to the HIREB Chair(s) and forwarded to:
HIREB Coordinator
293 Wellington St. N, Suite 102, Hamilton ON L8L 8E7
Tel. 905-521-2100 Ext. 42013 Fax: 905-577-8378

HAMILTON INTEGRATED RESEARCH ETHICS BOARD (HIREB)
AMENDMENT REQUEST

1. **Locally Responsible Investigator and contact information:** Dr. Joy MacDermid, ███████████

2. **Research Project Title:** The Development and Validation of the Pain GRADE Survey

3. **REB Project #:** 14-138

4. **Please list the NEW version number and version date of ALL documents being submitted for approval:**
   NOTE: THIS SECTION MUST BE COMPLETED.

5.	PROPOSED CHANGES AFFECT:	Y IF YES
(a)	**PROTOCOL (If you are submitting a protocol amendment we ask that you attach either a Summary of Changes or a detailed outline of each revision and the rationale)**	
	• Study objectives, statistical analysis, design or methods	
	• Study instruments, questionnaires, etc.	
	• Number of participants – **We are increasing the total sample size from 600 to 800 respondents**	Y
	• Participant recruitment methods – **We will recruit PT trainees through social media.**	Y
	• Eligibility criteria (inclusion/exclusion criteria)	
	• Study end date	
	• Principal and/or co-investigators: If PI is changing, include a letter signed by the outgoing PI and the incoming PI indicating they both agree to the change. Attach a revised consent form which reflects the change of PI/Co-I. **-We are adding PT student co-investigators.**	Y
	• Health Canada Therapeutic Products Directorate (TPD/HCNOL) approval: If TPD/HCNOL approved the original protocol, then TPD/HCNOL approval is also required for this amendment. We **CANNOT** accept without the TPD/HCNOL. **Copy of HCNOL Attached [ ].**	
	• Other	Y
(b)	**CONSENT FORM – Version 3 (February 9, 2017)**	Y
(c)	**INFORMATION SHEET – Version 3 (February 9, 2017)**	Y
(d)	**ADVERTISEMENT AND RECRUITMENT MATERIALS – New recruitment add for PT trainees v1 (February 10, 2017)**	
(e)	**ADMINISTRATIVE**	
	• Change in name of Sponsor	
	• Change in contact information	
	• Other (specify)	
(f)	**OTHER** (specify)	

6. Will there be any increase in risk, discomfort or inconvenience to the participants?   [ ] YES   [X] NO
   If YES, provide detailed explanation/justification.

7. **What follow-up action do you propose for participants who are already enrolled in the study?**

   Check [Y]:   [ ]   Inform study participants ASAP
                     [ ]   Re-consent participants with the revised the consent/assent forms (append)
                     [ ]   Other (please describe)
                     [Y]   No action required

███████████████

_____   _____February 13, 2017_____
Signature of Locally Responsible Investigator   Date

HIREB Amendment Form
Version May 2016

PARTICIPANT INFORMATION SHEET

Title of Study: The Development and Validation of the Pain GRADE Survey

Principal Investigator: Joy MacDermid, PhD, McMaster University

Co-Investigator: David Walton, PhD, Western University

Student Investigators: Joseph Chuang, MPT (c), Western University
Allyssa Kaplan, MPT (c), Western University
Stephanie Lupton, MPT (c), Western University
Deidra McDermid, MPT (c), Western University

Sponsor: Canadian Institutes of Health Research

You are being invited to participate in a research study conducted by Dr Joy MacDermid.

In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study. Please take your time to make your decision. Feel free to discuss it with your friends and family.

WHY IS THIS RESEARCH BEING DONE?

Pain is an important health concern, yet it is often poorly treated. It is important to understand how pain experiences and expectations are influenced by gender so that healthcare providers can manage patients with sensitivity to these gender differences. The researchers have developed a new survey that measures how people differ in their experiences and expectations of pain.

WHAT IS THE PURPOSE OF THIS STUDY?

To assess the reliability and validity of a new survey about gender and pain experiences and expectations.

WHAT WILL MY RESPONSIBILITIES BE IF I TAKE PART IN THE STUDY?

If you volunteer to participate, you will be asked to answer a surveys about your pain experiences and expectations and what you do to care for your home and family. It will take 20-25 minutes to answer all the surveys.

You may also be asked to answer the same surveys again within 1 week of the first completion.

Pain GRADE Survey Study
Consent Form Date: February 9, 2017   Page 1 of 4   Protocol # and version: 3
Pt. initial _____

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WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

There are no foreseeable risks associated with this study. You may feel worried about your responses. There are no right or wrong answers and your responses will be kept confidential so you should not worry about this.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

There will be a total of 800 participants in the study: 500 healthcare professionals and trainees; and 300 participants who have experienced pain

A subset of 200 participants will be asked to do the survey again after about 1 week.

WHAT ARE THE POSSIBLE BENEFITS FOR ME AND/OR FOR SOCIETY?

We cannot promise any personal benefits to you from your participation in this study. The results of this study may benefit society and the scientific community by providing health care providers with a survey tool that can help them improve their care of people experiencing pain.

WHAT INFORMATION WILL BE KEPT PRIVATE?

Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name and e-mail address will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed will be securely stored in a locked office in the research laboratory.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton Integrated Research Ethics Board may consult your research data. However, no records which identify you by name or initials will be allowed to leave the hospital. By signing this consent form, you or your legally acceptable representative authorize such access.

If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure.

CAN PARTICIPATION IN THE STUDY END EARLY?

If you volunteer to be in this study, you may withdraw at any time. You have the option of removing your data from the study. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

You will not be paid to participate in this study.

WILL THERE BE ANY COSTS?

There are no costs associated with this study.

Pain GRADE Survey Study
Consent Form Date: February 9, 2017   Page 2 of 4   Protocol # and version: 3
Pt. initial _____

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IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions about the research now or later, please contact:

I understand the terms of participation as outlined above and by clicking on the Agree button below I am giving my consent to participate in the study.

[Include an Agree and Submit button immediately following this statement]

Pain GRADE Survey Study
Consent Form Date: February 9, 2017   Page 3 of 4   Protocol # and version: 3
Pt. initial _____

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FOR PARTICIPANTS COMPLETING PAPER SURVEYS ONLY

CONSENT STATEMENT

Participant:

I have read the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I agree to participate in this study. I understand that I will receive a signed copy of this form.

_____

Name   **Signature**   **Date**

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

_____

Name, Role in Study   **Signature**   **Date**

Pain GRADE Survey Study
Consent Form Date: February 9, 2017   Page 4 of 4   Protocol # and version: 3
Pt. initial _____

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Curriculum Vitae

Name: Maryam Ghodrati

Post-secondary   University of Social Welfare and Rehabilitation Sciences
Education and   Tehran, Iran
Degrees: 2015 - 2017 MSc in Physical Therapy

                        Tabriz University of Medical Sciences
                        Tehran, Iran
                        2011 – 2015 BSc in Physical Therapy

Honours and Awards

- Aug 2020 - Accepted and completed the Cohort FIVE mentorship of the Level Up Initiative as a mentee.
- Jun 2020 - Master the Entrepreneur Skillset, University of Western Ontario, Canada.
- May 2020 - WESTERN CERTIFICATE IN UNIVERSITY TEACHING AND LEARNING, Centre for Teaching and Learning, University of Western Ontario, Canada.
- July 2019 - Connaught Summer Institute in Pain (University of Toronto) - "Individual Experience of Pain" – Registration + $500 (travel and accommodation)
- April 2019 - Recipient of the Trainee Travel Award from Canadian Pain Society.
- October 2018 - Nominated by the Western University for the national level of Vanier Canada Graduate Scholarship Awards.
- March 2019 - *3-Minute* Thesis Competition – The top 20 finalists of Western University)
- July 2015 - Ranked 1st among all BSc Students in Physiotherapy, School of Rehabilitation Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.
- January 2011 - Ranked 5th nationally in 12th Khwarizmi young award competition, Tehran, Iran.

Related Work Experience

- Physiotherapy Resident - CBI Health Centre, London, ON - May 2021 - ongoing
- Physiotherapist in Amin Physiotherapy Clinic, Tehran, Iran – 2015-2017
- Graduate Student Assistant (GSA), Research Assistant for Dr. Pamela Houghton, Faculty of Rehabilitation Sciences, Western University, London, ON, Canada - May 2020 – May 2021
- Teaching Assistantship, PT9511, Western University, Sep 1-Dec 31, 2020
- July 3rd, 2020, Volunteer poster judge, PT9590 virtual research day, Western University.
- July 12th, 2019, Volunteer poster judge, PT9590 virtual research day, Western University.
- Teaching Assistantship, PHYSTHER 9690, Western University, May 1- Aug 31, 2020
- Teaching Assistantship, PT9511, Western University, Sep 1-Dec 31, 2019
- Teaching Assistantship, PHYSTHER 9680, Western University, May 1- Aug 31, 2019
- Teaching Assistantship, PHYSTHER 9690, Western University, May 1- Aug 31, 2019
- December 2019, In the scheduling committee and reviewing abstracts, HRS Graduate Research Conference 2020, Western University.
- December 2018, In the scheduling committee and reviewing abstracts, HRS Graduate Research Conference 2019, Western University.
- Teaching Assistantship & Guest Lecturer, PT9511, Western University, Sep 1-Dec 31, 2018
- Teaching Assistantship, PT9550L, Western University, May 1- Aug 31, 2018
- July 2018-Present, Volunteer Reviewer, Physical Treatments: Specific Physical Therapy Journal (PTJ).
- Teaching Assistantship, PT9511, Western University, Sep1-Dec 31, 2017
- Scientific Editor and Co-Author, "Application of resistance and weight training techniques in corrective exercises", Book. Oct 2017, (in progress).
- Teaching Assistantship & Guest Lecturer, PT- Orthopedic, USWR, Sep 1-Dec 31, 2016
- Aug 2013, Assistant editor, fellow writer and scientific editor. "Relaxation massage based on Swedish Massage Techniques". Contribution Value: It was donated to Physiotherapists and Massage Therapists for improving their practical knowledge.
- Mar 2012, Assistant editor, fellow writer and scientific editor. "Abdominal and core muscles exercises". Contribution Value: It was donated to the Gyms and Athletes for principled exercises and correct training.

- Feb 2012, Assistant editor, fellow writer and scientific editor. "Diabetes and sports protocols". Contribution Value: Donated to the Diabetes Association for public use.
- Apr 2012, Workshop Facilitator, A free workshop "Sports training and diabetes" with the aim of promoting general knowledge and developing a healthy living. Organised by "Knowledge Enhancer Sport Science Institute (KESSI)"
- Jul 2010, Course Facilitator, Specialized course about the role of exercise in preventing osteoporosis. Organised by "Knowledge Enhancer Sport Science Institute (KESSI)"
- Feb 2010, Course Facilitator, Specialized course about the science of achieving fitness goals. Organised by "Knowledge Enhancer Sport Science Institute (KESSI)"
- May 2010, Assistant editor, fellow writer and scientific editor. "What you should know about Osteoporosis". Contribution Value: Improve knowledge of public about Osteoporosis.
- Jan 2007, Principal Investigator and Director of some documentaries.

Publications

Papers:

- **Maryam Ghodrati**, David M. Walton, and Joy C. MacDermid (2021). Exploring the Domains of Gender as Measured by a New Gender, Pain and Expectations Scale. Women's Health Reports. http://doi.org/10.1089/whr.2020.0109
- David M. Walton, Paul Tremblay, Wonjin Seo, James Elliott, **Maryam Ghodrati**, Curtis May, Joy C. MacDermid (2021). Adverse Childhood Experiences show a sex-differentiated influence on reaction to adulthood musculoskeletal trauma. European Journal of Pain.
- Mahboobeh Abdolalizadeh, Zahra Mosallanezhad, **Maryam Ghodrati**, Ahmad Saeedi, Hossein Kamyab (2021). Cross-cultural adaptation and validation of the Persian version of the Physical Therapy Outpatient Satisfaction Survey. International Journal of Therapy and Rehabilitation. https://doi.org/10.12968/ijtr.2020.0058
- Mahboobeh Abdolalizadeh, **Maryam Ghodrati**, Ahmad Saeedi, Hossein Kamyab, Ali Rezaie Rayeni Nejad (2021). Translation, Reliability Assessment, and Validation of the Persian Version of MedRisk Instrument for Measuring Patient Satisfaction With Physical Therapy Care (20-Item MRPS). Journal of Modern Rehabilitation
- Mahboobeh Abdolalizadeh, Zahra Mosallanezhad, Ahmad Saeedi, **Maryam Ghodrati**, Ali Rezaie Rayeni Nejad (2021). Measurement Properties of Physical Therapy Patient

Satisfaction Questionnaire in an Iranian Musculoskeletal Population. Physical Treatments-Specific Physical Therapy Journal

- Mohamad Rostami, Zahra Mosallanezhad, Sepideh Ansari, Dawson Kidgell, Tahere Rezaeian, Enayatollah Bakhshi, **Maryam Ghodrati**, Shapour Jaberzadeh (2020). The effects of consecutive sessions of anodal transcranial direct current stimulation over the primary motor cortex on hand function in healthy older adults. Archives of Gerontology and Geriatrics. https://doi.org/10.1016/j.archger.2020.104063.

- Armaghan Dabbagh, Joy C MacDermid, Joshua Yong, Tara L Packham, Luciana G Macedo, **Maryam Ghodrati** (2021). Diagnostic accuracy of sensory and motor tests for the diagnosis of carpal tunnel syndrome: a systematic review. BMC Musculoskeletal Disorders

- Walton DM, Pourkazemi F, **Ghodrati M**, Elliott JM (2020). A Mediational Analysis of Stress, Inflammation, Sleep, and Pain in Acute Musculoskeletal Trauma. The Clinical Journal of Pain. 10.1097/AJP.0000000000000790.

- Saber Jabari, Zahra Salahzadeh, Parvin Sarbakhsh, Mandana Rezaei, Mehdi Farhoudi, **Maryam Ghodrati**. (2020). Validity and reliability of the Persian version of the Henry Ford Hospital headache disability inventory questionnaire. Archives of Iranian Medicine. Accepted.

- **M. Ghodrati**, Z. Mosallanezhad, M. Shati, M. Noroozi, MR. Nourbakhsh (2019). Adding Temporomandibular joint treatments to routine physiotherapy for patients with non-specific chronic neck pain: A randomized clinical study. Journal of Bodywork & Movement Therapies. DOI:https://doi.org/10.1016/j.jbmt.2019.11.004.

- Modarresi SH, **Ghodrati M,** Aref-Eshghi E. (2018). Using precision medicine to reduce falls in people with Alzheimer's disease. Health Science Inquiry Journal. 33-35.

- **Ghodrati M**, Mosallanezhad Z, Shati M, Rastgar Koutenaei F, Nourbakhsh M R, Noroozi M. (2017). The Effect of Combination Therapy; Manual Therapy and Exercise, in Patients With Non-Specific Chronic Neck Pain: A Randomized Clinical Trial. PTJ (Physical Treatments - Specific Physical Therapy Journal). 7(2): 113_121.

- Forouzan Rastgar Koutenaei, Zahra Mosallanezhad, Mehrdad Naghikhani, Kamran Ezati, Akbar Biglarian, Mahdi Nouroozi, **Maryam Ghodrati**. (2017).The Effect of Low Level Laser Therapy on Pain and Range of Motion of Patients With Knee Osteoarthritis. PTJ (Physical Treatments - Specific Physical Therapy Journal). 7(1): 13-18.

- Ghazaleh Vahedi, Zahra Mosallanezhad, Yahya Sokhangooi, Hamideh Abyaneh, Fakhrosadat Jafari Mousavi, **Maryam Ghodrati**, Fatemeh Ehsani, Afsun Nodehi-Moghadam. (2016). Small Ball Exercise Program forPatients With Chronic Nonspecific Low Back Pain: A Randomized Clinical Trial. PTJ (Physical Treatments - Specific Physical Therapy Journal). 6(2): 71-78.

Submitted Papers:

- **Maryam Ghodrati**, David M. Walton, and Joy C. MacDermid (2021). Exploring the contributions of sex and traditionally genderized interpersonal-expressive traits to variability in post-trauma pain ratings. The Clinical Journal of Pain. Submitted
- Shirin Modarresi, Michael J. Lukacs, **Maryam Ghodrati**, Shahan Salim, Joy C. MacDermid, David M. Walton, CATWAD consortium group (2021). A systematic review and synthesis of psychometric properties of the Numeric Pain Rating Scale and the Visual Analog Scale for use in people with neck pain. The Clinical Journal of Pain. Submitted
- Afsoon Asadzadeh, Taha Soltani, Zahra Salahzadeh, **Maryam Ghodrati**, Peyman Rezaei (2021). Effectiveness of Virtual Reality Exercise Therapy in Rehabilitation. Informatics in Medicine Unlocked. Submitted.
- Afsoon Asadzadeh, Taha Soltani, Zahra Salahzadeh, Maryam Ghodrati, Peyman Rezaei (2019). Effectiveness of Virtual Reality Exercise Therapy in Rehabilitation: A Systematic Review. Physical Activity & Health. Submitted.

Peer-reviewed Abstracts / Presentations:

- **Maryam Ghodrati**, Joy MacDermid, David M. Walton (June 2021). Poster presentation: Exploring the contributions of sex and traditionally genderized personality characteristics to variability in post-trauma pain ratings). IASP 2021 Virtual World Congress on Pain
- Marudan Sivagurunathan, Joy MacDermid, **Maryam Ghodrati** (Oct 2020). Poster presentation: Qualitative Study on Gender and Post-operative pain management. American Society of Hand Therapists (ASHT) 2020 Virtual Conference
- **Maryam Ghodrati**, David M. Walton, Joy MacDermid (April 2019). Poster presentation: Exploring the dimensions of gender in the context of a new Gender, Pain and Expectations Scale for pain research. The 2019 Canadian Pain Society 40th Annual Scientific Meeting. Toronto, ON, Canada.
- The top 20 finalists of Western University 3-Minute Thesis Competition – Oral presentation (London, ON), March 21, 2019

- Western University 3-Minute Thesis Competition – Oral presentation (London, ON), March 5th, 2019
- David M. Walton, Mohamad F. Fakhereddin, Joshua Y. Lee, **Maryam Ghodrati**, James D. Eliot. Poster presentation: The Traumatic Injuries Distress Scale: Further Evaluation and Meaningful Thresholds for Predicting Pain and Functional Recovery after MSK Trauma. The 2019 Canadian Pain Society 40th Annual Scientific Meeting. Toronto, ON, Canada.
- **Maryam Ghodrati**, David M. Walton, Joy MacDermid (February 2019). Oral presentation: Exploring the influence of gender and biological factors on pain, stress, depression, and recovery after trauma. Health and rehabilitation sciences graduate research conference. London, ON, Canada.
- **Maryam Ghodrati**, Mosallanezhad Z, Shati M, Noroozi M, Nourbakhsh M R. (December 2018). Poster presentation: The effect of adding Temporomandibular joint treatments to routine physiotherapy on pain, disability, and range of motion in non-specific chronic neck pain patients: a randomized clinical trial. The 19th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- Joshua Y. Lee, Mohamad F. Fakhereddin, **Maryam Ghodrati**, David M. Walton. (September 2018). Poster presentation: Exploring non-linear and interactive relationships between psychological and physiological markers of post-traumatic pain and distress: toward a biopsychosocial model of pain. 17th World Congress on Pain 2018. Boston, USA.
- Mohamad F. Fakhereddin, Joshua Y. Lee, **Maryam Ghodrati**, James D. Eliot, David M. Walton. (May 2018). Poster presentation: Exploring Recovery Trajectories and Predicting Outcomes of Acute Musculoskeletal Trauma: Further Exploration of the Prognostic Validity of the Traumatic Injuries Distress Scale (TIDS). 17th World Congress on Pain 2018. Boston, USA.
- Joshua Y. Lee, Mohamad F. Fakhereddin, **Maryam Ghodrati**, David M. Walton. (May 2018). Poster presentation: Exploring non-linear and interactive relationships between psychological and physiological markers of post-traumatic pain and distress: toward a biopsychosocial model of pain. Canadian Bone and Joint Conference 2018. London, ON, Canada.
- Mohamad F. Fakhereddin, Joshua Y. Lee, **Maryam Ghodrati**, David M. Walton. (May 2018). Poster presentation: Exploring Recovery Trajectories and Predicting Outcomes of Acute Musculoskeletal Trauma: Further Exploration of the Prognostic Validity of the Traumatic Injuries Distress Scale (TIDS). Canadian Bone and Joint Conference 2018. London, ON, Canada.

- **Ghodrati M**, Mosallanezhad Z, Shati M, Nourbakhsh M R, Noroozi M. (1st February 2018). Poster presentation: The effect of combination therapy on neck pain. Health and rehabilitation sciences graduate research conference. London, ON, Canada.
- Zahra Mosallanehzhad, Reza Mohammadi, Gholam Reza Sotoudeh, Anahita Hasannejad, **Maryam Ghodrati**, Ghazaleh Vahedi. (28-29 December 2016). Oral presentation: Application of Myofascial Release Techniques in Managing Spinal Scoliosis. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Zahra Mosallanehzhad, Anahita Hasannejad, Hoda Fasihnia, Ghazaleh Vahedi. (28-29 December 2016). Poster presentation: The relation between neck pain and TMJ disorders. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Noureddin karimi, Vosen Chen. (28-29 December 2016). Poster presentation: The effect of whole-body vibration therapy on spinal cord injury patients. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- Ghazaleh Vahedi, Zahra Mosallanehzhad, Anahita Hasannejad, **Maryam Ghodrati**. (28-29 December 2016). Poster presentation: The effect of adding dry needling of pelvic muscles on improvement of patients with chronic low back pain. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran
- Anahita Hasannejad, Zahra mosallanehzhad, Hoda Fasihnia, **Maryam Ghodrati**. (28-29 December 2016). Poster presentation: Shockwave impact on the cellulite of buttocks in relation to low back pain. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- Anahita Hasannejad, Zahra mosallanehzhad, Hoda Fasihnia, **Maryam Ghodrati**. (28-29 December 2016). Poster presentation: The effect of Magnet Therapy in chronic pelvic pain. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- Ghazaleh Vahedi, Zahra Mosallanehzhad, Anahita Hasannejad, **Maryam Ghodrati**, Gholam Reza Sotoudeh. (28-29 December 2016). Oral presentation: The Effect of Electro-acupressure compared with Physiotherapy on Low Back Pain Patients. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Farideh Dehghan Manshadi. (28-29 December 2016). Oral presentation: Correlation between sagittal pelvic inclination and pelvic floor muscle dysfunction. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- Afsun Nodehi Moghadam, **Maryam Ghodrati**, Sirvan Ghorbanipour, Poorya Yaghmaei, Fatemeh Khassaf. (28-29 December 2016). Oral presentation: Hyper Mobility and Low Back Pain in the Athletic Population. The 17th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Zahra Mosallanehzhad, Mohammad Rostami, Parisa Anvari. (9-11 November 2016). Oral presentation: The Effect of Adding Electro acupuncture to

Physiotherapy on Improvement of Patients with multiple sclerosis. 13th international MS Congress of Iran, Tehran, Iran.

- **Maryam Ghodrati**, Afsun Nodehi-Moghadam. (26 May 2016). Poster presentation: Children's rehabilitation after burning. First Iranian wound and burn congress, Shiraz, Iran.
- Parisa Anvari, Zahra Mosallanehzhad, Mohamad Rostami, **Maryam Ghodrati**. (4-6 May 2016). Poster presentation: The effect of transcranial direct current stimulation on neuropathic pain in SCI patients. The 27th Iranian Annual Physiotherapy Congress Iran, Tehran, Iran.
- Arsalan Ghorbanpour, **Maryam Ghodrati**, Omid Ghasemi. (4-6 May 2016). Poster presentation: The effect of mobilization of peripheral joints on osteoarthritis. The 27th Iranian Annual Physiotherapy Congress Iran, Tehran, Iran.
- Mohadese Saghayian, Iraj Abdollahi, **Maryam Ghodrati**. (4-6 May 2016). Poster presentation: The effect of biofeedback on rehabilitation patients after stroke, The 27th Iranian Annual Physiotherapy Congress Iran, Tehran, Iran.
- Mohamad Rostami, Zahra Mosallanezhad, **Maryam Ghodrati**. (4-6 May 2016). Poster presentation: Does anodal transcranial direct current stimulation enhance the excitability of the motor cortex and motor function in healthy individuals and subjects with stroke, The 27th Iranian Annual Physiotherapy Congress Iran, Tehran, Iran.
- Fakhrosadat Jafari Mousavi, Zahra Mosallanehzhad, bijan khorasani, Enayatollah Bakhshi, **Maryam Ghodrati**. (4-6 May 2016). Poster presentation: Effect of Shock wave on fat thickness and skin quality in the thigh. The 27th Iranian Annual Physiotherapy Congress Iran, Tehran, Iran.
- **Maryam Ghodrati**, Iraj Abdollahi, Mohadese Saghayian. (4-6 May 2016). Poster presentation: Clinical scales for the assessment of spasticity. The 27th Iranian Annual Physiotherapy Congress, Tehran, Iran.
- **Maryam Ghodrati**, Noureddin karimi, Marjan Roshan Ghias, Mohadese Saghaeian. (4-6 May 2016). Poster presentation: The effects of rest position of hip and knee on post femoral angiography pain. The 27th Iranian Annual Physiotherapy Congress, Tehran, Iran.
- **Maryam Ghodrati**, Ghazaleh Vahedi, Zahra Mosallanehzhad. (3-4 March 2016). Oral presentation: The effect of adding dry needling of upper trapezius muscle on the improvement of patients with chronic neck pain. The 1st national congress of paramedical students. Mazandaran, Iran.
- **Maryam Ghodrati**, Noureddin karimi. (3-4 March 2016). Poster presentation: Relation between orofacial pain and neurovascular disorders. The 1st national congress of paramedical students, Mazandaran, Iran.

- **Ghodrati M**, Mosallanezhad Z, Gholam Reza Sotoudeh, Reza Mohammadi. (3-4 March 2016). Poster presentation: Head trauma after natural disasters and the role of rehabilitation. The 1st national congress of paramedical students, Mazandaran, Iran.
- **Maryam Ghodrati**, Sakineh Goljaryan. (24-25 February 2016). Oral presentation: Passive muscle shortening device (PMSHD), a new invention. The 5th national students' Congress on new horizons of rehabilitation sciences, Shiraz, Iran.
- Zahra Mosallanehzhad, **Maryam Ghodrati**, Gholam Reza Sotoudeh. (6-8 January 2016). Oral presentation: Rehabilitation in Disasters. The 7th international congress on health in emergencies and disasters, Tehran, Iran.
- **Ghodrati M**, Mosallanezhad Z, Gholam Reza Sotoudeh, Reza Mohammadi. (23-24 December 2015). Poster presentation: Spinal cord injury and physiotherapy in natural disasters. The 16th Seminar in Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Noureddin karimi. (23-24 December 2015). Poster presentation: Masticatory myofascial pain. The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Noureddin karimi. (23-24 December 2015). Poster presentation: Orofacial Pain and Headache. The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati,** Noureddin karimi. (23-24 December 2015). Poster presentation: Effect of spinal cord injury on the respiratory system. The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.
- Mitra Rouhani, Mohadese Saghayian, Noureddin karimi, **Maryam Ghodrati**. (23-24 December 2015). Poster presentation: Exercise training for Low Back Pain; which method? (Comparing the Motor Control exercise with other types). The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.
- **Maryam Ghodrati**, Mitra Rouhani, Mohadese Saghayian, Noreddin Karimi. (23-24 December 2015). Oral presentation: Smartphone syndrome (SPS). The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.
- Mohadese Saghayian, **Maryam Ghodrati**, Mitra Rouhani, Noreddin Karimi. (23-24 December 2015). Oral presentation: The effect of environmental, socio-economy and psycho-social factors on girls' posture during puberty. The 16th Seminar on Specific Spine Physical Therapy, Tehran, Iran.

Professional Development

Certifications

- Apr 2020, Articulate Storyline Essential Training, LinkedIn Learning
- Apr 2020, Articulate Storyline Quick Tips, LinkedIn Learning
- Apr 2020, Instructional Design Essentials: Models of ID, LinkedIn Learning
- Apr 2020, Teaching Techniques: Classroom Management, LinkedIn Learning
- Apr 2020, Learning to Teach Online, LinkedIn Learning
- Apr 2020, Learning How to Increase Learner Engagement, LinkedIn Learning
- Apr 2020, Teaching Techniques: Developing Curriculum, LinkedIn Learning
  Aug 2020, ACCEPTED and completed the Cohort FIVE mentorship of the Level Up Initiative as a mentee.
- Jun 2020, Master the Entrepreneur Skillset, University of Western Ontario, Canada.
- Jun 2020, Provisional Practice Certificate of Registration-Physiotherapy Resident, College of Physiotherapists of Ontario
- May 2020, WESTERN CERTIFICATE IN UNIVERSITY TEACHING AND LEARNING, Centre for Teaching and Learning, University of Western Ontario, Canada.
- Apr 2018, Standard operating procedures for clinical research module, Lawson Health Research Institute, London, Ontario, Canada.
- Apr 2018, Accessibility in Teaching (AODA), University of Western Ontario, Canada.
- Mar 2018, Standard First Aid & CPR/AED Level C, Canadian Red Cross.
- Jan 2018, The Teaching Assistant Training Program (TATP), University of Western Ontario, Canada.
- Feb 2018, Supporting the wellness of undergraduate students, University of Western Ontario, Canada.
- Feb 2018, Great ideas for teaching panel, University of Western Ontario, Canada.
- Nov 2017, Collaborative Institutional Training Initiative (CITI Program), CITI Program, Canada
- Nov 2017, Facilitating group work in diverse classrooms, University of Western Ontario, Canada.
- Oct 2017, Certificate of academic engagement, University of Western Ontario, Canada.
- Oct 2017, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics (TCPS 2: CORE), TCPS 2: CORE, Canada.
- Sep 2016, Myofascial Trigger Point Dry Needling, Iranian Physiotherapy Association including 5 level courses: 50 hours training of Upper extremity and shoulder girdle muscles, Lower extremities muscles, Trunk and chest muscles, Pelvic girdle Muscles, Head and cervical muscles.

- Jul 2016, Comprehensive approach in treating Cranio-Cervical-mandibular complex pain and dysfunctions: differential diagnosis and clinical reasoning, The University of North Georgia, Department of Physical therapy By Dr. M.Reza Nourbakhsh, PT, Ph.D., OCS, Professor of Physical Therapy at the University of North Georgia.
- Jan 2016, Spine manual therapy, the University of Social Welfare and Rehabilitation Sciences By Dr. Mohammad Jamali (Pt, Dpt), Associate Professor and Program Chair of the Physical Therapist Assistant Program at Bay State College.
- Dec 2015, Introduction to transcranial direct current stimulation (tDCS), Shahid Beheshti University By Dr. Shapour Jaberzadeh, Senior Lecturer, Physiotherapy, Postgraduate Research Coordinator at Monash University.
- Sep 2015, Nutrition program designing for weight gain and weight loss, Iran bodybuilding and fitness federation.
- Apr 2015, The International Computer Driving Licence (ICDL), ICDL Iran foundation.
- Nov 2014, Taping, Tabriz University of Medical Science, Tabriz, Iran.
- Nov 2014, Principal of upper limb palpation, Tabriz University of Medical Science, Tabriz, Iran.
- Aug 2014, Exercise science and principles of goal achievement, Iran Sports Medicine Federation.
- May 2014, Kinsio Taping, Iranian Physiotherapy Association, Tehran Iran.
- Feb & Jun 2014, Research methodology & Research electrical references, Tabriz University of Medical Science, Tabriz, Iran.
- Jul 2012, Sport injuries in fitness and weight training, Iran Sports Medicine Federation, Hamadan, Iran.
- Jul 2011, The elementary and relaxation massage, Iran Sports Medicine Federation, Hamadan, Iran.
- Mar 2011, Sport injuries in bodybuilding and weight training, Hamadan body building association, Iran.

Intellectual Property and Patents

- 2 patents submitted/pending, USA, 2018 – expired
- 4 patents, Iran

Memberships

- Trainee Member, Canadian Pain Society (2018-2020)
- Trainee Member, The Bone and Joint Institute (BJI), Western University (2018-present)

- Trainee Member, The Musculoskeletal Health Research (CMHR), Western University (2018-present)
- Committee Member, Health and Rehabilitation Sciences Graduate Students Society Council, University of Western Ontario, International Student Representative (2018-2020)
- Trainee Member, the International Association for the Study of Pain (IASP) (2018-2021)
- Registered Physiotherapist, Member of Iran Medical Council (IRIMC) (2015- present)
- Member of Education Development Center (EDC) of Tabriz, Special Talents department (2014-2015)