Heterogeneity in the experience of chronic pain

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Heterogeneity in the experience of chronic pain

Unravelling the biopsychosocial context and the quantification of treatment success

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Heterogeneity in the experience of chronic pain

Unravelling the biopsychosocial context and the quantification of treatment success

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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CHAPTER 1

GENERAL INTRODUCTION

Introduction into Chronic Pain

Chronic pain is one of the most frequent causes to seek medical care[23] and is one of the leading sources of human suffering and disability.[19; 29] Chronic pain is an acknowledged condition in its own right, that is defined as pain that lasts or recurs, for more than 3 months.[34] Chronic pain can affect daily functioning of the individual on different aspects of their lives, resulting in physical or social deconditioning, psychological problems, and a decrease in quality of life.[5; 14; 27; 36-38] The degree to which chronic pain influences these different aspects of life varies from patient to patient, resulting in a heterogeneous chronic pain population.[5; 13] Furthermore, the complexity of chronic pain transcends medical and therapeutic disciplines, as no single discipline has the expertise to assess and manage all aspects of chronic pain in full. Hence, the International Association for the Study of Pain (IASP) recommends multidisciplinary care for chronic pain patients in which '*practitioners from different disciplines work separately with their own therapeutic aim for the patient*'.[21]

The Biopsychosocial Model

The biopsychosocial model lays a foundation for multidisciplinary care in research, guidelines, and clinical practice.[1; 10; 41] The biopsychosocial model observes pain and the disability produced by pain in three dimensions; biological, psychological, and social. These dimensions are reasoned to reciprocally influence and interact with each other (Figure 1).[8; 16; 41] By considering psychological and social contextual factors when analyzing chronic pain, the biopsychosocial model centers the person in a personal context, including their experiences, attitudes, and expectations. The temporal context surrounding the person reflects a certain time in life and disease status. Conversely, the person interacts with others in social context in which behavior is expressed and meaning is attributed to those behaviors.[41]

Epidemiology of Chronic Pain

The prevalence of chronic pain is estimated at 18% of the Dutch population.[5] Prolonged chronic pain negatively impacts the person in pain and their nearby relatives, and it can impose financial burdens on multiple levels: not only due to increased use of medical healthcare services but also because of loss of job, reduced income or early retirement.[37] This leads to the total (in)direct costs in the Netherlands alone estimated at 20 billion euros per year, exceeding the cost of diabetes, heart failure and cancer combined.[18; 30; 37]

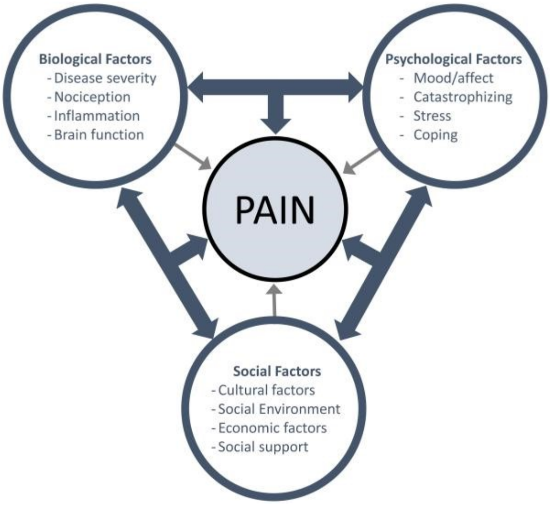

Figure 1, The biopsychosocial model (Fillingim 2017,PAIN. Published with permission of Wolters Kluwer Health, Inc.)

The understanding of risk factors associated with chronic pain is important when it comes to informing clinical management and minimising (the consequences of) chronic pain.[11; 37] Risk factors can provide context to medical interventions and are relevant in prediction, assessment, management, and prognosis of chronic pain.[25] Examples of biological risk factors associated with chronic pain are sex, age, tissue damage, disease comorbidity, pain characteristics such as severity, duration, amount of locations(s), and interference in daily life. While depression, anxiety, pain catastrophizing, and fear-avoidance are psychological risk factors, work (dis)ability, educational level, relationship status and employment status are social risk factors related to chronic pain.[11] In **chapter 2,** many of these risk factors are analysed in the chronic pain population of the University Pain Clinic Maastricht in the Netherlands.

Sex differences and Chronic Pain

In research of sex differences, two related but different terms are often used, namely sex and gender. In this thesis we will only focus on sex, that refers to inborn biological markers to classify human beings into males and females, founded on physical characteristics.[2; 3; 17; 26] In general population studies, women over represent pain disorders like headache, osteoarthritis, low back and neck pain.[2; 17; 26] Furthermore, women report on average higher pain severity than men and have a higher prevalence in multisite pain.[2; 17; 20; 26]

That may lead to an increase in pain related disability, higher susceptibility for psychological conditions and a plausible risk factor for onset of new pain conditions.[22]

Sociocultural factors and Chronic Pain

Systematic differences in health and quality of life partly depend on a person's position in society. Example of determinants that define someone's position in society are education, employment, relationship status and age.[24] In the Netherlands, people with a primary or lowest level of secondary education live six years shorter on average, and 15 years in less well-perceived health than people with a higher educational status such as university.[28] People with low levels of education and the unemployed are more likely to experience chronic pain, have more severe pain and experience a higher degree of pain-related disability.[25] Furthermore, relationship status is related to health and mortality outcomes as shown in demographic research: being in a relationship positively affects health,[4; 17] particularly in men.[22; 31; 32] However, the impact of these statuses on chronic pain outcomes have not been analyzed yet, let alone whether these statuses interact with sex. This is the topic of **chapter 3**.

Psychological factors and Chronic Pain

It is commonly accepted that characteristics as depression and anxiety can be the result of chronic pain, but it is less comprehended that these factors can also predispose to chronic pain.[8] Depressive episodes are defined 'as *the person experiencing a depressed mood (feeling sad, irritable, empty) or a loss of pleasure or interest in activities, for most of the day, nearly every day, for at least two weeks.*' Conversely, an anxiety disorder is '*having an anticipation of a future concern, that is out of proportion to the current situation, age inappropriate, and hinders normal ability to function'*.[6] Individuals with chronic pain have a significantly higher rate of anxiety disorders than those without, while more than the half of chronic pain patients fulfill the criteria of having a depression. These psychological factors are associated to pain severity, physical and emotional disability and are reasoned to be related to poor pain treatment outcomes when present in chronic pain patients (**Chapter 4**).[23; 37] Pain catastrophizing is defined as *'an exaggerated negative mental status brought to bear during actual or anticipated painful experiences'* [33] and thus misinterprets the pain experienced by imagining the worst possible.[9] Fear-avoidance is described as '*avoidance of movements or activities resulting from fear of pain'.[40]* These concepts induce physical disuse, pain-related disability, pain severity and distress (figure 2).[9; 24; 40]

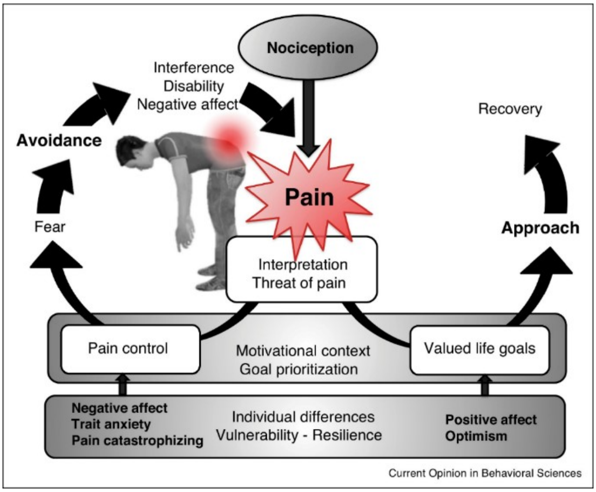

Figure 2. Fear avoidance model of pain (Meulders 2019, open access in Current Opinion in Behavioral Sciences).

Experience Sampling Method

A relatively novel way of analyzing associations between variables in prospective data is the experience sampling method (ESM). This method is a structured diary technique to appraise subjective experiences in daily life registered by a mobile application called *Psymate.*[39] This method allows detailed monitoring of states, which may help understand the condition by assessing real time reactions to events.[7] The sampling is signal contingent, meaning that individuals respond to semi-random signals (once randomly in every period of 90 minutes). The data collection focuses at every signal on affect (positive and negative), context, as in where, with whom, and events, collection of activities, like doing what, somatic symptoms of pain itself like pain intensity, and stress associated with momentary activities. Applying this technique has been said to have various advantages. It gives insight in the contingencies of experience, behavior, and somatic symptoms. It has an ecological validity, reflecting real life variations in response to real life challenges. Furthermore, as the person in pain reports at the actual moment, recall bias is eliminated.[39] The ESM study in this thesis focused on the well-established relationship between fear avoidance and pain intensity of chronic pain patients. Hitherto, it is not clear from the literature if men and women react different to the influence of fear avoidance on the severity of their pain (**Chapter 5**).

Methodology of Chronic Pain Research

In clinical practice, various aspects of pain are assessed at baseline and at follow up. In doing so, the effect of, for example, an intervention can be tested. Domains assessed can be pain characteristics (e.g., pain intensity), physical and emotional functioning, and treatment satisfaction, amongst others.[35] Within pain practice, emphasis is put on the change in pain intensity between assessment moments, often referred to as pain relief. Difficulties arise when the degree of pain relief is used to define treatment success, as pain relief only entails a part of the experience of chronic pain. With this emphasis in mind, a substantial effort is made to quantify the magnitude of change of pain relief that is considered clinically meaningful to the chronic pain patient.[12] For drug randomized controlled trials, a 2-point change on the Numeric Rating Scale is often reported as being clinically meaningful.[15] Yet, it is not known if this value is generalizable towards other methodological designs and if this holds in subgroups of the chronic pain population. The generalizability of this dichotomization of clinically meaningfulness is the subject of **chapter 6**.

Aim of this thesis

The primary objective of the present thesis was to unravel the heterogeneity of the pain experienced by chronic pain patients that was recorded on patient-reported outcome measures (PROM's). This was analyzed by both using cross-sectional and longitudinal study designs. The following research questions were established:

1. How does the chronic pain population of the University Pain Center Maastricht report on the following chronic pain domains: pain characteristics, psychological interference, quality of life and social demographics?
2. Do socio-cultural statuses influence patient-reported outcome measures of chronic pain patients, and to what extent does the influence of socio-cultural statuses differ between men and women?
3. Is the likelihood of treatment successes affected by the combination of high pain severity, depression or anxiety and pain catastrophizing, when compared with those who do not have this combination of cognitive and affective factors?
4. Is the association between fear avoidance and pain intensity modified by sex?
5. Can the average change from baseline to follow up of 2-points on the Numeric (Pain) Rating Scale regarded as a moderate clinical important improvement be generalized towards chronic pain

patients included in non-pharmaceutical interventional studies, cohort studies, or other subgroups of the chronic pain population?

Outline of the thesis

The **second chapter** of this thesis presents the DATA*PAIN* registry cohort and the chronic pain patients that were attended for their pain complaints at the University Pain Center Maastricht, in the Maastricht University Medical Center^{+} in the Netherlands. The DATA*PAIN* questionnaire was designed in accordance with the biopsychosocial model and recommendations of the Initiative of Method and Measurement and Pain Assessment of Clinical Trials (IMMAPCT guidelines).[35] Patient's (socio) demographics, pain characteristics, quality of life and pain interference at baseline were described to allow for the understanding of the complaints and complexity of chronic pain. This chapter provides an overview of the chronic pain population and incited us to formulate the research questions of the next two chapters. The **third chapter** further investigates to what degree socio-cultural statuses influence PROM's, and how men and women differ from each other in that association. The **fourth chapter** focuses on a specific subgroup of chronic pain patients that were identified in the second chapter and have been named the *complex chronic pain patient*. This group holds a set of specific psychological factors and pain characteristic. This fourth chapter provides answers if this combination of factors encountered at baseline influences the possibility of achieving successful treatment outcomes at 6 months follow-up. In the **fifth chapter**, we report on a study that included DATA*PAIN* participants that had agreed to use the Psymate application for the experience sampling method. This sample of chronic pain patients gave us insight in their daily functioning with chronic pain. To be specific, we quantify the association between fear avoidance and pain intensity, and analyze if there are differences between both sexes, while adjusting for possible confounding effect of positive and negative affect. In the **sixth chapter,** we assess whether the 2-point difference on the Numeric (Pain) Rating Scale as clinical important improvement can be generalized to chronic pain patients from different populations than those from the initial landmark publication.[15] We analyze what magnitude of change in pain relief reflects a clinical meaningful change for the chronic pain patient in different methodological settings as cohort and non-pharmaceutical interventional randomized controlled trials, and we compare these to the previously found changes. Moreover, by stratification on subgroups, we analyze whether the clinically meaningful change is representative for any whole population or if subgroups would need to be specified.

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CHAPTER 2

BIOPSYCHOSOCIAL BASELINE VALUES OF 11 214 PATIENTS SUFFERING FROM CHRONIC PAIN; THE DUTCH DATA*PAIN* STUDY

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Reg Anesth Pain Med 2020;**0**:1–9. doi:10.1136/rapm-2020-101476

ABSTRACT

Background and Objectives

Chronic pain affects many adults. To improve our daily practice, we need to understand multidisciplinary approaches, integrated treatment plans, and the biopsychosocial context of these patients. To date, almost 15,000 chronic pain patients have been referred to the Maastricht University Pain Center in the Netherlands.

Methods

This study describes 11,214 of these patients suffering from chronic pain. Patients provided informed consent, and ethical clearance was obtained from the medical ethical committee (METC). Chronic pain was analyzed using relevant IMMPACT instruments.

Results

Most patients were female (59.3%). The prevalence of low education was 59%, and unemployment/disability was 35.9%. Mean age was 55.6 years. Severe pain (NRS 7-10) was reported by 71.9% of the patients; psychological and quality of life values deteriorated when pain severity increased. Approximately 36% of patients showed severe signs of depression or anxiety, and 39% displayed high pain catastrophizing. Of all patients, 17.8% reported high values for pain severity, catastrophizing, and anxiety or depression.

Conclusions

Based on baseline biopsychosocial values, this study shows the complexity of patients referred to pain centers. Pain management with a biopsychosocial approach in an integrated multidisciplinary setting is indispensable. Above all, adjusted education on chronic pain and attention to its biopsychosocial aspects are deemed necessary.

1. INTRODUCTION

Chronic pain is a debilitating condition that affects a large population of adults globally, and poses a significant burden on both the individual and the society.[28; 36] Societal costs are even higher than those for cancer, diabetes, or heart disease. In the Netherlands, more than two million people suffer from chronic pain and the total costs are estimated to be around 20 billion euros per year.[2] Loss of working capacity is a major contributor to these costs, as around 25% of work absence is caused by complaints related to the musculoskeletal system. Although chronic pain is considered a disease in its own right, there is no consistency in diagnostic or therapeutic approaches to this condition, and 34-79% of treatment is considered inadequate.[4; 28] The inadequacy of treatment might be due to a mono-symptomatic approach to clinical pain practice instead of treating chronic pain based on an etiology driven nosology.[16] Beyond etiology factors, pain intensity and disability related pain should be reflected (ICD11).[32]

The biopsychosocial model provides a method to analyze chronic pain through the interaction between biological, psychological, and sociocultural variables that shape a person's individual response to pain.[34] It provides the means to analyze aspects of chronic pain otherwise overlooked, as is often the case regarding psychosocial aspects of pain.[6] Providing a broad, multidisciplinary pain management that is based on understanding the determinants of chronic pain, disability, pain severity, and chronic pain complexity can provide information useful to assess relevant and significant characteristics pertaining to patients that suffer from chronic pain.[14]

In 2003, the Comprehensive Multidisciplinary University Pain Center Maastricht (UPCM) developed a questionnaire that is used to study pain perception and quality of life values of patients suffering from chronic pain.[15] Since then, different patient-reported outcome measures have been added for the screening and diagnosis of these patients, as suggested by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.[33] The acquired insight and descriptions of subgroups of chronic pain patients contribute to a better understanding of pain chronicity and complexity.[8]

The aim of this study was to describe a large sample of patients suffering from chronic, non-cancer related pain, which have been referred to the UPCM, by quantifying chronic pain aspects into four main categories: social demographics, pain characteristics (including condition-specific measures of both neck and lower back pain), psychological measures, and quality of life measures.

2. METHODS

2.1 Patients

The patient population consists of chronic, non-cancer related pain patients referred to the UPCM between 2003 and 2018, housed within the department of Anesthesiology and Pain Management at the Maastricht University Medical Center (MUMC+). Patients were included if they could be classified as chronic pain sufferers in accordance with the International Association for the Study of Pain (IASP) criteria defining chronic pain as pain experienced over a period lasting longer than three months.[13] Patients were excluded if their chronic pain was cancer related, or if informed consent had not been granted.

2.2 Data Acquisition

All patients referred to the UPCM from 2003 to 2018 were requested to complete the UPCM questionnaire *before* their first consultation. Patients that were included from 2003 through 2014 received the questionnaire by standard mail to be completed on paper (n=10,444, Fig. 1). Patients included after 2014 completed the questionnaire digitally (web-based, number n=4248, Fig. 1). At the time of writing, over 15,000 patients had completed questionnaires. This study holds a description of socio-demographic, pain characteristics, psychological values and quality of life values as well as condition-specific measurements for neck (Neck Disability Index) or low back pain (Oswestry Low Back Pain Disability Questionnaire). In total 11,214 patients were included. Fig. 1. depicts the flow chart of the study population.

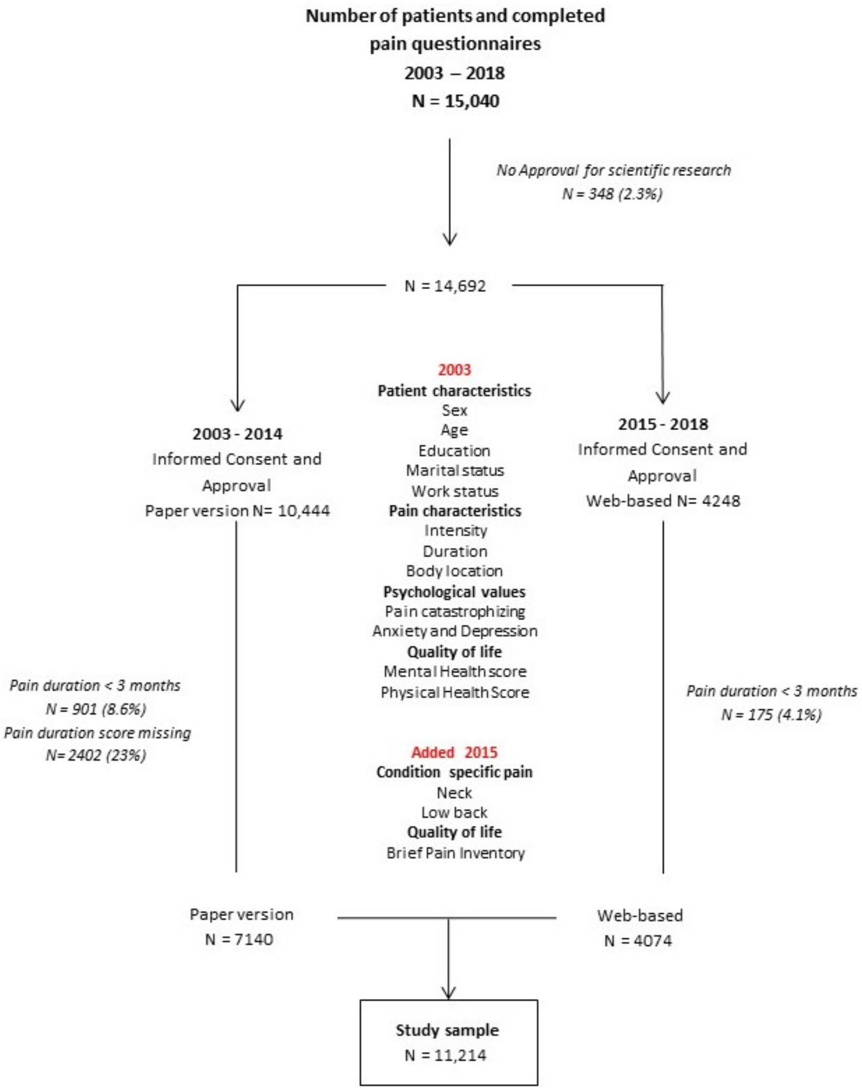


Fig. 1. Flow chart of the study sample

2.3 Data Measurements

The questionnaires used to measure pain characteristics, psychological values, quality of life values, and the condition-specific values of the neck and low back pain are shown in Table 1.

Table 1. Overview of measurement instrument

Measurements (n = number of patients available scores)	**Scaling score**
PATIENT Characteristics	
Sex (n=11203)	Male / Female
Age (n=11249)	Continue score
Pain duration (n=11214)	Weeks
Education (n=11096)	Low = < 8 years, elementary Middle = 9 years, elementary and secondary High = > 10 years, elementary, middle and college/university
Location of the pain complaint (n=11197)	Head Neck Arm Lower back Upper leg Lower leg Chest - abdomen Other
Work status (n-9187)	Paid job Unpaid / student Unemployed Retired Household
PAIN Characteristics	
Pain intensity (NRS) (n=10919)	11-point Numeric Rating scale, 0 - 10 Mild = 0-4 - Modest = 5-6 - Severe = 7-10
Neck Disability Index (NDI) (n=1297)	0 – 50 score 0-4 = no disability 5-14 = mild disability 15-24 = moderate disability >24 = severe disability
Oswestry Low Back Pain Questionnaire (OLBPDQ) (n=1933)	0 – 100 percentage 0-20% = minimal disability 20-40% = moderate disability > 40 = severe disability
PSYCHOLOGICAL Values	
Pain Catastrophizing scale (PCS) (n=10840)	0 – 52 score, cut-off >31
Hospital Anxiety and Depression Scale (HADS) (n=8916) HADS subscale anxiety HADS subscale depression	0-42 HADS total 0-21 Anxiety HADS, 0-21 Depression HADS Anxiety or depression, cut-off >10 Anxiety and depression, cut-off >10
QUALITY of LIFE Values	
Quality of life, physical (PHS) (n=8914) Quality of life, mental (MHS)	Physical Health Score, cut-off < 50 less physical quality of life. Max score 100 Mental Health Score, cut-off < 50 less mental quality of life. Max score 100
Brief Pain Inventory (BPI) (n=3979) BPI Interference BPI subscale WAW BPI subscale REM	0-10 score, does not interfere- complete interference BPI Interference = sum of seven questions. Max score 70 BPI WAW = walking, general activity, work and sleep. Max score 40 BPI REM= relations with others, enjoyment of life, and mood. Max score 30

Location of the pain complaint = Dichotomy (yes, no), possibility of pointing out more body locations
WAW = walking, general activity, working (sleep), REM= relations, enjoyment, mood

2.3.1 Patient Characteristics

Patients were asked to answer several questions regarding personal traits such as sex (male versus female), age (in years), education (elementary and first phase of secondary education; elementary and last phase secondary education; elementary, secondary and college/university), marital status (not married, married, living together, widow/widower, divorced, or other) and current work status (paid or unpaid job, student, unemployed, retired, or homemaker).

2.3.2 Pain Characteristics

Pain characteristics include: pain intensity, pain duration in weeks, and pain location on the body. In 2014, a Neck Disability Index (NDI) was added to the UPCM questionnaire for when the patient described pain as being located in the neck and the Oswestry Low Back Pain Disability Questionnaire (OLBPDQ) for patients with pain localized in the (lower) back. The 11-point Numeric Rating Scale (NRS) was used to quantify pain intensity. This instrument has proven to be efficient in measuring subjective pain experiences.[35] Pain was rated on a scale ranging from 0 ‘no pain at all’ to 10 ‘the worst pain possible’.

2.3.3 Psychological Values

The Pain Catastrophizing Scale (PCS) and the Hospital Anxiety and Depression Scale (HADS total, HADS anxiety, HADS depression) were administered to quantify the psychological aspects of chronic pain. The PCS contains 13 items, each describing thoughts or feelings related to pain, asking patients to reflect on their own painful experiences from the past, and rating the statements in accordance to their own experiences on a scale from 0 to 4.[30] In daily practice, we use the cutoff point of >31 for potential referral to rehabilitation specialist. The 14-item HADS includes seven items related to anxiety, and seven related to depression, with each item having four response options (0,1,2 or 3) following for a maximal score of 21 for either anxiety or depression. Total scores of 0 to 7 on each subscale are considered normal, scores between 8 and 10 are defined as doubtful or mild, and scores of 11 and higher are considered to indicate depression or anxiety.[3] At the UPCM, patients with a score above 10 on either HADS scales are referred to a psychiatrist. For that reason, we dichotomized the subscales using a cut-off point of 10.

2.3.4 Quality of Life

At the beginning of the study, we measured general health and quality of life using the RAND-36 quality of life instrument. This instrument is used to assess eight aspects related to health and daily functioning: physical functioning, role limitations because of physical health quails, role limitations due to emotional problems, social functioning, emotional wellbeing, energy/fatigue, pain, and general health perceptions.[12] In 2014, we replaced the RAND-36 for the SF-12V1 (short form). The total scores on the RAND36 and the SF-12V1 can be divided as a physical health summary score (PHS) and a mental health summary score (MHS). The higher the score, the lower the disability. For this study, we chose to stratify the scores of the RAND-36 and the SF-12V1 into PHS and MHS.

The Brief Pain Inventory (BPI) has been measured since 2014. For this study, we provided the mean numbers of seven items related to activity (walking, activity, work and supplemental sleep (WAW)) and affect (relations with others, enjoyment of life, and mood (REM)), and calculated the impact of pain on functioning (BPI Interference) (IMMPACT), the sum of all seven items were calculated.[5; 31]

2.3.5 Neck Disability Index

The NDI is a commonly used instrument, which is reliable and consistent for the self-assessment of patients suffering from neck pain in order to rate their level of disability. The NDI consists of ten items (pain intensity, personal care, lifting, sleep, driving, recreation, headaches, concentration, reading, and work) scored on a 0 to 5 scale, resulting in a total possible score of 50.[20] In this study, NDI scores were categorized as mild (score 0-14), moderate (score 15-24), or severe (score>24).

2.3.6 Oswestry Low Back Pain Disability Questionnaire

The OLBPDQ is a tool used to assess a patient’s functional disability in the context of low back pain.[9] There are ten sections (pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling) each scored 0 to 5 based on six given statements. Given that all sections are completed, the maximal score is 50, which is converted and the outcome to a percentage and referred to the total possible score. The OLBPDQ is reliable, and has a sufficient scale to be used in an outpatient population suffering from lower back pain. OLBPDQ outcomes were categorized as mild (score 0-20%), moderate (score 21-40%) or severe (score >41%).

2.4 Statistical analysis

Baseline patient- and socio- demographics were described using mean and standard deviation (SD) or percentage. Differences in questionnaire scores between groups were tested using the chi-squared test for categorical variables, and one-way analysis of variance (ANOVA) for continuous variables. We compared scores between male and female, groups based on pain score, groups based on the number of pain sites, and groups based on condition-specific scores. All analyses were performed using IBM SPSS version 23. A p-value of ≤0.05 was considered to indicate statistical significance.

3. RESULTS

In total, 15,040 patients were referred to the UPCM between 2003 and 2018 who completed the UPCM questionnaire. Of all patients, 2.3% (n=348) did not give permission to use their data for scientific research (Fig. 1.). After applying the inclusion criteria and omitting those for whom the pain duration was unclear, the final overall study sample consisted of 11,214 patients.

3.1 Patient Characteristics

Almost 60% of the patients were female. The most common education level was ‘low’ at 59%. The marital status was above 70% for either married or living together, and the active employment status of the patients was about one third having a paid job (32.7%) and being unemployed/incapacitated (35.9%). The mean age of the study population was 55.6 years (age range of 8-96 years old), 40% above the age of 61. An overview of characteristics of the chronic pain patients of the UPCM is shown in Table 2.

3.2 Paper versus web-based questionnaires

No difference was noticed in sex distribution between the patients’ completed questionnaires method (paper versus web-based), implying no change in sex distribution over time. Furthermore, only small differences were seen in the reported pain characteristics, psychological values, and quality of life values. Over the years, the mean age increased from 55 (sd. 15.3) to 57.1 (sd. 15.4). The education level also slightly changed throughout the years; as low education decreased from 61% (paper version) to 59% (web-based), middle education increased from 25% (paper version) to 27% (web-based), and higher education increased from 15% (paper version) to 17% (web-based).

Table 2: Socio-demographic characteristics of the UPCM chronic pain patient

Patient Characteristics		Mean (SD) / Percentage
Female		59.3%
Age in years		55.6 (15.4)
	0-20	1.6%
	21-30	4.8%
	31-40	9.8%
	41-50	19.4%
	51-60	25.1%
	61-70	20.6%
	71-80	14.0%
	≥81	4.7%
Education		
	Low	59.0%
	Middle	25.4%
	High	15.6%
Marital status		
	Not married	11.1%
	Married/living together	71.5%
	Widower/widow	7.9%
	Divorced	7.6%
	Various	1.9%
Current work status		
	Paid job	32.7%
	Unpaid/student	2.9%
	Unemployed/incapacitated	35.9%
	Retired	22.6%
	Household	5.9%

Education: Low = ≤ 10 years, elementary and first phase of secondary education; Middle = 11- 12 years, elementary and (last phase) secondary education; High = > 12 years, elementary, secondary and college/university. SD: Standard Deviation.

3.3 SEX specific pain characteristics, psychological values and quality of life values

The differences in pain characteristics, psychological values, and quality of life values between males and females were small. All results are reported in Table 3. For all patients, 70.2% reported the physical quality of life component under the Dutch norm score (NL Dutch norm score of 50), and 49.1% were under the Dutch mental component quality of life norm score (NL Dutch norm score of 50).

Table 3. Differences between groups based on sex

Year 2003 – 2018	**All patients** Mean (SD)/ %	**Male** Mean (SD)/ %	**Female** Mean (SD)/ %	***P-* Value**
PAIN Characteristics				
Pain intensity – NRS	7.2 (1.8)	6.9 (1.8)	7.3 (1.7)	*.001*
Mild 0-4	7.7	10.3	6.5	
Modest 5-6	20.2	21.6	17.8	
Severe 7-10	71.9	68.1	75.7	
Pain duration in weeks	271 (weeks)	280 (weeks)	264 (weeks)	
Pain duration categorized				*.029*
3 months – 1 year	29.0	27.8	30.3	
1 year – 5 years	38.5	38.2	37.9	
> 5 years	32.5	34.0	31.8	
Pain location				*.001*
Head	15.8	15.1	16.2	
Neck	31.5	33.2	31.0	
Arm	19.7	19.3	19.9	
Neck and arm	14.0	13.8	14.2	
Lower back	51.8	50.6	52.7	
Upper leg	31.4	28.9	33.0	
Lower leg	24.4	24.5	24.4	
Chest/abdomen	8.2	8.3	8.1	
Lower back and upper leg	24.0	21.9	25.5	
Lower back and lower leg	15.	14.9	15.0	
Lower back, upper leg and lower leg	11.6	11.1	12.0	
Other	24.6	26.4	23.6	
Multisite pain location				
1 location	46.5	47.1	46.1	*.021**
2 locations	22.8	23.0	22.7	
3 locations	12.0	12.5	11.6	
≥ 4 locations	18.9	17.7	19.7	
PSYCHOLOGICAL Values				
PCS	27.9 (12.1)	28.2 (11.9)	27.6 (12.7)	
PCS>31	38.8	39.7	38.2	*.032*
HADS				*.001*
HADS total	15.7 (7.8)	16.3 (8.0)	15.2 (7.7)	
HADS anxiety	7.8 (4.2)	8.0 (4.3)	7.6 (4.1)	
HADS depression	7.9 (4.4)	8.3 (4.4)	7.5 (4.3)	
HADS anxiety or HADS depression > 10	36.2	38.5	34.6	
QUALITY of LIFE Values				
PHS	31.4 (8.3)	32.2 (8.3)	30.9 (8.2)	*.001**
PHS<50	70.2	71.3	69.5	
MHS	42.8 (12.2)	42.8 (12.3)	42.8 (12.1)	
MHS<50	49.1	49.5	48.9	
BPI				*.009*
BPI General activity	6.1 (2.5)	6.0 (2.5)	6.2 (2.5)	
BPI Mood	4.5 (3.0)	4.6 (2.9)	4.5 (3.0)	
BPI Walking ability	6.0 (3.1)	6.0 (3.1)	5.9 (3.1)	
BPI Normal work	6.6 (2.6)	6.5 (2.7)	6.7 (2.6)	

BPI Relations with other people	3.7 (3.2)	3.9 (3.2)	3.7 (3.3)	
BPI Sleep	5.7 (3.1)	5.4 (3.1)	5.7 (3.1)	
BPI Enjoyment of life	4.4 (3.2)	4.6 (3.2)	4.2 (3.2)	
BPI Interference	36.9 (15.6)	36.7 (16.0)	36.9 (15.4)	
BPI WAW	24.3 (9.0)	23.8 (9.1)	24.6 (8.9)	
BPI REM	12. 6 (8.4)	13.0 (8.4)	12.3 (8.4)	

*NRS, Numeric rating Scale; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; PHS, Physical Health Score; MHS, Mental Health score; BPI, Brief Pain Inventory. BPI Interference, sum of seven scores; BPI WAW, walking, general activity, working and sleep; REM, relations, enjoyment and mood. P value = Pearson Chi-Square, *= One way ANOVA*

3.4 PAIN SEVERITY specific pain characteristics, psychological values and quality of life values

Most of the patients (71.9%) rated a pain intensity score $\geq$7. The bar plot (Fig. 2) shows the distribution of pain intensity reported by the patients. Differences between pain duration in weeks were shown to be statistically significant between the three pain score groups (p =0.001), although most prevalent was the pain severity group 7-10 (37.8%) with a pain duration 1- 5 years. The differences between groups based on patient's average pain score were seen in all analyzed pain characteristics, psychological values, and quality of life values (Table 4). Average psychological values increase as pain becomes more severe. This also applies to the mean scores of psychological values anxiety and depression. The mean scores of BPI interferences increase as the pain severity increases. The lower the mean PHS and MHS component score, the lower quality of life was reported and decreases as pain severity increases.

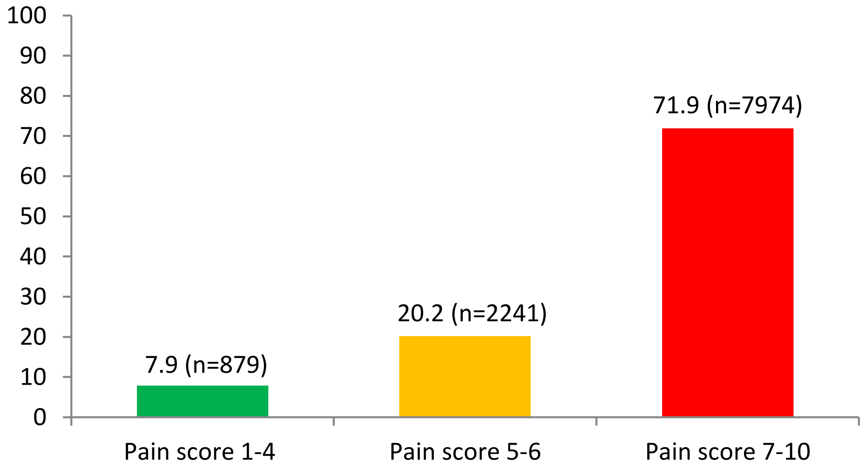


Fig. 2. Bar plot of groups based on patients reported pain intensity score

Table 4. Differences between groups based on patients' average pain score

Year 2003 – 2018	**Pain score 0-4** Mean (SD)/ %	**Pain score 5-6** Mean (SD)/ %	**Pain score 7-10** Mean (SD)/ %	***P* Value**
PAIN Characteristics				
Pain duration in weeks				*.001*
3 months – 1 year	32.5	31.1	29.0	
1 year – 5 years	40.2	38.8	37.8	
> 5 years	27.4	30.1	33.2	
Pain location				*.001*
Head	14.2	15.3	15.9	
Neck	29.6	30.1	32.2	
Arm	14.1	17.2	20.9	
Neck and arm	8.6	11.8	15.4	
Lower back	36.9	48.3	54.6	
Upper leg	18.6	29.6	33.4	
Lower leg	17.2	21.3	26.2	
Lower back and upper leg	13.0	22.0	26.0	
Lower back and lower leg	8.7	12.5	16.5	
Lower back, upper leg and lower leg	5.8	9.7	12.8	
Chest/abdomen	6.6	7.8	8.7	
Other	28.4	26.3	23.4	
Multisite pain location				*.001*
1 location	58.7	49.0	44.8	
2 locations	19.9	23.6	22.8	
3 locations	8.6	11.1	11.9	
≥ 4 locations	12.7	16.3	20.5	
PSYCHOLOGICAL Values				
PCS	19.1 (10.8)	22.9 (11.0)	30.0 (16.6)	*.001*
PCS>31	15.0	21.3	46.1	
HADS total	11.9 (6.5)	13.5 (6.8)	16.5 (7.9)	*.001*
HADS anxiety	6.1 (3.6)	6.9 (3.7)	8.1 (4.3)	
HADS depression	5.8 (3.7)	6.7 (3.9)	8.4 (4.4)	
HADS anxiety or HADS depression > 10	20.3	25.5	40.8	
QUALITY of LIFE Values				
PHS	36.9 (8.1)	33.5 (7.7)	29.9 (7.9)	*.001**
MHS	48.1 (11.1)	45.8 (11.8)	41.6 (12.2)	*.001**
BPI				*.001*
BPI General activity	3.2 (2.5)	4.6 (2.4)	6.8 (2.2)	
BPI Mood	2.3 (2.4)	3.2 (2.6)	5.1 (2.9)	
BPI Walking ability	3.2 (2.9)	4.7 (3.0)	6.6 (2.9)	
BPI Normal work	3.8 (2.8)	5.3 (2.6)	7.2 (2.3)	
BPI Relations other people	1.8 (2.3)	2.5 (2.8)	4.3 (3.3)	
BPI Sleep	2.8 (2.6)	4.3 (2.9)	6.2 (3.0)	
BPI Enjoyment of life	2.4 (2.7)	3.2 (2.9)	4.8 (3.2)	
BPI Interference	19.2 (13.7)	27.9 (14.1)	40.7 (14.0)	
BPI WAW	12.8 (8.4)	18.9 (8.4)	26.7 (7.8)	
BPI REM	6.4 (6.6)	9.0 (7.5)	14.1 (8.2)	

*NRS, Numeric rating Scale; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; PHS, Physical Health Score; MHS, Mental Health score; BPI, Brief Pain Inventory. BPI Interference, sum of seven scores; BPI WAW, walking, general activity, working and sleep; REM, relations, enjoyment and mood. P value = Pearson Chi-Square. *= Oneway ANOVA*

3.5 MULTISITE (location) specific pain characteristics, psychological values and quality of life values

The category of pain location was classified as one, two, three, or four and more pain locations (multisite pain locations). Many patients (46.8%) reported one pain location on the body. Over 22.8% of the patients reported two pain locations, 11.4% reported three locations, and 18.9 % reported four pain locations. There was a statistical significant difference ($p = 0.001$) concerning pain severity and the multisite pain location; the percentage of patients with 4 or more pointed pain locations was higher in the severe pain group compared with modest or mild pain groups (20.5%, 16.3%, and 12.7% respectively). Furthermore, there were significant differences between the number of pain locations in all psychological values and quality of life values. All results are reported in Table 5.

Table 5. Differences between groups based on patients' multisite pain location

Year 2003 – 2018	**1 Pain location** Mean (SD)/ %	**2 Pain locations** Mean (SD)/ %	**3 Pain locations** Mean (SD)/ %	**≥4 Pain locations** Mean (SD)/ %	***P* Value**
PAIN Characteristics					
Pain duration in weeks					*.001*
3 months – 1 year	35.5	29.2	25.9	19.4	
1 year – 5 years	40.0	37.8	38.5	35.6	
> 5 years	26.5	33.0	35.6	45.0	
Pain location					
Head	2.4	16.4	22.6	44.1	
Neck	11.2	34.3	46.4	69.2	
Arm	4.7	11.7	26.2	62.5	
Neck and arm		7.7	18.6	53.8	
Lower back	36.7	56.4	72.3	72.0	
Upper leg	6.7	37.5	57.9	69.4	
Lower leg	9.7	17.3	44.1	58.1	
Lower back and upper leg		29.9	49.8	60.9	
Lower back and lower leg		7.8	34.6	49.0	
Lower back, upper leg and lower leg			28.9	43.9	
Chest/abdomen	3.9	5.2	7.4	22.8	
Other	24.9	21.2	23.9	29.8	
Pain severity					*.001*
Mild 0-4	9.9	7.0	6.1	5.3	
Modest 5-6	21.2	20.9	19.6	17.2	
Severe 7-10	68.9	72.1	74.4	77.5	
PSYCHOLOGICAL Values					
PCS	26.8 (12.0)	27.7 (11.8)	28.7 (12.0)	29.8 (12.3)	*.001*
PCS>31	35.8	38.4	41.2	45.4	
HADS total	17.5 (7.9	15.4 (7.5)	16.4 (7.6)	18.0 (8.1)	*.001*
HADS anxiety	7.2 (4.0)	7.6 (4.0)	8.2 (4.1)	9.1 (4.5)	
HADS depression	7.4 (4.3)	7.8 (4.2)	8.2 (4.3)	8.9 (4.5	
HADS anxiety or HADS depression > 10	31.5	34.1	40.0	49.1	
QUALITY of LIFE Values*					
PHS	32.1 (8.4)	31.3 (8.1)	30.2 (7.7)	30.4 (8.3)	*.001**
MHS	44.5 (12.2)	43.4 (12.1)	41.7 (12.1)	39.4 (11.7)	*.001**
BPI					*.001*
BPI General activity	5.9 (2.7)	6.0 (2.5)	6.3 (2.9)	6.7 (2.2)	
BPI Mood	4.3 (3.0)	4.4 (2.9)	4.8 (2.9)	5.2 (2.8)	
BPI Walking ability	5.6 (3.3)	5.8 (3.2)	6.4 (2.8)	6.6 (2.5)	
BPI Normal work	6.4 (2.7)	6.5 (2.7)	6.8 (2.6)	7.2 (2.3)	
BPI Relations other people	3.4 (3.2)	3.7 (3.2)	4.0 (3.2)	4.6 (3.2)	
BPI Sleep	5.2 (3.3)	5.5 (3.1)	6.0 (2.9)	6.4 (2.8)	
BPI Enjoyment of life	4.0 (3.2)	4.3 (3.2)	4.6 (3.1)	5.1 (3.2)	
BPI Interference	34.7 (16.2)	36.1 (15.5)	38.7 (15.0)	41.9 (13.8)	
BPI WAW	23.1 (9.5)	23.7 (9.0)	25.4 (8.3)	27.1 (7.4)	
BPI REM	11.6 (8.5)	12.3 (8.3)	13.3 (8.1)	14.8 (8.1)	

NRS, Numeric rating Scale; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; PHS, Physical Health Score; MHS, Mental Health score; BPI, Brief Pain Inventory. BPI Interference, sum of seven scores; BPI WAW, walking, general activity, working and sleep; REM, relations, enjoyment and mood.
*P value = Pearson Chi-Square. * Oneway ANOVA*

3.6 CONDITION SPECIFIC VALUES of the Neck Disability Index and the Oswestry Low Back Pain Disability Questionnaire

Of all patients who completed the NDI, 91.4% reported severe neck pain, and 67.0% of all patients with low back pain reported severe low back pain (Table 6). Table 7 describes all pain characteristics, psychological values and quality of life values of the neck and low back pain condition specific values.

Table 6. Condition specific values between groups based on patients' sex and pain intensity score

Year 2003 - 2008	**All patients** Mean (SD)/%	**Male** Mean (SD)/%	**Female** Mean (SD)/%	***P* Value**	**Pain score 0-4** Mean (SD)/%	**Pain score 5-6** Mean (SD)/%	**Pain score 7-10** Mean (SD)/%	***P* Value**
NDI	48.3 (17.5)	45.6 (17.8)	50.1 (17.0)	*.009*	31.8 (14.3)	41.6 (14.0)	51.2 (17.2)	*.001*
NDI mild	3.4	5.1	2.4		14.3	2.4	2.6	
*NDI mod**	5.2	7.3	4.1		17.6	7.7	3.6	
*NDI sev***	91.4	92.5	95.7		68.1	89.8	93.8	
OLBPDQ	48.8 (17.7)	46.5 (18.3)	50.6 (17.0)	*.053*	29.2 (14.0)	40.3 (15.8)	52.6 (16.7)	*.001*
OLBPDQ mild	6.7	8.5	5.3		31.1	12.2	3.7	
OLBPDQ mod	26.4	31.0	22.9		50.0	41.2	21.5	
OLBPDQ sev	67.0	60.5	71.7		18.9	46.6	74.8	

*P value = Pearson Chi-Square. NDI = Neck Disability Index, OLBPDQ = Oswestry Low Back Pain Disability Questionnaire. * mod =moderate. ** sev = severe. NDI mild: 0-14, NDI moderate: 15-24, NDI severe: >24, OLBPDQ mild: 0-20, OLBPDQ moderate: 21-40, OLBPDQ severe: >41*

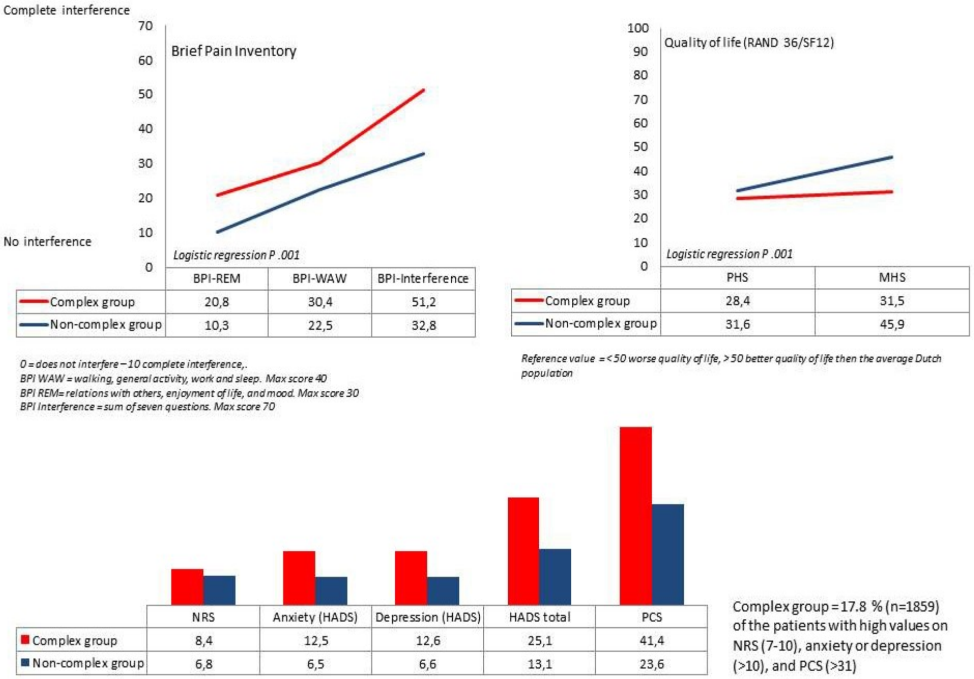
Table 7. Condition specific values between groups based on pain characteristics, psychological values, and quality of life values

Measurement	**Neck Disability Index Disability Questionnaire**				**Oswestry Low Back Pain**	
Mean scores (SD)	*NDI mild 0-14 (n=44)*	*NDI moderate 15-24 (n=68)*	*NDI severe>24 (n=1185)*	*OLBPDQ mild 0-20 (n=129)*	*OLBPDQ moderate 21-41 (n= 540)*	*OLBPDQ severe >41 (n=1294)*
PAIN Characteristic						
Mean pain score (0-10)	6.1(2.3)	6.1(2.0)	7.5 (1.5)	5.7 (2.0)	6.7 (1.7)	7.8 (1.3)
PSYCHOLOGICAL Values						
PCS (0-52)	21.3(12.8)	21.8(12.3)	28.3 (12.5)	19.0(11.6)	22.7 (11.2)	30.6 (11.8)
HADS total (0-42)	12.0(12.7)	12.1(7.0)	17.0 (7.6)	11.3 (5.6)	12.8 (6.4)	17.8 (7.6)
HADS anxiety (0-21)	6.6(3.8)	6.4(4.0)	8.8 (4.3)	6.1 (3.5)	6.8 (3.7)	9.1 (4.5)
HADS depression (0-21)	5.6(3.5)	5.7(3.6)	8.2 (4.0)	5.2 (2.8)	6.0 (3.3)	8.7 (3.9)
QUALITY of LIFE values						
SF12 Physical CS (0-100)	35.0(9.9)	34.3(8.7)	28.6 (6.5)	37.1 (8.1)	31.4 (5.8)	40.6 (11.2)
SF12 Mental CS (0-100)	50.4(8.9)	50.5(11.2)	41.6 (11.5)	52.1 (9.9)	49.0 (10.8)	40.6 (11.2)
BPI General Activity (0-10)	3.8(2.9)	4.1(3.0)	6.4 (2.3)	3.5 (2.9)	5.1 (2.3)	7.1 (1.9)
BPI Mood (0-10)	3.0(2.9)	2.8 (3.1)	4.9 (2.8)	2.6 (2.8)	2.6 (2,8)	5.3 (2.8)
BPI Walking ability (0-10)	4.3(3.3)	3.9 (3.5)	5.6 (3.1)	3.6 (3.1)	5.3 (2.6)	7.3 (2.1)
BPI Normal work (0-10)	4.8(3.0)	4.4 (3.2)	6.8 (2.4)	4.1 (2.9)	5.8 (2.4)	7.6 (2.0)
BPI Relations with people (0-10)	2.2(3.0)	1.7 (2.7)	4.1 (3.1)	1.6 (2.4)	2.6 (3.0)	4.8 (3.1)
BPI Sleep (0-10)	4.0(3.3)	3.5 (2.8)	6.4 (2.8)	3.2 (3.0)	4.6 (2.9)	6.5 (2.7)
BPI Enjoyment of life (0-10)	2.8(3.0)	2.9 (3.1)	4.7 (3.1)	2.1 (2.7)	3.3 (3.0)	5.2 (3.0)
BPI Interference (0-70)	25.0(16.4)	23.4 (17.7)	38.9 (14.6)	21.0(15.3)	30.4 (13.2)	43.9 (12.5)
BPI WAW (0-40)	16.9(10.2)	16.0 (10.7)	25.1 (8.3)	14.4 (9.5)	20.8 (7.4)	28.6 (6.5)
BPI REM (0-30)	8.1(7.5)	7.4 (8.0)	13.8 (8.1)	6.6 (7.1)	9.7 (7.6)	15.0 (7.9)

Mean scores with standard deviation. NDI = Neck Disability Index, OLBPDQ = Oswestry Low Back Pain Disability Questionnaire. PCS = Pain Catastrophizing Scale. HADS = Hospital Anxiety and depression Scale. SF12 = Quality of life scale, short version. BPI = Brief Pain Inventory. WAW = walking, general activity, working.

3.7 REPORTED HIGH VALUES of pain intensity, anxiety or depression, and pain catastrophizing (complex group)

Of all patients, 17.8 % reported high values on the NRS (7-10), depression or anxiety (>10), and pain PCS (>31) scales. There were significant differences in patient characteristics (sex: *P* =.018, age: *P* =.001, marital status: *p*=.001, education: *p*=.001, multisite pain: *p*=.001,) and quality of life values between ‘complex groups’ versus ‘not complex’ groups (Fig. 3).



	BPI-REM	BPI-WAW	BPI-Interference
Complex group	20,8	30,4	51,2
Non-complex group	10,3	22,5	32,8

	PHS	MHS
Complex group	28,4	31,5
Non-complex group	31,6	45,9

0 = does not interfere – 10 complete interference,.
BPI WAW = walking, general activity, work and sleep. Max score 40
BPI REM= relations with others, enjoyment of life, and mood. Max score 30
BPI Interference = sum of seven questions. Max score 70

Reference value = < 50 worse quality of life, > 50 better quality of life then the average Dutch population

	NRS	Anxiety (HADS)	Depression (HADS)	HADS total	PCS
🟥 Complex group	8,4	12,5	12,6	25,1	41,4
■ Non-complex group	6,8	6,5	6,6	13,1	23,6

Complex group = 17.8 % (n=1859) of the patients with high values on NRS (7-10), anxiety or depression (>10), and PCS (>31)

Fig. 3. Complex group.

4. DISCUSSION

This study provides an overview of the average biopsychosocial scores of chronic pain patients referred to the UPCM. A large sample of patients was appropriate for analysis.

4.1 Patient characteristics

At the time of referral, 36% of chronic pain patients were unemployed or incapacitated (as reference: 3.3 % of the Dutch labor force is unemployed), 59% reported low education (compared to 29% in the Dutch population), and 40% of all patients were older than 61 years (24.8% of the Dutch population is over 60 years of age).[29] It is well known that socioeconomic status (a combination of (1) material circumstances; (2) skills, knowledge and capabilities; and (3) social network) has an impact on patients' experience and treatment choice with regard to their chronic pain condition.[19] Vulnerable subgroups such as advanced age, unemployed patients, and long- lasting chronic pain patients display complex interrelationships.[19] Another observation was the high prevalence of severe pain experience (71.9%), and extended pain duration. Over 30% of the patients suffered from long-lasting pain (> 5 years).[4] The high prevalence of long-lasting pain can be explained by the fact that UPCM is an academic tertiary referral center, and almost 20% of the patients, simultaneously experienced high values of pain severity, anxiety or depression, and pain catastrophizing, demonstrating symptom- or case-complexity.

4.2 Sex

The UPCM sample of chronic pain patients had a majority of female patients (59.3%), which conforms to most epidemiological studies on chronic pain and affective conditions.[19] Although the findings are less consistent, literature regarding sex and pain concludes that the prevalence of the most common forms of pain is higher among females than males (back pain, widespread pain, and intensity pain in multiple anatomic regions), and that women display enhanced sensitivity to most forms of experimentally induced pain.[1] This study confirmed higher pain intensity among females. However, our study also showed that female patients scored less on average than males for pain catastrophizing, and failed to illustrate a difference in the number of pain locations (multisite or widespread pain) between males and females. Another discrepancy with current literature on pain and sex is that male patients in the present study appeared to suffer more psychologically from chronic pain than female patients. A possible explanation could be that females are more willing to accept psychological interventions, which may have prevented females from being referred to a tertiary academic pain clinic due to longer lasting and thus far unexplained chronic pain conditions. This is in contrast with a large systematic review which found that sex differences might not affect pain perception in depression, and no clear association between anxiety and sex was observed.[25] Interestingly, it is not clear to what extent interactions between sex and sociodemographic characteristics (such as age, marital status, employment, and level of education) play a role in our cohort. This should be explored more in future intersectional research approaches.

4.3 Pain severity

In consonance with the current literature,[22] a higher reported pain severity corresponded to a higher average interference on quality of life. This was similar to the psychological aspects. Lower pain severity scores showed a higher prevalence of only one pain location, whereas higher pain severity had a higher distribution (> 4 locations). Almost half of the patients who reported high pain severity had either significant depression or anxiety scores on the HADS scale, which were and much higher than the scores of those reporting lower pain severity. This is in line with the literature.[10]

4.4 Multisite pain locations

Patients with four or more pain locations reported having chronic pain for a longer time (>5 years) than those with fewer pain locations. The theory of central sensitization or nociplastic pain suggests that acute and localized pain may develop to affect more parts of the body and possibly lead to a condition known as ‘widespread pain’.[23] Further exploration of the role of central sensitization and the development of widespread pain in relation to pain duration and patient wellbeing is needed. Concerning symptom formation, momentary assessment tools could be used to monitor how pain may impact wellbeing and affective states and vice versa.[21] As a functional disorder, chronic widespread pain might be the result of an alarm-falsification process related to psychosocial stressors, which remain undetected with regard to somatic and psychiatric comorbidities.[16]

4.5 Condition-specific values

Increased reports of pain severity clearly showed increased disability on both NDI and OLBPDQ (Table 6). Previous studies have shown that low back pain is associated with a lower quality of life and physical functioning.[15] The results presented here support the conclusion that chronic lower back pain is a debilitating condition.

4.6 Reported high values (complex group)

Analysis of the complex group (high values of pain intensity, anxiety or depression, and pain catastrophizing) and the non-complex group showed significant differences in patient characteristics and quality of life values. The literature states that psychological variables influence pain mechanism and that this may explain sex differences in pain processing and may be related to differences in clinical presentation.[26] Clinical research has also revealed that patients with high pain catastrophizing often have a greater risk of developing chronic pain and disability. How this interacts with emotional factors such as anxiety and depression is not fully understood. Part of which might be related to personality traits, given that functional somatic conditions and affective conditions are both associated with neuroticism.[16] More research on these interactions is needed.[11] Furthermore, other characteristics are needed to explore this complex group, for example, the possible sex differences in the relationship between anxiety and opioid (mis)use.[27]

4.7 Strengths and Limitations

The strength of the study is the large sample of patients, which provides insight into the average biopsychosocial values of chronic pain patients referred to an academic multidisciplinary pain center. Although the findings are limited by the cross-sectional nature of the data, the descriptions can be used as reference data in the field of pain practice and used to evaluate, monitor, or improve chronic pain care in settings nationwide and internationally. Moreover, it can be used to compare patient characteristics in other treatment settings and/or scientific publications, which is highly needed in clinical pain practice and research as well. As far as we know, this is the first large sample of patients suffering from chronic pain in the Netherlands. Therefore, it cannot be compared with other Dutch samples. However, there are similar findings in the literature, for example, the complexity of advanced age and chronic pain, sex-specific differences in pain perception, and high prevalence of chronic pain in patients who are unemployed.[19] These findings necessitate more complex research between sex and gender differences in the context of the biopsychosocial model. In the future, we will compare our findings with epidemiologic studies nationwide.

The cohort provides two condition-specific pain complaints (neck and low back), although more condition-specific questions, such as neuropathic pain complaints, would contribute to further knowledge on chronic pain management. For this, the ICD-11 classification recognizing clinically important conditions may contribute to research in the near future.

4.8 Clinical implications and conclusions

The overall high scores of the patient-reported outcome values in the complex group stretch the need for a personalized medical approach in the treatment of chronic pain. One of the challenges that have been defined to improve and innovate personalized medicine, is patient empowerment.[24] It is conceivable that in the management of patients suffering from chronic pain, taking patients' preferences into account may increase their likelihood of treatment success.[18]

Therefore, adequately involving patients in their treatment choices is important. Above all, we think that knowing patients' preferences in what they consider high-quality pain health care is crucial.[7] Furthermore, care for complex patients should be organized as an integrated care approach, transitionally crossing the boundaries of medical specialties and settings. A detailed review on shortcomings, benefits and aspirations of multidisciplinary integrated care has been published recently.[17] As a multidisciplinary pain-center we intent to deliver our personalized care for the complex pain patient as a transitional network approach.

In conclusion, based on patients' reported biopsychosocial values, we would like to emphasize the importance of a multidisciplinary approach to individualized chronic pain management. For instance, in patients suffering from chronic pain and having a lower socioeconomic status, more attention is needed on occupational factors such as work (reintegration), job control, and job satisfaction. In the context of matched care, it is strongly recommended to intensify the pain clinic care based on the psychometric outcomes of the patient. Additionally, further research (regarding follow-up treatment) is warranted from the outcome of this individualized multidisciplinary pain management.

Conflict of interest
None to declare

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CHAPTER 3

SEX DIFFERENCES AND THE SOCIOCULTURAL INFLUENCE ON PATIENT REPORTED OUTCOMES OF CHRONIC PAIN PATIENTS, A DATA*PAIN* II STUDY

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ABSTRACT

Background and Objectives

Differences in pain reporting within the sexes are often larger than for those between. Intersectionality theorists belief that the socio-cultural construct may generate health disparities. Therefore, we hypothesized to detect differences in patient reported outcomes (PRO's) associated with sociocultural variables in men and women with chronic pain.

Methods

We explored the association between the sociocultural construct (age, marital status, employment, and educational level) and PRO's and assessed interactions between sex and the socio-cultural construct. Subsequently, we stratified on sex to illustrate the differences in all the PRO's for pain intensity, quality of life, pain interference, anxiety, depression, and pain catastrophizing.

Results

We analyzed the cross-sectional records of 11060 patients with chronic pain; 59% were women and the mean age was 56 years (18-96). The average pain intensity was 7.2 ± 1.8 and was statistically different for men (6.92 ± 1.8) and women (7.33 ± 1.7). The socio-cultural variables showed a larger significant impact on men than women; for example, the impact of having a paid job on anxiety revealed a coefficient of ▪=-1.35; $p<0.001$ in men and a ▪=-0.52; $p<0.001$ in women.

Conclusions

This study shows modifications due to the sociocultural construct on PRO's. There is a need for further clinical research to observe if similar sex interactions exist in perceiving treatment effects. Such information could contribute towards identifying relevant socio-cultural statuses that are of importance to the pain experience and outcome of interventions.

1. INTRODUCTION

A higher prevalence and severity of pain is reported in women when compared to men.[3; 13; 27] Also, women are at higher risk of onset of new pain, which may lead to further decrease in quality of life (QoL), increase in physical disability and psychological comorbidities.[19] In most chronic pain research, health disparities are compared between men and women. Yet, the differences found within the sexes are often larger than those between sexes.[2] Recent literature indicates that the socio-cultural construct may play a role and may generate health disparities.[9; 14; 15; 24] In case of chronic pain, it has been argued that taking into account the socio-cultural construct may explain a substantial part of the heterogeneity that is present within the population.[2] In clinical practice, the applied biopsychosocial model[2; 9; 14; 15; 24; 33] observes an individual's response to pain, viewed from a biological, psychological, and socio-cultural standpoint. Yet, little is known on how the socio-cultural health determinants interact with biological and psychological domains of the pain experience.[2] It is unclear whether the socio-cultural construct influences the pain experience differently for men and women [6; 13; 15] We hypothesized to detect disparities between men and women associated with the socio-cultural construct. Therefore, this study aimed to assess the effect of sex and socio-cultural variables (age, marital status, education, and employment) on pain intensity, QOL, pain interference, pain catastrophizing, depression, and anxiety scores, and moreover asses if there is an interaction between sex and socio-cultural variables. The results may improve the understanding of the heterogeneity observed in daily practice[21] and may provide information that could contribute towards identifying relevant socio-cultural statuses that are of importance to the pain experience and ultimately to the outcome of interventions. Accordingly, governmental bodies and stakeholders request individualized pain care, where precision is critical.[21]

2. METHODS

2.1 Study design

This study used data from a large prospective cohort study called DATA*PAIN*, entailing chronic pain patients from the south of Limburg in the Netherlands, that were referred to the University Pain Center Maastricht (UPCM). Data collection (pre-intake) was initiated in 2003 and is still ongoing.[18] The cohort

(15,000 patients) contains intake data, including PROM’s, sociodemographic, and pain-related data.[6]

2.2 Study Population

Patients with chronic pain and referred to the UPCM of the Maastricht University Medical Care Centre+ were invited to complete a pain questionnaire before their first consultation. This pain questionnaire collects information on pain perception, pain interference, psychological aspects, QoL, and socio-demographic values. For this study, all patients who gave informed consent, who were at least 18 years old and had been experiencing pain for more than three months, were included (n=11060). Ethical clearance was obtained from the medical ethical committee (METC 2020-1568).

2.3 The Socio-cultural Construct

We hypothesized to observe disparities associated with the socio-cultural construct between men and women who had been experiencing chronic pain. The socio-cultural construct we measured consisted of age, marital status, education, and employment.[9-11; 14] These statuses are useful to observe differences in the pain experiences of men and women and can recognize groups of the chronic pain population with certain status that may do better or worse. Hereby, identifying a source that produces heterogeneity in the chronic pain population.[14] The intersectional approach was applied to observe the disparities, this is a specific method of analysis and useful tool for observing differences between (patient) groups composed of specific variables.[14] These disparities often remain implicit during analysis based on sex only. Consequently, a stratification by sex was applied to observe the disparities produced by the socio-cultural statuses for men and women separately.[14] The socio-cultural variables applied in this study are discussed here below.

2.3.1 Age

In this study, we analyzed age as a binary variable: 18-56 years and 57-96. We chose 56 years as the cutoff point, as this was the study sample’s average age.

2.3.2 Relationship status

Several theories suggest that chronic pain population’s marital status is related to pain severity, physical ability, and depression.[2] This counts for being in a relationship as well, therefore relationship status was dealt with as a binary variable divided into having a relationship or not having a relationship.

2.3.3 Education

We used the educational level of the participants as a surrogate measure for socio-economic status, as this is one of the most reliable ways to collect the socio-economic status. The literature shows that educational level is associated with the development, maintenance and perception of pain.[20; 30; 31] A review of low back pain observed that the level of education might be a predictor for pain frequency and an indicator of the treatment outcome.[8] We dichotomized the variable into a low level of education (up to 10 years of education: elementary school and secondary education) and high level of education (a minimum of 12 years of education: secondary education onwards, bachelors, university or higher).[28]

2.3.4 Employment

The studies of Breivik show that chronic pain is more prevalent in manual workers and unemployed persons.[4; 5] In full- and part-time workers, one out of 4 persons stated that chronic pain impacts their ability to work. Nineteen percent of the surveyed participants lost their jobs because of chronic pain, 16% had changed responsibilities, and 13% had changed jobs due to chronic pain.[4] In this study, employment was divided into having a paid job and not having a paid job.

2.4 Pain variables

The pain variables discussed here below were absorbed in the analysis as confounders, as literature indicates their importance in the pain experienced by people in pain. Pain duration was taken into account and presented as a binary variable: <1 year (3-12 months), and > 1 year.[7] Moreover, the locations of pain in the patients was documented. The observed locations of pain were the head, neck, arm, lower back, upper leg, lower leg, and chest/abdomen. If patients reported more than one pain location, the number of pain locations was identified as 1 pain location or 2 - 8 pain locations. This variable is not a synonymous with widespread pain or multisite pain found in central sensitization cases; it represents only the sum of pain locations that may reflect the physical impact of the pain experienced.

2.5 Patient-Reported Outcome Measures as the Dependent variables

The patient reported outcome measures (PROM'S) that were included in this study were the Numeric (Pain) Rating Scale (NRS) for pain intensity, the RAND-36 for QOL, the Brief Pain Inventory (BPI) for interference of pain in daily life, the Hospital Anxiety and Depression Scale (HADS) for depression and anxiety, and the Pain Catastrophizing Scale (PCS) for pain catastrophizing.[6] The RAND-36 was subdivided into two subscales, named the Physical Health Scores (PHS) and the Mental Health Scores (MHS).[17] The BPI was subdivided into the BPI-REM containing the items relationship with others, enjoyment of life, mood and sleep, while the BPI-WAW contained the items walking, general activity and work.[29]

2.6 Statistical analysis

Overall the socio-cultural variables, pain variables, and PROM’s were described with means and standard deviations and counts and proportions for the continuous and binary variables, respectively. We used the independent sample t-test and chi-square test to test for differences between groups on continuous and categorical variables. The specific statistical steps that were taken are explained below.

2.6.1 Regression analysis: Do sex and socio-cultural variables influence PROM’s?

First, by using linear regression we explored the association of sex and the socio-cultural variables for each PROM. As well, these associations were adjusted for the confounding variables (pain variables). The mean differences per group were calculated and reported with standard errors. Then a stepwise backward elimination in combination with clinical expertise was conducted to select only significant determinants for the dependent outcome using a p-value of <0.05 for selection. The variance inflation factor was computed to detect multi-collinearity, as well, the assumptions of linear regression were assessed using scatter- and residual plots, and histograms.

2.6.2 Interaction analysis: Do the regression analyses show significant interactions?

Secondly, interaction terms of sex and socio-cultural variables (age, marital status, employment, and educational level) were added to the regression models. This was done to assess if there were any differences between men and women in the association with the socio-cultural variables. Including only those statistical significant interaction terms for each PROM individually.

2.6.3 Stratified regression analyses: Do the socio-cultural variables influence, men and women, equally?

At last, the analyses were stratified on sex for each PROM. This, to allow for ease in interpretation of the sex-specific effect of socio-cultural variables on the selected PROM's.

All analyses were performed using R, version 3.6.1. The results of the statistical analyses were assessed on clinical relevance and the preciseness of measurement, not only on p-values, as the considerable size of the cohort has ample power to detect clinically irrelevant differences. This approach is in line with recent recommendations by the American Statistical Association.[34]

3. RESULTS

Table 1 shows the summary statistics of the 11060 chronic pain patients of the cohort, taken before the first visit to the pain clinic. Statistically significant sex differences were observed for the PROM's: NRS, HADS-depression, and for both subscales of the BPI. In table 2 the results of the statistical analyses are found.

Table 1. Variables of the cohort DATAPAIN

Variables cohort DATA*PAIN*	**Total cohort** N = 11060 (%) or mean(SD)	**Men** N(%)	**Women** N(%)	**P value**
Intersectional variables				
Sex		4514(41%)	6539(59%)	
Age (years)				.030
Low age: 18-55	5923(54%)	2362(52%)	3559(54%)	
High age: 56-96	5137(46%)	2152(48%)	2980(46%)	
Marital status				<.001
No relationship	2861(27%)	947(22%)	1913(30%)	
Relationship	7820(73%)	3421(78%)	4393(70%)	
Educational level				<.001
low	6419(59%)	2436(55%)	3977(61%)	
High	4529(41%)	2033(45%)	2495(39%)	
Employment				<.001
No paid job	6098(67%)	2442(63%)	3652(70%)	
Paid job	2975(33%)	1409(37%)	1566(30%)	
Pain variables				
Pain duration				.010
< 1 year	3198(29%)	1248(28%)	1950(30%)	
> 1 year	7862(71%)	3266(72%)	4589(70%)	
Multisite pain				.200
No	5150(48%)	2146(49%)	3000(48%)	
Yes	5551(52%)	2239(51%)	3309(52%)	
Pain location		-	-	
Head	1742(16%)	676(15%)	1065(16%)	.070
Neck	3491(31%)	1454(32%)	2037(31%)	.020
Arm	2176(20%)	870(19%)	1306(20%)	.400
Lower back	5759(52%)	2288(51%)	3467(53%)	.020
Upper leg	3473(31%)	1308(29%)	2163(33%)	<.001
Lower leg	2701(24%)	1106(25%)	1595(24%)	.900
Chest/abdomen	892(8%)	371(8%)	521(8%)	.700
PROM's				
NRS	7.16(1.78)	6.92(1.83)	7.33(1.72)	<.001
PHS	31.45(8.29)	31.42(8.27)	31.48(8.30)	.700
MHS	42.87(12.23)	43.02(11.98)	42.76(12.39)	.300
BPI-REM	12.64(8.42)	13.03(8.43)	12.37(8.40)	.010
BPI-WAW	24.31(8.97)	23.81(9.09)	24.65(8.86)	.004
HADS-Anxiety	7.77(4.19)	7.84(4.24)	7.72(4.16)	.200
HADS-Depression	7.85(4.36)	8.25(4.42)	7.57(4.30)	<.001
PCS	27.79(12.07)	27.98(11.75)	27.65(12.29)	.200

Counts may not add up to the total due to missing values as some questionnaires were not included since the beginning of the cohort inclusion.

Table 2. Influence of socio-cultural variables on PROM's and stratification by sex

Variables	Coefficient (CI)	p-value	Men coefficient (CI)	p-value	Women coefficient (CI)	p-value
NRS						
Sex (female)	0.30(0.22, 0.38)	<.001	-	-	-	-
Age (56-96)	-0.22(-0.30, -0.14)	<.001	-0.22(-0.35, -0.09)	.001	-0.17(-0.28, -0.07)	.002
Marital status (in relationship)	-0.14(-0.22, -0.05)	.002	-0.20(-0.35, -0.06)	.006	-0.10(-0.21, 0.01)	.063
Educational level(high)	-0.36(-0.44, -0.29)	<.001	-0.42(-0.54, -0.30)	<.001	-0.32(-0.42, -0.22)	<.001
Employment (paid job)	-0.44(-0.53, -0.35)	<.001	-0.44(-0.57, -0.30)	<.001	-0.42(-0.54, -0.31)	<.001
RAND-36 - PHS						
Sex (female)	0.01(-0.39, 0.41)	.960	-	-	-	-
Age (56-96)	0.19(-0.25, 0.62)	.398	0.18(-0.47, 0.83)	.590	0.28(-0.31, 0.86)	.350
Marital status (in relationship)	-0.20(-0.65, 0.24)	.379	-0.27(-0.99, 0.46)	.470	-0.18(-0.76, 0.40)	.540
Educational level (high)	0.07(-0.34, 0.48)	.733	-0.22(-0.82, 0.39)	.480	0.32(-0.23, 0.87)	.250
Employment (paid job)	0.24(-0.23, 0.70)	.315	0.30(-0.38, 0.99)	.390	0.25(-0.38, 0.88)	.440
RAND-36 - MHS						
Sex (female)	-0.56(-1.15, 0.02)	.059	-	-	-	-
Age (56-96)	-0.27(-0.91, 0.38)	.420	-0.53(-1.49, 0.42)	.274	-0.21(-1.08, 0.66)	.634
Marital status (in relationship)	0.81(0.14, 1.48)	.017	0.78(-0.28, 1.83)	.148	1.86(-0.01, 1.73)	.053
Educational level (high)	-0.21(-0.81, 0.39)	.501	-0.47(-1.35, 0.41)	.295	0.01(-0.82, 0.84)	.975
Employment (paid job)	-0.71(-1.40, -0.02)	.045	-0.83(-1.84, 0.17)	.104	-0.48(-1.43, 0.47)	.322
BPI-REM						
Sex (female)	-2.87(-4.01, -1.73)	<.001	-	-	-	-
Age (56-96)	-1.79(-2.64, -0.93)	<.001	-1.77(-2.66, -0.89)	<.001	-0.32(-1.09, 0.45)	.410
Marital status (in relationship)	-2.58(-3.55, -1.61)	<.001	-2.53(-3.49, -1.56)	<.001	-0.83(-1.57, -0.08)	.029
Educational level (high)	-1.51(-2.06, -0.97)	<.001	-1.59(-2.41, -0.78)	<.001	-1.32(-2.05, -0.58)	<.001
Employment (paid job)	-2.37(-2.99, -1.74)	<.001	-2.47(-3.40, -1.54)	<.001	-1.86(-2.72 -1.01)	<.001
Interaction: Sex* Age	1.10(0.03, 2.18)	.043	-	-	-	-
Interaction: Sex* Marital status	1.69(0.49, 2.90)	.006	-	-	-	-
BPI-WAW						
Sex (female)	0.27(-0.28, 0.83)	.336	-	-	-	-
Age (56-96)	-1.86(-2.46, -1.26)	<.001	-2.17(-3.11, -1.23)	<.001	-1.45(-2.24, -0.66)	<.001
Marital status (in relationship)	-0.75(-1.36, -0.13)	.017	-1.09(-2.12, -0.07)	.037	-0.58(-1.35, 0.19)	.138
Educational level (high)	-1.73(-2.30, -1.16)	<.001	-2.25(-3.12, -1.38)	<.001	-1.32(-2.08, -0.56)	<.001
Employment (paid job)	-2.80(-3.46, -2.14)	<.001	-3.15(-4.15, -2.16)	<.001	-2.52(-3.41, -1.64)	<.001
PROM: HADS ANXIETY						
Sex (female)	-1.47(-1.94, -1.01)	.001	-	-	-	-
Age (56-96)	-0.88(-1.21, -0.56)	.001	-0.84(-1.16, -0.51)	<.001	0.07(-0.22, 0.34)	.651
Marital status (in relationship)	-0.79(-1.15, -0.43)	.001	-0.78(-1.14, -0.42)	<.001	-0.12(-0.40, 0.15)	.374
Educational level (high)	-1.08(-1.28, -0.88)	<.001	-1.20(-1.50, -0.91)	<.001	-1.02(-1.29, -0.76)	<.001
Employment (paid job)	-1.54(-1.88, -1.20)	<.001	-1.35(-1.69, -1.01)	<.001	-0.52(-0.83, -0.22)	<.001
Interaction: Sex*Age	0.75(0.33, 1.18)	.006	-	-	-	-

Interaction: Sex* Marital status	0.60(0.15, 1.06)	.010	-	-	-	-
Interaction: Sex* Employment	0.86(0.41, 1.31)	.002	-	-	-	-
HADS-DEPRESSION						
Sex (female)	-2.07(-2.55, -1.60)	<.001	-	-	-	-
Age (56-96)	-1.04(-1.37, -0.72)	<.001	-0.99(-1.32, -0.66)	<.001	-0.31(-0.59, -0.02)	.033
Marital status (in relationship)	-0.99(-1.36, -0.63)	<.001	-0.99(-1.36, -0.62)	<.001	-0.20(-0.47, 0.08)	.164
Educational level (high)	-0.96(-1.16, -0.76)	<.001	-0.75(-1.05, -0.45)	<.001	-1.13(-1.40, -0.86)	<.001
Employment (paid job)	-1.83(-2.17, -1.49)	<.001	-1.81(-2.15, -1.46)	<.001	-1.03(-1.34, -0.72)	<.001
Interaction: Sex*Age	0.62(0.19, 1.06)	.005	-	-	-	-
Interaction: Sex* Marital status	0.76(0.30, 1.22)	.001	-	-	-	-
Interaction: Sex* Employment	0.66(0.20 1.12)	.005	-	-	-	-
PCS						
Sex (female)	-2.91(-4.02, -1.80)	<.001	-	-	-	-
Age (56-96)	-0.12(-0.92, 0.67)	.763	-0.31(-1.14, 0.52)	.466	2.04(1.30, 2.78)	<.001
Marital status (in relationship)	-1.92(-2.85, -0.98)	<.001	-1.69(-2.63, -0.76)	<.001	-0.72(-1.46, 0.02)	.057
Educational level (high)	-4.95(-5.47, -4.44)	<.001	-4.59(-5.36, -3.83)	<.001	-5.26(-5.96, -4.56)	<.001
Employment (paid job)	-2.54(-3.13, -1.96)	<.001	-2.99(-3.87, -2.12)	<.001	-1.78(-2.59, -0.97)	<.001
Interaction: Sex* Marital status	1.21(0.03, 2.39)	.044	-	-	-	-

3.1 Average pain Intensity measured by the NRS

In table 2, we can observe that women reported a higher NRS score on average for pain intensity (β=0.30; p<0.001) when adjusted for the socio-cultural variables (age, marital status, employment, and education) and confounders (pain variables: pain duration, pain location(s), and multisite pain). There were no statistically significant interactions between sex and the socio-cultural variables. Yet, the stratified analysis on sex showed that a relationship status indicated a lower pain intensity in men only (β=-0.20; p=0.006). In women, there was no significant difference in pain intensity for relationship status. Additionally, the level of a high education or a paid job had a similar reducing effects on the pain intensity for both sexes (see Table 2 and Figure 1.1).

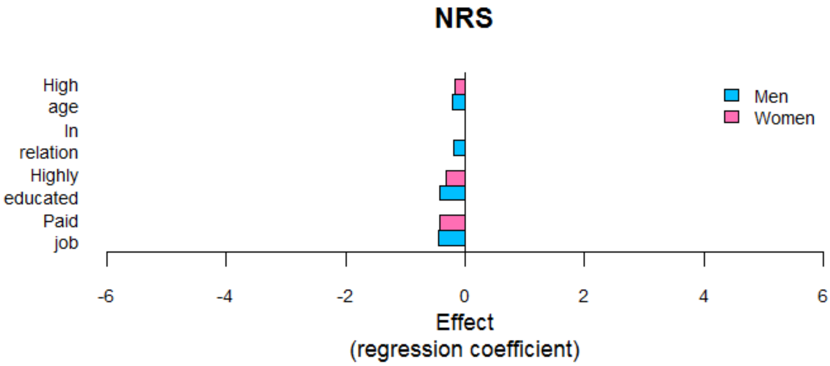

Figure 1.1

3.2 Quality of life

3.2.1 Physical and mental health scores on the RAND-36

No differences between sexes were found after adjustment (PHS β=0.01; p=0.960 and MHS β=-0.56; p=0.059)(see table 2). As well, no significant effects of the socio-cultural variables were observed in both analyses.

3.2.2 Pain interference in activities of daily life; Brief Pain Inventory

3.2.2.1 Relation with others, enjoyment of life, mood, and sleep (BPI-REM)

After adjustment, the BPI-REM subscale was more favorable for women on average (β=-2.87; p<0.001), suggesting that pain interfered less in women's daily activities. In the sex-stratified analysis, an average lower pain interference was found in men for those with a higher age compared to a lower age (β=-1.77; p<0.001). Besides, a substantial difference in the effect of relationship status on pain interference was found between men (β=-2.53; p<0.001) and women (β=-0.83; p=0.029). The variables education and employment, reduced pain interference on functioning in daily activities for both sexes. Nonetheless, these effects were larger for men than for women (Table 2 and figure 1.2*)*.

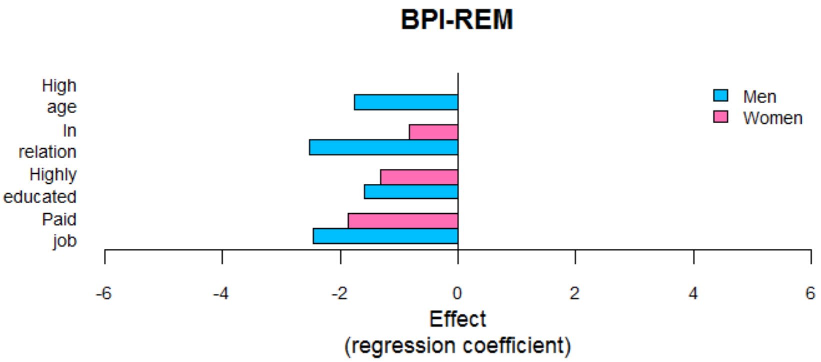

Figure 1.2

3.2.2.1 Walking, general activity, and work (BPI-WAW)

No significant difference for sex (β=0.27; p=0.336) was reported on BPI-WAW after adjustment (Table 2). Nonetheless, all the socio-cultural variables (age, marital status, education and employment) showed disproportions in pain interference for men and women separately in the sex-stratified analysis. A relationship indicated a lower average of pain interference in daily activities in men, yet it had no significant effect on women. Higher age, high level of education or a paid job, had a reducing impact on functioning in daily activities, with a larger effect for men (see table 2 and figure 1.3).

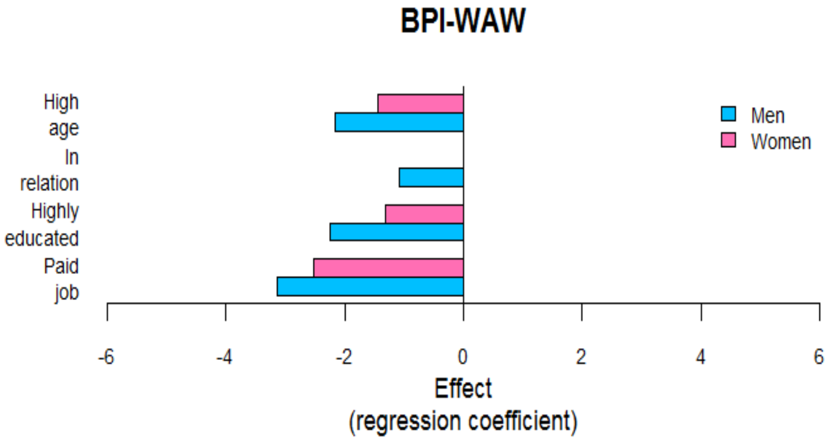

Figure 1.3

3.3 Psychological outcome measures

3.3.1 Anxiety

The average on the HADS anxiety scale was lower for women after adjustment (β=-1.47; p<0.001), indicating less anxiety (see Table 2). The sex-stratified analysis showed that being older (β=-0.84; p<0.001) or a relationship (β=-0.78; p<0.001) produced on average a lower anxiety score, in men only. Conversely, in women no significant influence of age or relationship was found. A small difference in the effect of education on anxiety was found between sexes. Having a paid job reduced the anxiety score both in men and women when compared to not a having a paid job. Yet, the effect was almost three times larger for men (β=-1.35; p<0.001) than for women (β=-0.52; p<0.001) (Table 2 and figure 1.4).

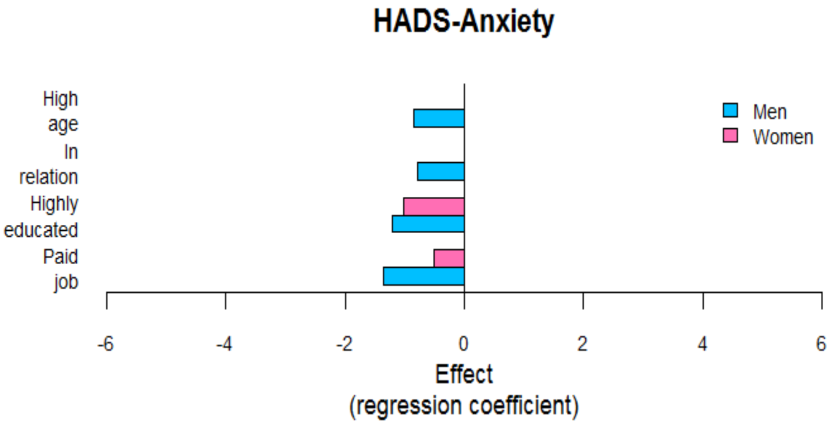

Figure 1.4

3.3.2 Depression

The mean HADS depression score was initially lower in women after adjustment (β=-2.07; p<0.001), indicating a lower rate of depressive complaints (Table 2).The sex-stratified analysis showed that having a relationship compared to no relationship indicated a lower average depression score in men only (β=-0.99; p<0.001). In women, no significant difference was found on average depression between those in a relationship and those not. Being older reduced the depression score for men and women. Yet, the reduction was three times larger for men (β=-0.99; p<0.001) than for women (β =-0.31; p=0.033). Similar observation was made in having a paid job. Nevertheless, education had a larger effect on women than on men. (Table 2 and figure 1.5).

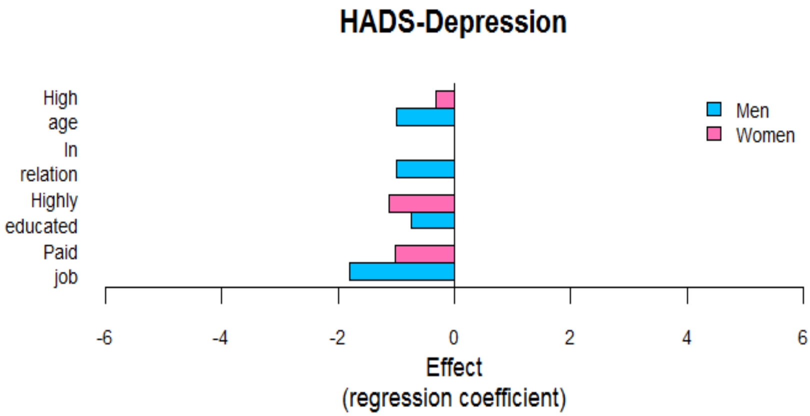

Figure 1.5

3.3.3 Pain catastrophizing

The PCS score indicated a lower average catastrophizing score for women after adjustment (β=-2.91; p<0.001) (Table 2). The sex-stratified analysis showed that at older age increased on average the pain catastrophizing score in women only (β=2.04; p<0.001), while a relationship status indicated a lower score in men only (β=-1.69; p<0.001). Besides, a disparity in catastrophizing was found between men and women due to education and employment. Education indicated a coefficient of β=-4.59; p<0.001 in men and a β=-5.26; p=0.033 in women and employment generated a coefficient of β=-2.99; p<0.001 in men and a β=-1.78; p<0.001 in women (Table 2 and figure 1.6).

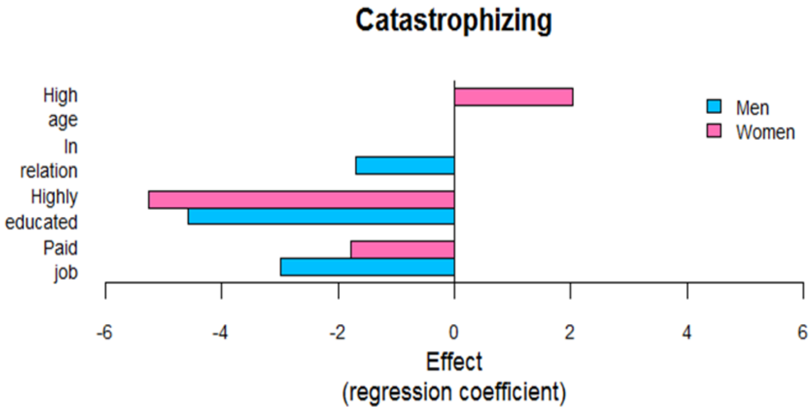

Figure 1.6

4. DISCUSSION

We observed a strikingly different impact of the socio-cultural variables on PROM's for men and women. For example, the significant impact of a relationship was found on pain intensity, pain interference, anxiety, depression, and pain catastrophizing in men, while in women the impact of relationships status was only found to be significant on a subscale of the BPI. The results of this study indicate that these statuses are of influence on patient reported outcomes, which had been suggested by others.[1; 10; 14] The importance of testing the impact and the subsequent stratification on sex was stressed by the fact that the interactions gave a different interpretation than the main effect of the same variables. This shows that the analysis based on sex only would have kept important issues unrevealed.

This study used data from a large and heterogeneous population-based cohort from an academic hospital in which we measure multiple PROM's covering many aspects of chronic pain. In all analyses, there was sufficient statistical power as a result of the large sample size. Although studies have identified associations between socio-demographic variables and PROM's,[22] to our knowledge, this is the first study to report in detail the impact of socio-cultural variables on pain and the associated complaints for both sexes separately. Caution should be taken as this data is collected in a tertiary pain clinic and may not be generalizable to all chronic pain patients. The database shows high representations of low education and unemployment compared to the total Dutch population.[6] Correspondingly, higher percentages of low levels of education and unemployment are found in poorer general health populations.[23; 32] Lame et al. identified sex differences on multiple domains of the RAND36, while we didn't find evidence of sex differences on the mental and physical subscales.[18] This may be due to the different application of subscales; multiple domains versus two subscales.

Our study may be an important contribution to the limited clinical pain research addressing socio-cultural variables in chronic pain.[2; 13] These results identify that age, marital status, education, and employment affect the outcome of pain intensity, pain interference, anxiety, depression, and pain catastrophizing. Moreover, the socio-cultural variables produced important sex disparities in these PROM's.

At an older age, average pain interference appear to be lower. Similar findings are shown for anxiety and depression scores. Yet, all the averages are lower in men than women. Vice versa occurred in pain catastrophizing in women.

Marital status occurs as a positive factor in men, while it does not influence women. The literature on general health recognizes that women stay ‘unaffected’ by the negative physical health consequences of divorce, widowhood, or none relational statuses.[26]

Employment is an important social determinant of health and well-being, as it provides financial security and opportunity to fulfill a social role and contributes positively to mental and physical health.[23; 32] In all cases, the effect of employment reduced the patient reported outcome, yet the average reduction was larger for men in many cases. Nonetheless, studies show no consensus on the impact of employment status and sex differences.[23]

Education is observed as a key in reducing health disparities, as education is one of the most important determinants for maintaining employment.[32] Research indicates that even relative changes in socioeconomic status can affect health.[25] Yet, the reasoning for disparities in sex differences remains unrevealed.

Consequently, our results add to the existing literature by suggesting that the heterogeneity found in the chronic pain population may be partly explained by patients' sociocultural variables rather than by biological sex variables only.[1; 2; 10; 14; 15]

The largest and most challenging limitation of this study is that other variables of importance for this study were not routinely collected. The analyses could have benefitted from those confounders such as the classification of disease (ICD) and current medication intake. The original DATA*PAIN* cohort recorded many variables with multiple categories. For example, employment consisted of household, part-time paid job, paid job, unpaid job or student, unemployed or incapacitated, and retired. These categories may have reflected more explicit social constructs. However, we changed them into binary variables for ease of interpretation and included relatively simple interaction terms in the statistical models. The next step could be to present interactions using all the different categories present in the data. Nevertheless, we think that how we analyzed the socio-cultural construct concerning sex and chronic pain is in agreement with the current literature.[1; 2; 9; 11; 12; 16]

4.1 Future perspective

There is a need for further clinical research to observe if similar interactions exist, and how they relate to, treatment effect. Such information would be the next step towards personalized management for CP as, if those interactions are observed, a patient’s sex and socio-cultural variables could guide individual treatment. The question remains if subsequent adaptation in pain treatment optimizes treatment response for these specific subgroup(s) of the chronic pain population, and what influence these treatment options will have on the clinical practice.

Although the factors identified in this study may seem non-modifiable through medical intervention, they form a target approach to chronic pain assessment and management. Providing opportunities for interventions as personalized treatment through stratification on the socio-cultural status and adapting pain treatment to their needs.[20; 30; 31] Nevertheless, these non-modifiable variables may influence future prevalence and severity of CP, thereby necessitating its placement on political and societal agendas.[20]

In conclusion, socio-cultural disparities help understand the heterogeneity of the chronic pain population. We have shown that men's social positions have a significantly more positive influence on how they perceive pain and associated complaints. The identified sociocultural position(s) may be collected in addition to screening and diagnosis when assessing patients with chronic pain in clinical practice.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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CHAPTER 4

THE COMPLEX CHRONIC PAIN PATIENT AND THE CHANCE OF SUCCESSFUL TREATMENT OUTCOME, A DATA*PAIN* III STUDY

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ABSTRACT

Background

Insights on how clusters of biopsychosocial factors influence patient outcome of chronic pain(CP) patients is missing. The documentation of patients experiencing combinations of symptoms is assumed to have negative consequences on treatment outcome, deteriorate health states and quality of life.

Methods

Categorization of CP patients was made in the prospective DATA*PAIN* registry cohort, in which CP patients with pain severity(Numeric Rating Scale(NRS):7-10), depression *or* anxiety(Hospital Anxiety and Depression Scale: >10), *and* pain catastrophizing(Pain Catastrophizing Scale:>31) were identified as the complex group. Patient outcomes; treatment satisfaction on the Patient Global Impression of Change(PGIC), pain relief on the NRS, pain interference on the Brief Pain Inventory(BPI) and quality of life indicator General Perceived Health(GPH) were evaluated. Logistic regression analyzed if belonging to the complex group modified the PGIC or GPH outcome. Linear regression observed if the complex group differed in average reduction in pain relief and interference compared to non-complex patients.

Results

1637 CP patients were included, of which 345(21.08%) were considered complex. The change scores of pain relief and BPI active subscale were not significantly different. The BPI affective subscale had a different change score(-0.509;P: 0.002). The complex group had an odds ratio(OR) of 0.59(95% confidence interval (CI): 0.36-0.77) on treatment satisfaction compared to non-complex patients, and an OR of 0.28(95% CI: 0.11-0.56) on the GPH.

Conclusion

When treating complex patients, desired treatment outcome(s) should be recognized by specialist and patients, as these may be less likely to occur and thus may guide treatment decision.

1. INTRODUCTION

Chronic pain (CP) affects about 20% of the general population and available treatment strategies do not always provide satisfactory results for the patient.[1] This may be due to the heterogeneity that is present in the pain population. CP is recognized as a biopsychosocial phenomenon in which biological, psychological, and social factors dynamically interact.[1-3] Cognitive and affective factors as pain catastrophizing, anxiety, and depression contribute to the pain response and are, amongst other factors, associated with sex.[4] In cross-sectional analyses, the presence of these cognitive and affective factors have been associated with high pain severity, and with low quality of life and functional status.[4-8] Insights on how this cluster of biopsychosocial factors influence patient outcome(s) is still missing. Moreover, this information may inform pain management of this specific group. A reliable option to observe the aforementioned interaction is clustering. Consequently, a categorization of patients with high pain severity, presence of depression *or* anxiety *and* pain catastrophizing were identified and clustered as the complex group and compared to their non-complex counterparts.[7, 8] The documentation of patients experiencing this combination of symptoms is of importance, as they represent a large sum of CP patients attended at tertiary pain clinics[7] and is assumed to have negative consequences on treatment outcome, deteriorate health states and quality of life.[9, 10] The hypothesis of this study was, that the complex group has a lower likelihood in treatment successes, when compared to CP patients regarded as not being complex. The primary treatment outcomes were pain relief on the Numeric Rating Scale (NRS) and treatment satisfaction on the Patient Global Impression of Change (PGIC).[11] The secondary treatment outcomes selected were the General Perceived Health (GPH) of the patient and pain interference analysed on active and affective subscales of the Brief Pain Inventory (BPI).

2. METHODS

2.1 Study design

This study employed data of a large prospective registry cohort called DATA*PAIN,* and contains patient reported outcome measures (PROM’s), socio-demographic factors and CP related data.[7] The cohort entails CP patients referred to the University Pain Centre Maastricht (UPCM) since 2003. As of March 2016, treatment outcomes of the pain patients were gathered as well. For this article, data collected between March 2016 and June 2020 was used in the longitudinal analyses, with two measurement moments, baseline and follow-up.

2.2 Study population

Patients suffering from CP who are referred to the UPCM of the Maastricht University Medical Centre+ are requested to complete a pain questionnaire before their first consultation. Collecting information conform the biopsychosocial model on pain characteristics, quality of life, and psychological aspects. Additionally, demographic characteristics as sex, age, level of education, marital status and employment were gathered. At 6 months follow-up, patients were asked to fill in a second pain questionnaire, with additional questions concerning the pain care received. [12] For this study, 1637 patients gave additional informed consent to be contacted at 6 months follow-up, had an age above 18 years and pain at baseline for more than 3 months. Ethical clearance was obtained from the medical ethical committee (METC 2020-1568).

2.3 Measurements

The NRS reflects pain intensity on an 11-point scale, ranging from zero (no pain) to ten (the most pain imaginable).[13] In the DATA*PAIN* cohort, pain intensity was collected as the average NRS of the past week at both, baseline and follow-up.

At follow up, the PGIC was collected on a 7-point scale varying from ‘very much improved’ to ‘very much worse’. The scale was categorized into two categories, in which ‘very much improved’ and ‘much improved’ specified a successful treatment outcome and ‘minimally improved’ to ‘very much worse’ a non-successful outcome.

The quality of life indicator GPH was evaluated at follow up on a 5-point scale, varying from ‘excellent’ to ‘very poor’. Two categories were created, in which ‘excellent’ and ‘above average’ reassembled positive general health and ‘average’ to ‘very poor’ indicated negative general health.

The BPI measured pain interference in daily activities. The activities were categorized into an affective subscale called REM, consisting of the activities; relations with others, enjoyment of life, mood and sleep and the active subscale named WAW consisting of walking, general activity and work. This questionnaire was measured at baseline and follow-up. [14]

2.4 Complex versus non-complex group

Based on clinical expertise the complex patient was defined, as those who presented an average pain intensity score of 7 to 10 (≥ 7) on the NRS, in combination with a depression *or* anxiety score above 10 (>10)on the Hospital Anxiety and Depression Scale (HADS), *and* in combination with pain catastrophizing of above 31 (>31) on the Pain Catastrophizing Scale (PCS). These aforementioned cut off scores are based on recommendations of Boonstra et al, stern at al, and Sullivan et al.[15-18]

2.5 Statistical Analysis

The above-mentioned variables were described with mean and standard deviations count and proportion for the continuous and binary variables, respectively Subsequently, analyses of differences between the complex and non-complex group were performed with the independent sample t-test or chi square test depending on weather the variables were continuous or binary of kind.
Logistic regression was applied to determine the likelihood of success for both complex and non-complex groups, by calculating odds ratios (OR) with confidence intervals (CI) for the PGIC and the GPH. Moreover, the difference scores between baseline and follow up of the NRS and BPI were calculated and applied as the dependent variables of the linear regression. To observe, if both complex and noncomplex group have the same possibility of the specified difference score.

In both logistic and linear regression analyses, a backward stepwise elimination was conducted to select potential confounding variables. The results of the statistical analyses were evaluated on clinical relevance and preciseness of measurement, recommended by the American Statistical Association.[19] The statistical analyses were executed in R, a language for statistical computing, through R version 3.6.1 with R Studio1.4.

3 Results

3.1 Description of the population

The summary table (Table 1) displays the socio-demographics, pain characteristics and measurements of the study population, consisting of 1637 CP patients who had completed both pre- and post-treatment questionnaires. Figure 1 shows a flowchart of the chronic pain patients included in both complex and non-complex groups. The complex group was represented by 345 patients (21%), with an average age of 61 years and consisted for 52% of men. Twenty-eight percent of the complex group had no relationship, 89% had a low level of education and 77% had no paid job. The non-complex group that consisted of

1291 CP patients (79%), with an average age of 60 years and of which 41% was men (comparable to the complex group).

Table 1. Baseline characteristics of the cohort DATAPAIN III

Baseline characteristics cohort DATAPAIN III				
Variables Baseline	**Total = n (%)**	**Non-complex group n(%)**	**Complex group n(%)**	**P value**
Demographic variables	1637(100)	1292(78.92)	345(21.08)	
Sex				
Male	706(43.13)	533(41.25)	173(50.14)	0.004
Female	931(56.87)	759(58.75)	172(49.86)	
Age (mean (SD))	60.38(13.46)	60.24(13.22)	60.88(14.32)	0.451
Marital status				
No relationship	372(23.08)	274(21.54)	98(28.82)	0.006
Relationship	1240(76.92)	998(78.46)	242(71.18)	
Educational level				
low	1253(76.54)	947(73.30)	306(88.70)	<0.001
High	384(23.46)	345(26.70)	39(11.30)	
Employment				
No paid job	1128(68.91)	862(66.72)	266(77.10)	<0.001
Paid job	509(31.09)	430(33.28)	79(22.90)	
Pain characteristics				
Pain duration				
< 1 year	562(34.33)	451(34.91)	111(32.17)	0.376
> 1 year	1075(66.67)	841(65.09)	234(67.83)	
Pain location				
Head (mean(SD))	215(13.15)	149(11.54)	66(19.19)	<0.001
Neck (mean(SD))	493(30.15)	374(28.97)	119(34.59)	0.051
Lower back (mean(SD))	883(54.01)	687(53.26)	196(56.81)	0.264
Arm (mean(SD))	292(17.86)	203(15.72)	89(25.87)	<0.001
Upper leg (mean(SD))	608(37.16)	465(36.02)	143(41.45)	0.073
Lower leg (mean(SD))	476(29.11)	345(26.72)	131(38.08)	<0.001
Chest/abdomen (mean(SD))	195(11.93)	136(10.53)	59(17.15)	0.001
Outcomes				
PGIC (mean(SD))				
Non successful	1274(77.83)	978(90.33)	296(96.23)	<0.001
successful	363(22.17)	314(9.67)	49(3.77)	
GPH (mean(SD))				
Negative health	1499(91.57)	1167(75.69)	332(85.79)	<0.001
Positive health	138(8.43)	125(24.30)	13(14.20)	
BPI REM (mean(SD))				
Baseline	4.32(2.53)	3.69(2.27)	6.72(1.97)	<0.001
Follow up	3.79(2.68)	3.26(2.54)	5.77(2.35)	<0.001
Change	-0.54(2.4)	-0.43(2.38)	-0.98(2.44)	<0.001
BPI WAW (mean(SD))				
Baseline	6.09(2.39)	5.69(2.38)	7.58(1.76)	<0.001
Follow up	5.26(2.71)	4.93(2.72)	6.66(2.19)	<0.001
Change	-0.81(2.45)	-0.77(2.54)	-0.93(2.1)	0.231
NRS (mean(SD))				
Baseline	7.21(1.65)	6.91(1.68)	8.37(0.93)	<0.001
Follow up	5.91(2.41)	5.61(2.43)	7.1(1.94)	<0.001
Change	-1.30(2.35)	-1.3(2.43)	-1.32(2.01)	0.854

SD: standard deviation

The sociocultural variables statistically differed with the complex group; 23% had no relationship status, 77% had a low level of education and 69% had no paid job at the moment of intake. Pain characteristics of both groups are shown in table 1.

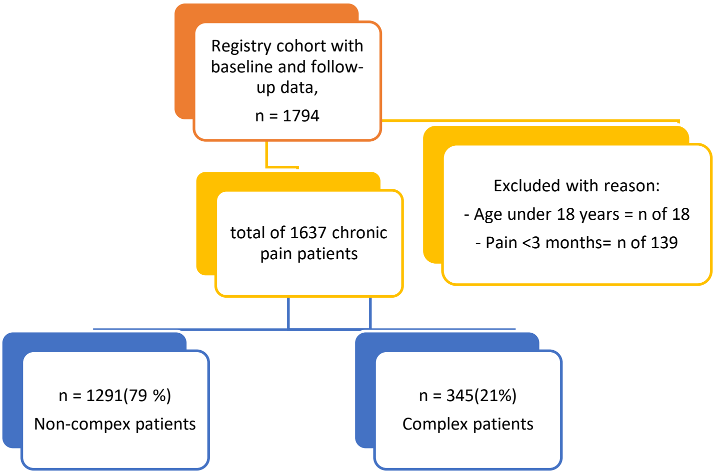

Figure 1. Flowchart of study sample

3.2 Primary outcomes; Pain relief on the NRS and treatment success on the PGIC

3.2.1 Differences and similarities of the NRS for the complex and non-complex group

Baseline NRS scores differed between groups, a mean NRS of 6.91(SD:1.68) was found for the non-complex group, a mean of 8.37(SD:0.63) for the complex group (p <0.001). Yet, the change in scores between baseline and follow up were similar for both groups. A mean change of -1.3(SD:2.43) on the NRS for the non-complex group compared to and a mean change of - 1.32(SD:2.01) for the complex group, p: 0.9. This was confirmed by linear regression, indicating that both pain groups had a similar amount of pain relief (ß =-0.07(Standard Error(SE): 0.17); p: 0.617) (table 2).

Table 2. Results of linear regression analyses for the NRS change

NRS difference scoring Baseline - Follow up	**B(SE)**	**P value**
Crude model Complex CP	-0.034(0.14)	.869
Adjusted model Complex CP	-0.070(0.14)	.617

Results of the linear regression of NRS for a crude and adjusted model. The latter was adjusted for the variables that we statistically significant in the backward stepwise elimination, the variables were: age, pain duration > 1 year***, pain location chest***
P-value < 0.05, P-value < 0.01,*** P-value < 0.001*

3.2.2 Differences in outcome of the PGIC for complex and non-complex group

At follow up, the general success rates of the PGIC were significantly lower for the complex group (p>0.001). Figure 2 is a visual presentation of the outcome of this patient-rated measure, in which can be observed that the complex group was distributed more among the ineffective categories of the PGIC. This observation were confirmed by the odds ratio, resulting in an adjusted OR on the PGIC of ß =0.52(95% Confidence Interval (CI):0.37-0.78) for the complex group (table 3). This demonstrates that complex patients had a significantly lower likelihood of treatment success.

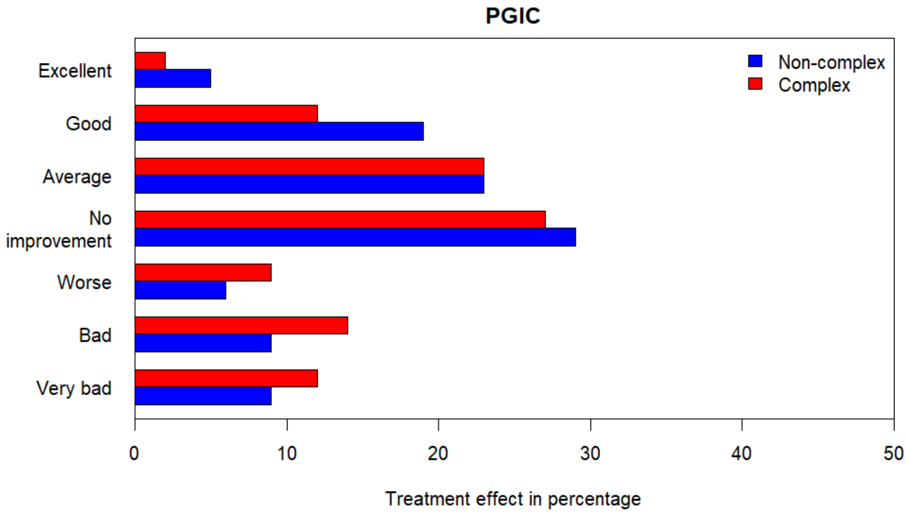

Figure 2. The PGIC rated at follow-up by the complex and non-complex group

Table 3. Results of the logistic regression analyses of the PGIC

GLM PGIC	**B(SE)**	**P value**	**95% CI for odds ratio**		
			Lower bound	**OR**	**Upper bound**
Crude model Complex CP	-0.655(0.19)	<.001	0.37	0.52	0.74
Adjusted model Complex CP	-0.646(0.18)	<.001	0.37	0.52	0.78

Results of the logistic regression of PGIC for a crude and adjusted model. The latter was adjusted for the variables that we statistically significant in the backward stepwise elimination, the variables were: sex(women), pain duration > 1 year***.*
P-value < 0.05, P-value < 0.01,*** P-value < 0.001*

3.3 Secondary outcomes; general health on the GPH and pain interference in daily life on the BPI

3.3.1 Differences in outcome of the GPH for complex and non-complex group

The general success rates of the GPH were significantly lower for the complex group (p>0.001). In figure 3 can be observed that the complex group was distributed more among the ineffective categories of the GPH. Confirmed by the adjusted OR on the GPH of ß =0.32(95% CI: 0.15-0.61) (table 4). Demonstrating a significantly lower likelihood of positive general health for the complex group than their counterparts.

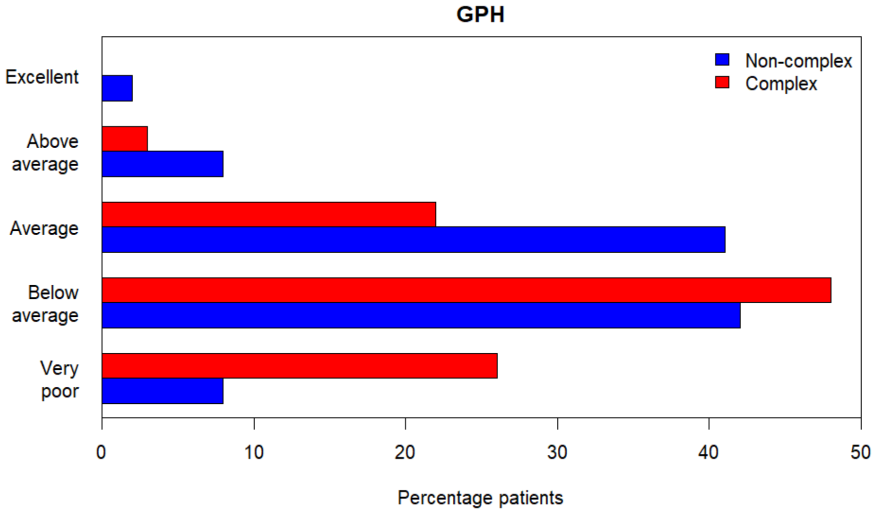

Figure 3. The GPH rated at follow-up by the complex and non-complex group

Table 4. Results of the logistic regression analyses of the GPH

GLM GPH	B(SE)	P value	95% CI for odds ratio		
			Lower bound	OR	Upper bound
Crude model Complex CP	-1.275(0.37)	<.001	0.12	0.28	0.55
Adjusted model Complex CP	-1.134(0.35)	.001	0.15	0.32	0.61

Results of the logistic regression of GPH for a crude and adjusted model. The latter was adjusted for the variables that we statistically significant in the backward stepwise elimination, the variables were: work(having paid work), pain duration > 1 year****
P-value < 0.05, P-value < 0.01,*** P-value < 0.001*

3.3.2 Differences and similarities of the BPI for the complex and non-complex group

The BPI-WAW showed an average difference between groups of almost two points on the 11-point NRS at baseline, with a mean of 5.69(SD:2.38) for the non-complex group and 7.58(SD:1.76) for the complex group(p <0.001). This difference remained at follow-up, as the change in scoring between baseline and follow-up on the BPI-WAW was alike (non-complex: -0.77(SD:2.54) and complex: -0.93(SD:2.1) with a p value of 0.231). Furthermore, the linear regression of the BPI-WAW indicated no statistically significant association with an adjusted coefficient of -0.21(SE:0.15); p: 0.153, (Table 5).

The mean BPI-REM score at baseline was 3.69(SD:2.27) for the non-complex group and 6.72(SD:1.97) for the complex group. The difference score of the complex group (-0.98(SD:2.44)) was twice as large as for the non-complex group (-0.43(SD:2.38)) (p: 0.004), the difference between groups remained existent at follow-up (Figure 4). Linear regression confirmed the aforementioned findings of the BPI difference scores: the adjusted regression coefficient for the complex group was -0.57(SE:0.15); p: 0.002 on the BPI-REM.

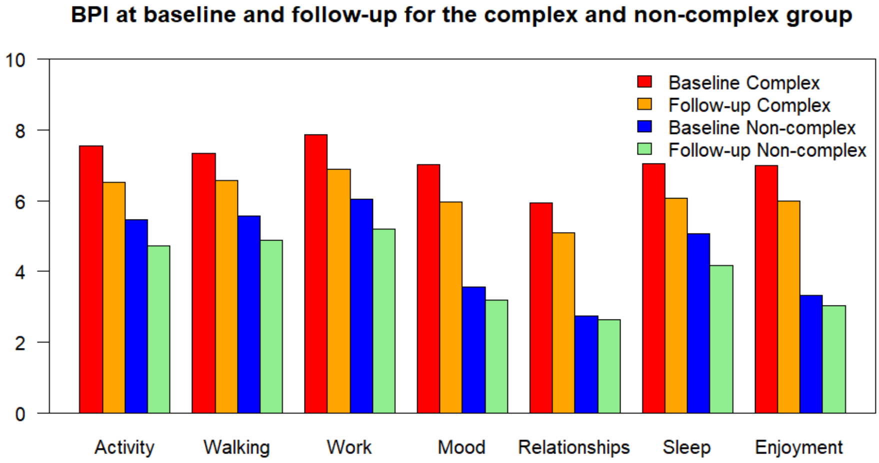

Figure 4. The BPI rated at baseline and follow-up by the complex and non-complex group

Table 5. Results of linear regression analyses for the BPI change on both subscales

BPI difference scoring Baseline - Follow up	**B(SE)**	**P value**
BPI WAW change **Crude model** Complex CP	-0.162(0.15)	.281
Adjusted model Complex CP	-0.213(0.15)	.153
BPI REM change **Crude model** Complex CP	-0.556(0.163)	<.001
Adjusted model Complex CP	-0.570(0.145)	.002

*Results of the linear regression of BPI subscales for a crude and adjusted model. The latter was adjusted for the variables that we statistically significant in the backward stepwise elimination, the variables were in the BPI WAW: pain duration > 1 year***, pain location chest**. For the BPI REM the variable adjusted for: pain duration > 1 year****

P-value < 0.05, P-value < 0.01,*** P-value < 0.001*

4. Discussion

This study has provided, upon baseline profiles, a prospect of plausible successes on clinically relevant patient outcomes, that may help guide decision making in clinical practice. In summary, depending of the patient outcome the complex pain patient has a reduced likelihood of successes. This accounts for treatment satisfaction, general perceived health and affective interference of pain on daily activities. Yet, no differences in pain relief and physical interference were stated when compared to the non-complex counterparts.

4.1 Primary outcomes

4.1.1 Pain relief on the NRS

The findings show that the complex and non-complex group have a similar change score in pain relief, even though cognitive and affective values were existent parallel to pain severity. Our findings relate to the ones found by Farin et al, in which 262 chronic pain patients, undergoing inpatient rehabilitation, were surveyed and found that pain intensity and negative affectivity at baseline are no risk factors for a reduced pain relief.[20] The results of this study suggest that although high pain severity and psychological values were present, complex patients do not respond differently on pain relief. Though, no motive is found to disregard complex patients for treatments that have their primary focus on pain relief, such as spinal cord stimulation of nerve blocks for pain relief. On the other hand, greater numbers of pain relief were thought to be found, because the literature indicates that when subdividing pain at baseline into severe (≥ 7 on the NRS), modest (5 – 7 on the NRS) and mild (0-5 on the NRS) pain groups, a larger NRS change is found in the severe groups when compared to the modest group. Indicating that the combination of risk factors present in the complex group influences pain relief after all.

4.1.2 Treatment success on the PGIC

Treatment satisfactions is an important outcome in pain studies and the practicality of the PGIC for patient and doctor is an appealing quality. The straightforwardness and quickness allows the evaluation of an important aspect of treatment. However, when transition time is long the patients may have difficulty taking their baseline status into account, while the influence of the current health status increases, named availability bias.[21] In the literature a negative association is found between pain catastrophizing at baseline and treatment satisfaction at follow up. As well, the satisfaction with the received care, decreases when affective factors such as depression or anxiety are present.[20] What is not clear yet, is if cognitive and affective factors have an accumulative negative effect on treatment satisfaction or modification takes place. In case of our study, we do see that the chance of having treatment success is reduced by almost 50 % when both cognitive and affective factors are present.

4.2 Secondary outcomes

4.2.1 General health on the GPH

A body of evidence discusses the decline of the general perceived health observed when patients have a combination of pain severity with cognitive or affective factors. What we see in our study is that the likelihood of positive health drops remarkably, when both cognitive and affective factors these are present.[22, 23]

4.2.2 Pain interference in daily life on the BPI

The complex group shows on baseline a high pain interference on psychical and emotional activities of daily life. Mittienen et al., found that when both dimensions are affected, patients had higher prevalence's of pain catastrophizing and anxiety compared to when pain interfered highly in only one of the two dimensions. When both dimension were affected, almost every other subject was unable to participate in any type of exercise (Figure 3).[24] The distinct negative cognitive-emotional reaction to pain in complex patients is high, and catastrophical thoughts about activity or feeling of helplessness may overwhelm. Adding to this the comorbid anxious or depressive factors may bring further emotional load. Besides the negative interaction of the cognitive and affective factors with pain, the complex group is vulnerable in the sense that the majority of them have a lower socio-economic status in society, exemplified as higher rates of low educational level, not having a paid job, and/or no relationship status. We may assume that the personalized tailored care at a multidisciplinary pain clinic may not be fully compatible with the needs of the complex patient when it comes down to treatment satisfaction and quality of life. The main focus of multidisciplinary tertiary pain clinics are on pain relief, physical, psychological improvement, yet topics that may improve societal participation are lacking. A suggestion would be to combine the personalized multidisciplinary approach together with a rehabilitation and societal approach. Including social workers can provide help on topics such as education and work. Moreover, interventions as pain education, self-management, and specific information for family and caregiver(s) may improve patient outcome.

4.3 Limitations

The most challenging limitation of this study is the fact that other factors important were not routinely collected, due to the limitations of a registry cohort.

The analyses could have profited from confounders such as the classification of disease (ICD), intervention and current medication intake. However, we have adjusted our findings for many potential confounding variables in the multivariable analyses. The study is a large academic prospective cohort with a heterogeneous population in which multiple PROM's cover many aspects of CP, making cross sectional and longitudinal analyses possible.

4.4 Future perspective

There is a need of further clinical research to observe if similar findings exist in the likelihood of treatment outcomes for this particular group. This information may contribute in the search to relevant predictors and/or treatments that benefit the complex group in improving treatment satisfaction and quality of life.

In conclusion, this study indicates that the psychological health statuses in combination with pain severity, reduces the likelihood on treatment satisfaction, general perceived health and pain interference of emotional activities. Yet, belonging to the complex group does not interfere with the change score on pain relief nor of pain interference of the physical activities. When treating complex patients, the desired treatment outcome(s) should be recognized by the specialist and patient before initiating treatment, as these may be less likely to occur depending on the outcome and thus may guide treatment decision.

4.5 Acknowledgement

No acknowledgements to declare nor conflicts of interest.

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CHAPTER 5

DO MEN AND WOMEN HAVE A DIFFERENT ASSOCIATION BETWEEN FEAR AVOIDANCE AND PAIN INTENSITY IN CHRONIC PAIN? AN EXPERIENCE SAMPLING METHOD COHORT-STUDY

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ABSTRACT

Background and objectives

Fear-avoidance is one of the factors associated with chronic pain. However, it remains unclear whether the association between fear-avoidance and pain depends on sex. The present study aimed to investigate whether the association between fear-avoidance and pain intensity differed between men and women in chronic pain patients. Additionally, the potential confounding effect of affective experiences on the association between fear-avoidance and pain intensity was analyzed.

Methods

This cohort study included hospital referred chronic pain patients (n = 45). Short momentary assessment questions according to the experience sampling method (ESM) were used to repeatedly assess patients' pain intensity, level of fear-avoidance and positive as well as negative affect during their daily life. Linear mixed-effects models were applied in the statistical analysis. Unadjusted and adjusted models were made, in which the latter corrected for statistically significant affective experiences and baseline variables, taking the Akaike Information Criterion into account to assess a better model of fit.

Result

The results demonstrated an association between fear-avoidance and pain intensity that differed for men and women. In men (n = 13), no association between these variables was found (−0.04 (95% CI: −0.14, 0.06) with a p-value of 0.48), whereas in women (n = 32), an increase in fear-avoidance was associated with a (slight) increase in pain intensity (0.18 (95% CI 0.06, 0.30) with a p-value of 0.003). Affect did not confound the above-mentioned findings.

Conclusions

Our data supports previous research highlighting the importance of sex differences in pain experience. These findings may be relevant for clinicians to consider more personalized (i.e., gender specific) pain management in chronic pain patients.

1. INTRODUCTION

Chronic pain affects more than 30% of people worldwide and has a large impact on both patients and society.[5] Due to the complex interactions between biological, psycho-logical and social factors,[5; 17] it is difficult to manage chronic pain. One of these factors is fear-avoidance, which refers to the avoidance of movements or activities resulting from fear of pain.[32] According to the fear-avoidance model, pain may be interpreted as threatening (i.e., pain catastrophizing), which can lead to avoidant behaviors and hypervigilance to bodily sensations. Conversely, fear-avoidance and hypervigilance may induce physical disuse and disability, contributing to long-term consequences, including maintenance of chronic pain disability or an increase in the pain experience.[32] Although the association between fear-avoidance and chronic pain has been well-established, only sparse research has been conducted on potential sex differences regarding this association. As a growing number of articles suggests the importance of sex differences in relation to pain, and specifically in pain catastrophizing,[11; 14; 21] it is important to further investigate whether the association between fear-avoidance and pain also depends on sex.

Furthermore, the biopsychosocial model of pain shows that emotional distress or affective states may influence pain intensity[5] and may, therefore, also confound the association between sex and fear-avoidance. It is known that dynamic fluctuations regarding positive and negative affect are observed in various mental disorders,[16] such as depression. Given that depression and pain share pathways,[1] fluctuations in emotion regulation as observed in depression and other mental disorders may also be found in chronic pain patients. However, the effect of affective states, such as happiness, anxiety and irritation on the association between fear-avoidance and pain has not been adequately studied. The cross-sectional design of studies that have investigated the association between affective states and chronic pain could not capture the fluctuations of emotional distress over time.

Hence, the present study aimed to investigate whether the association between fear-avoidance and pain intensity in chronic pain patients differs between men and women. Additionally, the potential confounding effect of specific affective experiences on the association between fear-avoidance and pain intensity was analyzed by using the experience sampling method (ESM).

2. METHODS

2.1. Study Design

This cohort study used questionnaires administered according to ESM. Experience sampling is a structured digital diary technique to appraise subjective experiences in daily life, often applied in patients with psychiatric disorders or somatic illnesses.[29] Patients are repeatedly asked to complete short questionnaires during the day, which allows for the assessment of moment-to-moment changes in both symptoms and mental states, aiming to map daily functioning.[7] This study was approved by the local medical ethical committee (METC-number: 2018-0955).

2.2. Study Population

The cohort of the present study consisted of chronic pain patients who were referred to the University Hospital Pain Centre of the Maastricht University Medical Centre+ (MUMC+). The patients were recruited from March 2019 until July 2021 while performing their digital intake at the pain center, during which they were asked whether they wanted to be approached for participation in this study. If their answer was positive, patients were contacted by a research nurse for a more extensive explanation about the ESM-procedures. Patients with any type of pain at any location were eligible for participation. To be included, patients had to be 18 years or older and to have experienced pain complaints for at least three months. Additionally, the patient had to be in possession of a smartphone and able to use the ESM application named Psymate. Patients who were interested in participation also received all required information by an information letter, complemented with a consent form. Before the start of the study, all patients who wanted to participate provided informed consent.

2.3. Experience Sampling

Both outcome (pain intensity), predictor (fear-avoidance) and potential confounders (affect) were measured by repeated ESM assessments. These ESM assessments consisted of 18 questions and were completed through a smartphone application (Psymate). The items in the Psymate application illustrate adequate psychometric properties, and sensitivity to change over time.[29] Patients were asked to answer the questions 10 times a day, for six consecutive days. The questionnaires were completed in semi-random time blocks of 112.5 min from 7:30 a.m. until 10:30 p.m. during the patients' daily life, whenever patients received a notification ('beep') from the Psymate-app on their smartphone.[8; 30] Fear-avoidance was assessed by the statement 'due to fear for (more) pain I did not make unnecessary movements since the last beep', asking the participants about their fear-avoidance behavior since the last beep.

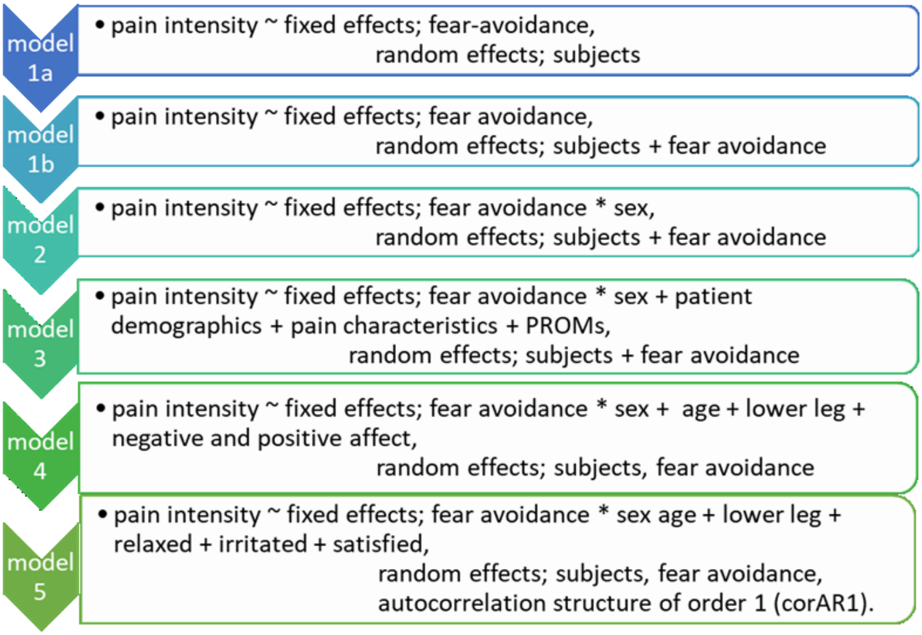
The items of positive and negative affect come originally from the validated PANAS questionnaire[6; 18; 34] and were assessed thoroughly be-fore the application in the ESM. Positive affect was assessed by the following statements ‘I feel cheerful, ‘I feel relaxed’, ‘I feel satisfied, and ‘I feel enthusiastic’, whereas negative affect was measured by the statements ‘I feel insecure’, ‘I feel irritated’, ‘I feel lonely’, ‘I feel anxious’, ‘I feel guilty’ and ‘I am worrying’. The 10 different items concerning the affective state, as well as the item assessing the level of fear-avoidance, were answered on a 7-point Likert scale, ranging from 1 (not at all) to 7 (very much). The outcome variable ‘pain intensity’ was assessed by the statement ‘I am in pain’, and could be answered on an 11-point scale, ranging from 0 (no pain) to 10 (worst pain possible).

2.4. Baseline Variables

As part of the standard digital intake at the MUMC+, patients were asked to complete a set of questionnaires that reflected the pain complaints, quality of life, anxiety and depressive symptoms. These questionnaires consisted of the Hospital Anxiety and Depression Scale (HADS), Numeric Rating Scale (NRS) for pain intensity, Pain Catastrophizing Scale (PCS), Brief Pain Inventory (BPI) and the 12-item Short-Form Health Survey (SF-12)[4; 10; 12; 25; 27] An explanation of how these measurement instruments were assessed is provided in more detail by the article of Brouwer et al.. During intake, patients also had to indicate how long they had been experiencing pain and at which location(s). Moreover, demo-graphic variables including sex, age, marital status, education level and employment were collected. In addition to the intake questionnaires, patients had to complete one additional questionnaire that assessed the level of fear-avoidance at baseline. The ‘TAMPA Scale for Kinesiophobia’ (TSK) (Dutch translated), which includes 17 questions on a 4-point scale, was used for this. TSK-scores range from 17 to 68, and scores greater than 37 indicate a high degree of fear-avoidance.[31] Similar to the ESM-measurements, the TSK was completed through the Psymate-app once before the start of the ESM-examination period.

2.5. Statistical Analysis

Baseline characteristics of the cohort are described as mean and standard deviation for continuous variables, and as count and percentage for categorical variables. Sex differences in baseline characteristics were tested using the independent-samples t-test for continuous variables, and Pearson’s chi-square test or Fisher’s exact test for categorical variables. ESM-data were analyzed using linear mixed-effects models with random intercept and slope on three levels; patients, days, and beeps. The model was built in several steps. First, the crude association between fear-avoidance and pain was assessed as fixed and as random effect. Second, the interaction of fear avoidance and sex was added. The third and fourth model assessed for potential confounders concerning baseline variables and affect. Consequently, two backward stepwise elimination processes were applied. The third model assessed the first backward stepwise elimination of the baseline variables (patients sociodemographic variables, pain characteristics and PROM’s of Table 1). The fourth mod-el assessed the items of negative and positive affect (‘I feel cheerful, ‘I feel relaxed’, ‘I feel satisfied, ‘I feel enthusiastic’, ‘I feel insecure’, ‘I feel irritated’, ‘I feel lonely’, ‘I feel anxious’, ‘I feel guilty’ and ‘I am worrying’) as being potential confounders by the backward step-wise elimination process. Autocorrelation by using a first-order continuous time covariate autoregressive structure was added in the fifth model. The stipulated models are presented in Figure 1. Analyses were performed using R, version 4.1.2, with the function lme (linear mixed effects models) from the statistical package nlme (3.1–153). All tests were investigated two-sided against a significance level (α) of 0.05.



model 1a
- pain intensity ~ fixed effects; fear-avoidance,
  random effects; subjects

model 1b
- pain intensity ~ fixed effects; fear avoidance,
  random effects; subjects + fear avoidance

model 2
- pain intensity ~ fixed effects; fear avoidance * sex,
  random effects; subjects + fear avoidance

model 3
- pain intensity ~ fixed effects; fear avoidance * sex + patient demographics + pain characteristics + PROMs,
  random effects; subjects + fear avoidance

model 4
- pain intensity ~ fixed effects; fear avoidance * sex + age + lower leg + negative and positive affect,
  random effects; subjects, fear avoidance

model 5
- pain intensity ~ fixed effects; fear avoidance * sex age + lower leg + relaxed + irritated + satisfied,
  random effects; subjects, fear avoidance,
  autocorrelation structure of order 1 (corAR1).

Figure 1. *Construction of linear mixed-effects model applied to the data. ~ Separation of the dependent and independent variables. * Indicative of an interaction term and the original variables themselves.*

Table 1. Baseline description of the chronic pain patient cohort.

Patient baseline characteristics	**Total cohort, n=45**	**Men, n=13**	**Women, n=32**	**P value**
Demographic characteristics				
Age in years, *mean (SD)*	47.6 (12.8)	52.8 (13.8)	45.5 (12.0)	.086
Marital status, *n (%)*				.411
Relationship	36 (80.0)	9 (69.2)	27 (84.4)	
No relationship	9 (20.0)	4 (30.8)	5 (15.6)	
Education, *n (%)*				.287
Low *(<9 years of education)*	32 (71.1)	11 (84.6)	21 (65.6)	
High *(≥9 years of education)*	13 (28.9)	2 (15.4)	11 (34.4)	
Employment, *n (%)*				1.000
Unemployed *(no paid job)*	29 (64.4)	8 (61.5)	21 (65.6)	
Employed *(paid job)*	16 (35.6)	5 (38.5)	11 (34.4)	
Pain characteristics				
Pain duration in months, *mean (SD)*	73.2 (81.1)	45.9 (55.5)	84.3 (87.8)	.088
Pain location, *n (%)*				
Head	5 (11.1)	1 (7.7)	4 (12.5)	1.000
Neck	15 (33.3)	3 (23.1)	12 (37.5)	.492
Arm	7 (15.6)	1 (7.7)	6 (18.8)	.654
Lower back	25 (55.6)	10 (76.9)	15 (46.9)	.066
Upper leg	19 (42.2)	5 (38.5)	14 (43.8)	.745
Lower leg	12 (26.7)	3 (23.1)	9 (28.1)	1.000
Chest/abdomen	4 (8.9)	2 (15.4)	2 (6.3)	.567
Other	10 (22.2)	2 (15.4)	8 (25.0)	.698
PROM's scores				
NRS, *mean (SD)*	7.1 (1.7)	6.8 (1.9)	7.3 (1.6)	.391
PCS, *mean (SD)*	23.2 (11.9)	26.8 (14.1)	21.8 (10.9)	.207
BPI REM *mean (SD)*	11.6 (8.1)	14.2 (9.6)	10.5 (7.2)	.095
BPI WAW, *mean (SD)*	24.7 (10.0)	25.6 (9.2)	24.3 (10.5)	.440
TSK, *mean (SD)*	36.2 (6.0)	39.6 (6.5)	34.8 (5.2)	.013*
TSK>37, *n (%)*	21 (46.7)	9 (69.2)	12 (37.5)	.053
HADS-A, *mean (SD)*	6.8 (3.8)	8.2 (4.2)	6.2 (3.6)	.125
HADS-D, *mean (SD)*	7.5 (4.9)	9.2 (5.2)	6.8 (4.7)	.127
PHS, *mean (SD)*	29.4 (6.8)	29.6 (6.4)	29.2 (7.0)	.862
MHS, *mean (SD)*	45.7 (12.1)	43.1 (12.5)	46.8 (12.0)	.367

Abbreviations: NRS, Numerical Rating Scale for pain intensity; PCS, Pain Catastrophizing Scale; BPI-REM, Affective Subscale of the Brief Pain Inventory; BPI-WAW, Active Subscale of the Brief Pain Inventory; TSK, Tampa Scale of Kinesiophobia; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; PHS, Physical Health Score; MHS, Mental Health Score; PROM, Patient Reported Outcome Measure.

* P-value <0.05

3. RESULTS

3.1. Description of the Sample

Initially, 217 patients indicated they were interested in the study and were therefore approached. Out of these 217 patients, 168 patients (77%) declined to participate after receiving all the information about the study procedures, whereas 49 patients (23%) provided informed consent. Three patients were excluded from analysis because their pain com-plaints were present for less than three months, and one patient was excluded due to missing data on sex at baseline. This resulted in a sample of 45 chronic pain patients, from which 13 (21%) were men and 32 (71%) women (Figure 2). The mean level of fear-avoidance (TSK) at baseline was significantly (p = 0.013) higher for men (39.6; SD ± 6.5) than for women (34.8; SD ± 5.2). Moreover, a high degree of fear-avoidance (TSK-score > 37) was also more frequently present in men (69%) than in women (38%), although not significantly different (p = 0.053). Mean pain intensity (NRS) was 6.8 (SD ± 1.9) for men and 7.3 (SD ± 1.6) for women (p = 0.391), indicating no statistically significant sex difference in pain intensity at baseline. Other baseline variables, as well as the p-values of the differences between men and women, are presented in Table 1.

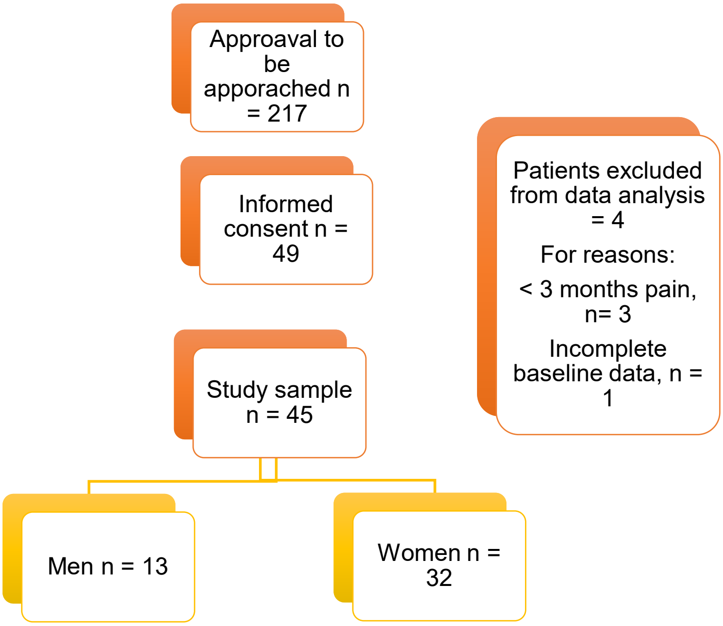


Figure 2. Flowchart of the study sample.

3.2. Sex Differences in the Association between Fear-Avoidance and Pain Intensity and the Influence of Affective States

The crude association between fear-avoidance and pain intensity had a coefficient of 0.17 (95% CI: 0.12, 0.22), p = 0.000, indicating that an increase in fear-avoidance of 1 unit was associated with an average pain increase of 0.17. The model that also included the interaction between fear-avoidance and sex showed that the association differed between men and women: the interaction term had a coefficient of 0.18 (95% CI: 0.05, 0.31), p = 0.005 (Table 2; model 2). For men, a 1-point increase in fear-avoidance was associated with a −0.02 decrease in pain intensity, whereas for women a 1-point increase in fear-avoidance was associated with a 0.18 increase in pain intensity (Table 2 and Figure 3).

In the subsequent model, potential confounders were added. Backward stepwise elimination resulted in a model with the baseline variables ‘age’ and ‘lower leg’ and affective experiences ‘relaxed’, ‘irritated’, and ‘satisfied’ included (Table 2; model 5, and Figure 4). By adding the confounders, the association between fear-avoidance and pain intensity in the model with the interaction did not change considerably from a coefficient of −0.02 (95% CI: −0.12, 0.09) with a p-value of 0.78 to a coefficient of −0.04 (95% CI:−0.14, 0.05) with a p-value of 0.48. Although these three affective experiences all had a significant association with pain intensity, the estimate of the interaction term between fear-avoidance and sex did not change by adding affect to the model (Table 2; model 5).

Table 2. Unadjusted and adjusted model regarding sex differences in the association between fear-avoidance and pain intensity.

	Model 2 AIC = 4476.42			**Model 5 [a] AIC = 4376.42**		
	Estimate	**CI**	**Sig.**	**Estimate**	**CI**	**Sig.**
Intercept	9.08	6.47, 11.7	.000***	9.52	6.86, 12,18	<.001***
Fear-avoidance	-0.02	-0.12,0.09	.78	-0.04	−0.14, 0.06	.51
Sex (men=0; women=1)	-0.53	-1.96,1.89	.45	-0.4	−1.82, 1.02	.94
Fear-avoidance x sex	0.18	0.05,0.31	.005**	0.18	0.06,0.30	.004**

Dependent variable: pain intensity; CI = confidence intervals; a Adjusted for baseline variables: age , lower leg and the emotions: relaxed *** , irritated *** and satisfied *** ; ** p-value < 0.01; *** p-value < 0.001

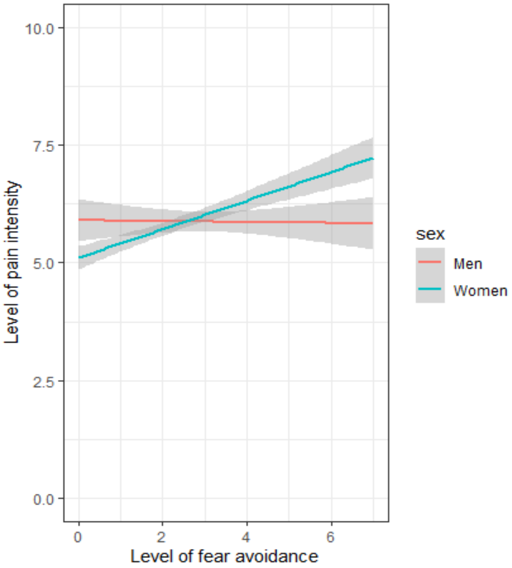


Figure 3. Visualization of the interaction between fear-avoidance and sex in relation to pain intensity. Note: the grey area is the 95% confidence interval of the estimates.

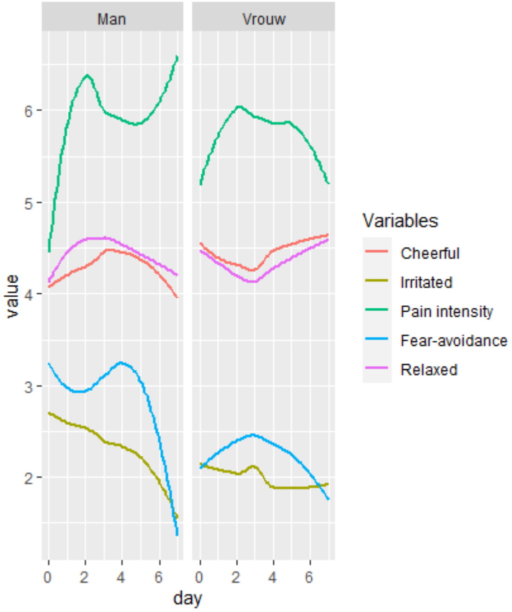


Figure 4. Visualization of the fluctuation of pain intensity, fear avoidance and affective experiences for men and women separately. Note: fear-avoidance and the affective experiences are measured on a 7-point Likert scale and pain intensity is measure on the eleven-point numeric rating scale. Each line represents the average of the 10 beeps per day per variable.

4. DISCUSSION

4.1. Summary of Main Findings

To our knowledge, this is the first study using the experience sampling method to investigate sex differences in the association between fear-avoidance and pain intensity in chronic pain patients, including the potential confounding effect of affective experiences. Cross-sectional results demonstrated that men had on average more fear-avoidance than women. However, results from the longitudinal data of the ESM suggest that no association between fear-avoidance and pain intensity was found in men, whereas in women, an increase in fear-avoidance was associated with a (slight) increase in pain intensity. Nonetheless, affect did not confound these findings.

4.2. Differences in the Association of Fear-Avoidance and Pain Intensity

The fact that men had a higher mean TSK-score than women in the present study is consistent with the literature from previous cross-sectional studies that investigated sex differences in TSK-scores concerning chronic pain patients.[2; 22] It remains debatable why male chronic pain patients tend to have more fear-avoidance than female patients, although it has been suggested that this could depend upon social norms, higher expectations or a deeper concern about losing work capacity or productivity as a result of re-injury.[23] However, the results of our study indicate that the tendency of having more fear-avoidance does not seem to influence pain intensity in men. Moreover, whether the increase in fear-avoidance in men at baseline influences (negatively) pain treatment outcomes remains unanswered.

4.3. Sex Differences in the Association between Fear-Avoidance and Pain Intensity

Both the unadjusted and adjusted model concerning the interaction between fear-avoidance and sex in relation to pain intensity showed that this interaction was significant, and hence, the association between fear avoidance and pain differs between men and women. The adjusted model was corrected for the affective experiences ‘relaxed’, ‘irritated’, and ‘satisfied’, but did not lead to a different conclusion. In the unadjusted and adjusted models, the association between fear-avoidance and pain intensity for men was negligible (0.02 and −0.04, respectively). In contrast, for women, the model demonstrated that the association between fear-avoidance and pain intensity was equal to a coefficient of 0.18 in both models (Table 2), indicating that increases in fear-avoidance were associated with (slight) increases in pain intensity. Whether this (small) association was clinically significant, it may yet be debated. We propose to further investigate if this association holds when applied to other pain populations, preferably with larger sample sizes and equal percentage of both sexes.

Ramirez et al. in 2014[19] analyzed differences in pain experience between men and women in patients with spinal chronic pain and found a contrasting result, in that fear-avoidance was associated with pain intensity in men, but not in women. However, because of the cross-sectional design of the study the strength of the evidence is limited. Moreover, previous studies suggest that women are more sensitive to threat-related stimuli than men, and this would generally lead to an increased pain perception[20; 21] and have greater catastrophic thoughts than men, which would generally lead to an increased pain perception. The results found in the present study are in line with these suggestions.

No previous studies have investigated the potential confounding effect of affective states on the association between fear-avoidance and pain intensity with the ESM. In a review by Baets et al. in 2019 the predictive moderating and mediating roles of emotional factors were examined on pain and disability following shoulder treatment.[9] A predictive role was found for fear-avoidance of pain and disability when surgical treatment was given, yet not when receiving physiotherapy. Moreover, this study indicated a moderating role for optimism in the relationship between catastrophizing and shoulder disability in patients receiving physiotherapy. However, this role was not found in the relationship between fear-avoidance and disability of the shoulder. The results of our ESM study specified that affect has a moderating effect on pain intensity itself, but not on the relationship between fear-avoidance and pain intensity. The statistically significant effect of positive affective experiences, such as feeling relaxed (−0.15, p = <0.001) and satisfied (−0.10, p = <0.001), on pain intensity itself may indicate that there is a potential role for positive affect, such as optimism, self-efficacy and positive expectations in future research and treatment.[9; 13]

4.4. Strengths and Limitations

The present study has a few important advantages. First, due to the use of the ESM, symptoms were assessed in the actual moment, eliminating the potential influence of recall and contextual biases, which is a common problem with traditional retrospective questionnaires.[15; 24] Moreover, symptoms such as pain and fear, as well as affect, are likely to fluctuate over time.[16] Due to the many repeated measurements in ESM, these fluctuations could be captured, in contrast to cross-sectional studies. Because of these advantages and the low cost of the ESM method, it might be an attractive and effective method to use more often in future (clinical) studies, or even treatment trajectories, since ESM is feasible due to the widespread use of smartphones. Moreover, ESM may be applied as an additional tool in clinical practice to provide feedback as part of personalized pain intervention.[28]

On the other hand, this study has a few limitations. First, seventy-two percent of the participants completed the full 6 days from the ESM examination-period, which resulted in 28% missing data. As experience sampling is time-consuming, these missed assessments were expected beforehand, and the repeating character of ESM accounts for, and decreases, the influence of missing data.[33] However, missed assessments might be a concern, as a sub-group of pain patients might have missed assessments as a consequence of their current mood or level of pain. This may have resulted in overestimation of functioning.[29] Moreover, the sample size in this study was rather small, with an especially low number of men. The percentage of 29% of men deviates from the 40% of men in the overall pain registry cohort DATA*PAIN*.[3] Accordingly, a lack of power could explain why no significant association was found between fear-avoidance and pain intensity for men. Many patients who initially indicated to be interested in the study chose not to participate after receiving all information about the study procedures (Figure 1). This indicates that ESM may be (too) burdensome, at least with the current number of questions and repeated measures. As the usability of ESM in chronic pain patients has not yet been validated, it remains difficult to conclude whether this method is suitable for the chronic pain population. Although momentary assessment is recommended in different somatic and psychiatric conditions, and the benefits of the ESM are becoming more and more apparent,[26] it is important to perform more research about ESM and to evaluate its validity and reliability in chronic pain patients.

Fear-avoidance was assessed by the statement ‘due to fear for (more) pain I did not make unnecessary movements since the last beep’, asking the participant how the behavior of fear has influenced the level of movement since the last beep. As a result, a time frame is assessed between the afore-appointed beep until the actual beep, representing a lagged item. This was the main reason why we did not add a lagged model, as in our case that would be regressing two time points in time instead of one. Moreover, as mentioned before, no intention of causality was intended, meaning that the direction of predictor and outcome could have been reversed: an analysis we want to recommend for future research.

Furthermore, even though the dataset covered a vast number of relevant factors for chronic pain, some factors such as pain etiology were not accounted for at baseline, and other important factors such as pain catastrophizing were missing in the daily assessments, which could explain the sex differences found in our results.

4.5 CONCLUSIONS

The results in this study indicate that the association between fear-avoidance and pain intensity differs between men and women. For men, no association between these variables was found, whereas for women, an increase in fear-avoidance was associated with a (slight) increase in pain intensity. Affective experiences, however, did not confound the association between fear-avoidance and pain intensity in either men or women. Our findings support research highlighting the importance of sex differences in pain experience, which may be important for clinicians to consider for a more personalized pain management approach in chronic pain patients. Nevertheless, further research with a larger sample and equal numbers of sexes is needed to confirm these findings and their clinical implication.

Conflict of interest

The authors have no conflicts of interest to declare

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CHAPTER 6

CLINICAL IMPORTANT IMPROVEMENT OF CHRONIC PAIN PATIENTS IN RANDOMIZED CONTROLLED TRIALS AND THE DATA*PAIN* COHORT

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ABSTRACT

Background and objectives

The change on the Numeric Rating Scale (NRS) is constructed on subjective pain experiences, hampering the establishment of the clinically important improvement. Hence, an anchor based method; the Patients Global Impression of Change (PGIC) is added to determine. A 2-point change on the NRS is equivalent to a moderate clinically important improvement in randomized controlled trials (RCT’s), when treating chronic pain patients with medication. We contemplated whether these findings would be assessed in the DATA*PAIN* cohort and non-drug interventional RCT’s of our pain medicine department.

Methods

The NRS change was quantified by subtracting the NRS of baseline from the NRS at 6 months follow-up. Categorization of success/nonsuccess was applied on the PGIC and their average NRS raw changes were calculated. The Spearman correlation coefficient quantified the overall relationship, while the discriminative ability was explored through the receiver operating characteristic curve. Data was stratified on design, sex and pain intensity at baseline. Besides, the cohort evaluated treatment status at follow-up.

Results

The records of 1661 patients were examined. Overall, the observed NRS change needed for moderate clinically important improvement was larger than the average 2 points. Yet, the changes of the cohort were smaller compared to the RCT’s. Moreover, it modified with pain intensity at baseline and treatment statuses indicated differences in mean clinical importance of -4.15(2.70) when finalized at 6 months and -2.16(2.48) when treatment was ongoing.

Conclusions

The moderate clinically important improvement varied substantially. Representing heterogeneity in pain relief and its relation to treatment success in chronic pain patients.

1. INTRODUCTION

The clinically important improvement in measurement scores is a critical consideration when evaluating treatment effect based on patient-reported outcome measures (PROM's).[3] The IMMPACT recommendations list the 11-point Numeric Rating Scale (NRS) to quantify pain intensity and to summarize the subjective interpretation of the pain experienced. An essential step in clinical research is to determine the statistical significance and confidence intervals of the change in measurements scores within or between groups, as these reflect on the magnitude, variability of treatment effect and sample size.[3; 4] To determine the clinically important improvement an anchor-based method can be applied by relying on a global item completed by the patient, such as the Patients Global Impression of Change (PGIC). The PGIC does not primarily measure pain relief, but evaluates the overall improvement of the pain treatment. By anchoring these two measures the relationship between pain relief and overall improvement can be examined from a patient point of view.[3; 4; 6; 15]

Several studies have quantified the clinically important improvement for several core domains in the chronic pain population.[3; 4; 7; 10; 11; 15] The landmark paper of Farrar, et al. assessed the clinical importance of pain relief. This was based only on data from randomized controlled trials (RCT's) on the effect of pregabalin treatment.[4] Ever since, an average change from baseline of 2 points or a 30 % change on the NRS has often been regarded as a moderate clinically important improvement, that is equivalent to the categories 'very much improved' and 'much improved' on the PGIC.[4] However, the chronic pain population is heterogeneous in pain relief and burden, and it is unclear whether these findings can be generalized towards patients included in interventional studies that analyze the effect of non-drug treatments (e.g. spinal cord stimulation, intradiscal injection), cohort data, or subgroups of the chronic pain population. The aim of this study was to assess the generalizability of the aforementioned definition of the clinically important improvement on the NRS to non-drug interventional RCT's and heterogeneous cohort data. These results may contribute to the design of future studies, inform sample size calculations, and may set specific criteria for cohort studies. Such information will facilitate comparison of the results across studies and set the value for therapeutic meaningfulness in clinical practice.

Stratification on sex was applied as the literature indicates a higher prevalence and average of pain intensity in women when compared to men.[2; 19] Also women seem to report greater functional limitations for the same pain intensity.[5] It may be plausible that there are differences in overall improvement between sexes, due to qualitative differences in interpretation of the PGIC.

2. METHODS

For more than 20 years the department of Anaesthesiology and Pain Medicine of the Maastricht University Medical Center+ in the Netherlands has routinely collected both the NRS and PGIC of chronic pain patients for both interventional studies and a cohort data. For this study, we used data of the RCT's of van Eerd, et al.,[18] Kallewaard et al.,[13] Slangen, et al.,[16] and Kemler et al.[14] and cohort data of the DATA*PAIN* cohort, initiated in 2003 by the Comprehensive Multidisciplinary University Pain Center Maastricht.[2] To perform this secondary analysis, approval was obtained by the medical ethical committee of the Maastricht University (METC approval number: 2020-2391). All studies included followed the recommendations of the IMMPACT guidelines on core outcomes for an adequate evaluation of the treatment efficacy and effectiveness.[3; 17] For this secondary analysis, patients were included if they were 18 years or older, had been experiencing pain for more than 3 months and had completed both the NRS and the PGIC at 6 months follow up.

2.1 Measurements

The 11-point NRS was used to quantify pain intensity ranging from zero (no pain) to ten (the most pain imaginable).[12] In the RCT's, the average momentary NRS was computed from a 4-day diary at baseline and 6-month follow up. In the cohort, the average NRS of the past week was collected at both measurement moments using a single item.

The PGIC was used to collect the status of the patient's global impression of change on a 7-point Likert scale ranging from "very much improved" to "very much worse". In addition, a dichotomous PGIC score was computed in which "very much improved" and "much improved" indicated a successful treatment outcome and "minimally improved", "no change", "minimally worse", "much worse" and "very much worse", a non-successful outcome. The PGIC was used as an anchor based criterion to distinguish between successful and non-successful treatment at follow up.[3]

2.2 Stratification

Because the literature suggests analyzing both sexes separately as there may be different values for clinically important improvement on treatment outcome,[3] we stratified on sex in addition to study design (i.e., cohort and RCT). Moreover, baseline NRS scores were cut off into 3 different pain categories: mild, with a pain intensity of 0 to 5 on the NRS; modest, with a 5 to 7 on the NRS; and severe, with a 7 to 10 on the NRS.[1] In the DATA*PAIN* cohort, patients could have been treated for more than 6 months (the follow-up time used to compute change from baseline) due to receiving more than one treatment or elongation of a specific treatment. Therefore, the cohort was stratified on treatment status at follow up; completed or ongoing.

2.3 Statistical analysis

Study-level characteristics (age, sex and NRS scores) were described as means and standard deviations (SD) or percentages. The NRS change was quantified by subtracting the baseline NRS from the follow-up NRS and described as a mean difference with 95% confidence interval (CI). To test within-group changes the paired sample t-test was applied.

Average raw and relative changes of the NRS were calculated for each of the 7 outcome categories of the PGIC and the Spearman correlation coefficient was calculated to quantify this relationship. Furthermore on the PGIC, patients were classified into treatment success or nonsuccess and the respective NRS changes were calculated. To assess the discriminative ability of the NRS for treatment success, the area under the curve receiver operating characteristic curve was computed, or AUC, with 95% CI . The AUC can range between 0.5 (no discriminative ability) and 1.0 (perfect discriminative ability).

Subsequently, the data was stratified and analyses were repeated for the study designs (RCT and cohort), sex categories, baseline NRS categories and treatment status in the cohort data. The statistical analyses were executed in R, a language for statistical computing, version 3.6.1.

3. RESULTS

Table 1 summarizes the study characteristics and baseline variables of the cohort and RCT’s. In case of the latter, the variables were presented for each separately and all RCT’s combined. The results of the Spearman correlations and ROC curve analyses are summarized in table 2. In total, the records of 1661 chronic pain patients were examined. In this study, an average raw NRS change of -3.58 (SD: 1.89) was associated with a clinically important improvement as defined on the PGIC. This average was much higher than expected based on the 2 points or more raw change found in the literature. Moreover, the NRS change required in the cohort data differed from the RCT’s.

Table 1. Study and patient characteristics

Study name	**N pts. (%)**	**Age mean (SD)**	**Women in %**	**Baseline pain mean (SD)**	**Follow up pain mean (SD)**	**Mean difference (CI)**	**P value** [a]
DATA*PAIN* cohort	1424(100)	60.24 (13.24)	55.66	7.21(1.67)	5.92(2.40)	-1.30 (-1.42,-1.17)	<.001
All RCTs	237(100)	49.12 (14.43)	55.60	6.80(1.66)	4.86(2.79)	-1.94 (-2.28,-1.60)	.006 [b]
RCT: PDP [c]	32(13.5)	57.59 (10.67)	31.25	6.87(1.69)	5.15(2.74)	-1.72 (-0.80,-2.65)	<.001
RCT: IMBI [d]	76(32.08)	41.45 (9.74)	69.74	6.58(0.99)	5.14(2.56)	-1.44 (-0.89,-1.99)	<.001
RCT: RFD [e]	75(31.65)	60.45 (11.15)	44	6.96(1.08)	4.15(2.78)	-2.81 (-2.19,-3.44)	<.001
RCT: ESES [f]	54(22.78)	38.63 (10.90)	68.52	6.84(1.41)	5.27(3.01)	-1.57 (-0.84,-2.29)	<.001
DATA*PAIN* WOMEN	793(55.69)	59.10 (14.07)	100	7.32(1.64)	6.02(2.43)	-1.30 (-1.47,-1.14)	<.001
DATA*PAIN* MEN	631(44.31)	61.68 (12.21)	-	7.09(1.70)	5.79(2.37)	-1.29 (-1.47,-1.11)	<.001
RCT WOMEN	133(56.12)	43.35 (14.36)	100	6.79(1.25)	4.97(2.75)	-1.82 (-2.27,-1.37)	<.001
RCT MEN	104(43.78)	52.39 (14.36)	-	6.81(1.22)	4.72(2.85)	-2.10 (-2.62,-1.58)	<.001
DATA*PAIN* TX finished	416(34.44)	61.19 (13.04)	52.42	7.03(1.03)	4.90(2.71)	-2.13 (-2.39,-1.86)	<.001
DATA*PAIN* TX ongoing	520(43.05)	58.96 (13.68)	58.05	7.36(1.59)	6.61(1.94)	-0.75 (-0.91,-0.59)	<.001
DATA*PAIN* Mild NRS	107(7.51)	60.93 (13.70)	49.53	3.30(0.92)	394(2.40)	0.65 (0.16,1.13)	.009
DATA*PAIN* Modest NRS	253(17.77)	60.21 (12.82)	53.75	5.57 (0.50)	4.99 (2.24)	-0.57 (-0.85,-0.30)	<.001
DATA*PAIN* Severe NRS	1064(74.72)	60.18 (13.43)	56.77	8.00(0.89)	6.34(2.28)	-1.66 (-1.79,-1.53)	<.001
RCT's Mild NRS	14(5.91)	47.29 (14.98)	57.14	4.20(0.44)	2.59(1.84)	-1.60 (-2.75,-0.45)	.009
RCT's Modest NRS	91(38.40)	47.23 (14.84)	58.24	5.90(0.53)	4.34(2.63)	-1.57 (-2.11,-1.03)	<.001
RCT's Severe NRS	132(55.70)	50.4 (13.87)	54.55	7.69(0.68)	5.46(2.79)	-2.23 (-2.70,-1.77)	<.001

[a] *paired t-test*

[b] *ANOVA*

[c] Study; PDP , Diagnosis; DPN, Intervention; SCS

[d] Study; IMBI , Diagnosis; CDLBP, Intervention; IMBI

[e] Study; RFD , Diagnosis; CCFJP, Intervention; RFD

[f] Study; ESES , Diagnosis; RSD, Intervention; SCS

Abbreviations: pts.: patients, TX finished: patient treatment finished at 6 months follow up, TX ongoing; patient treatment ongoing at 6 months follow up, PDP: Painful Diabetic Poli-neuropathy, *DPN:* Diabetic Peripheral neuropathy, SCS: Spinal cord stimulation, CDLBP: Chronic discogenic low back pain, IMBI: Intradiscal methylene blue injection, CCFJP: Chronic cervical facet joint pain, RFD: Radiofrequency denervation, RSD: Reflex sympathetic dystrophy

Table 2, Roc curve analyses and correlations

Strata		**Area under the ROC curve (CI)**	**Percent agree-ment**	**Chi square test. P value**	**Spearman correlation = rho, P value**
Study design	cohort	0.79(0.76,0.82)	72.6	<.001	0.46, <.001
	RCT's	0.93(0.76,0.85)	84	<.001	0.72, <.001
Sex in cohort	women	0.79(0.73,0.82)	19.4	<.001	0.46, <.001
	men	0.80(0.76,0.84)	18.5	<.001	0.43, <.001
Sex in RCT's	women	0.95(0.91,0.98)	13.8	<.001	0.79, <.001
	men	0.91(0.86,0.97)	18.3	<.001	0.75, <.001
Duration pain treatment in cohort	< 6 months	0.81 (0.76,0.85)	22.6	<.001	0.58, <.001
	> 6 months	0.69(0.63,0.77)	16.9	<.001	0.31, <.001
NRS baseline scores - Cohort	mild	0.75(0.44,0.86)	21.5	.006	0.50, <.001
	modest	0.78(0.71,,0.85)	19.8	<.001	0.48, <.001
	severe	0.82(0.79,0.83)	18.6	<.001	0.48, <.001
NRS baseline scores – RCT's	mild	0.86(0.61,1)	21.4	.11	0.63, .01
	modest	0.96(0.93,1)	12.1	<.001	0.77, <.001
	severe	0.92(0.88,1)	17.4	<.001	0.71, <.001

3.1 Cohort versus RCT's

When comparing the cohort data with the RCT's, the average NRS changes differed for each of the PGIC categories (figure 1). Similarly, the success/nonsuccess PGIC differed in average raw NRS changes, with averages of -3.33 (SD: 2.72) for the cohort and -4.56 (SD: 1.85) for the RCT's ($p < 0.001$). Hence, cohort participants reported treatment success at smaller changes in pain relief, on average. Moreover, the percentage of treatment success diverged considerably between the cohort with 316 (22.19%) patients and 81(34.18%) in the RCT's ($p < 0.001$).

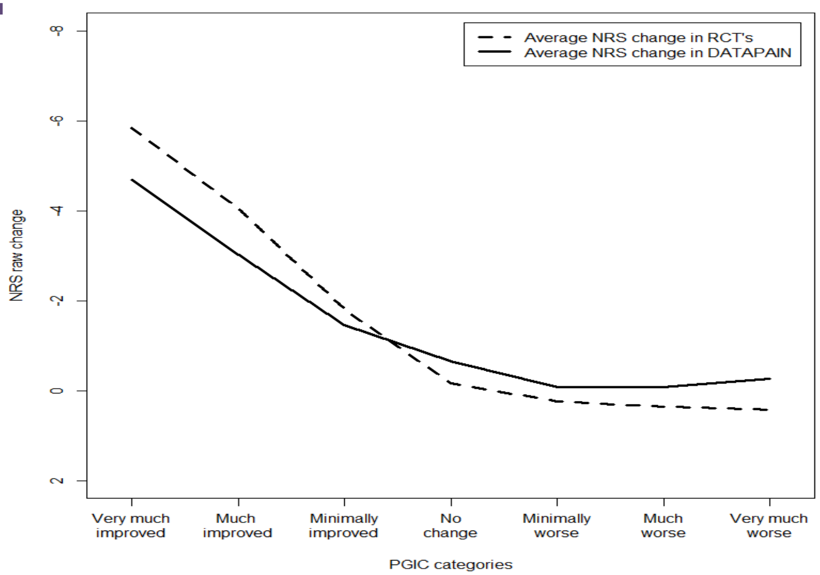

Figure 1, average NRS change score for the PGIC categories of the cohort and RCT's

3.2 Stratification on sex

In both the cohort and RCT's, the stratification on sex resulted in different mean values of clinically important improvement in the 'very much improved' categories of the PGIC (figure 2 and figure 3). Women indicated to need, on average, 1 point more in NRS change to label their improvement as 'very much improved'. Nonetheless, the average NRS changes for treatment success did not differ between the sexes, in the DATAPAIN cohort; -3.38 (SD: 2.82) for women and -3.28 (SD: 2.61) for men, nor in the RCT's; -4.49 (SD:1.84) for women and -4.65 (SD: 1.88) for men.

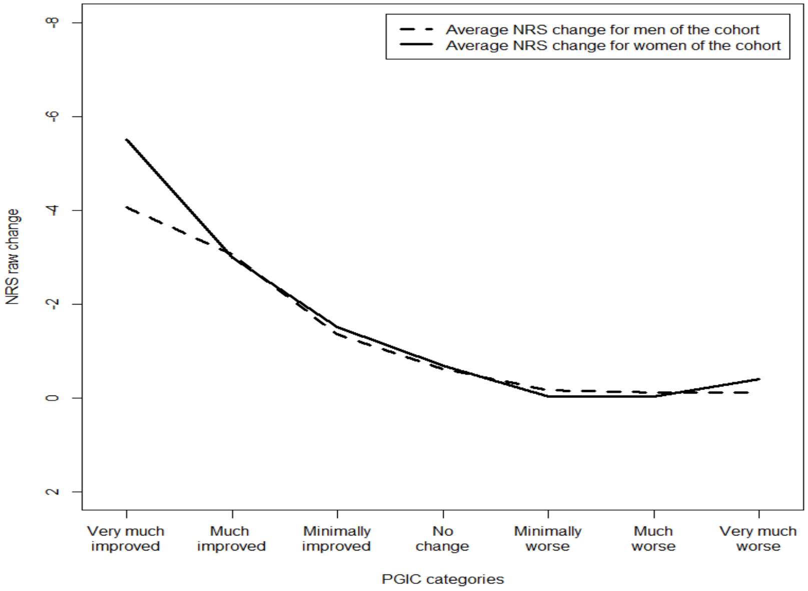

Figure 2, average NRS change score for the PGIC category in men and women of the cohort

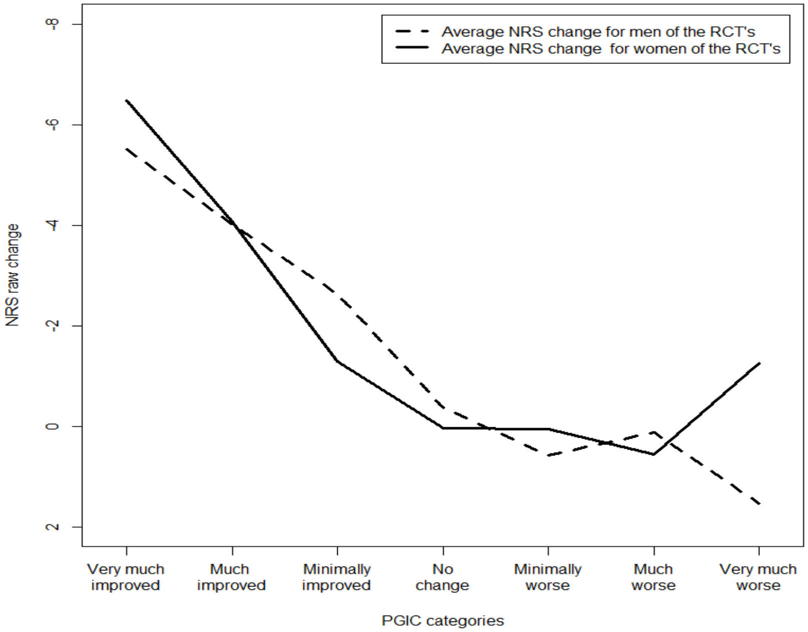

Figure 3, average NRS change score for the PGIC category in men and women of the RCT's

3.3 DATAPAIN cohort; stratification on treatment status

In the cohort, the treatment duration resulted in considerably different NRS changes between baseline and follow up. The average raw NRS change, for the completed treatment group was -2.13 (95% CI:-2.39, -1.86) and -0.79 (95% CI:-0.95, -0.63) for the ongoing treatment group (p <0.001) (figure 4). Besides, the percentage of treatment success differed significantly, for those who had completed treatment (151 patients, 36.3 %) and those ongoing in treatment (72 patients, 13.85%), p <0.001. To report clinically important improvement, an average NRS change of -4.15 (SD: 2.70) was needed for the completed group and a -2.16 (SD: 2.48) for the ongoing group. Thus, the ongoing treatment group reported to experience treatment success at a much lower average NRS change compared to those with completed treatment.

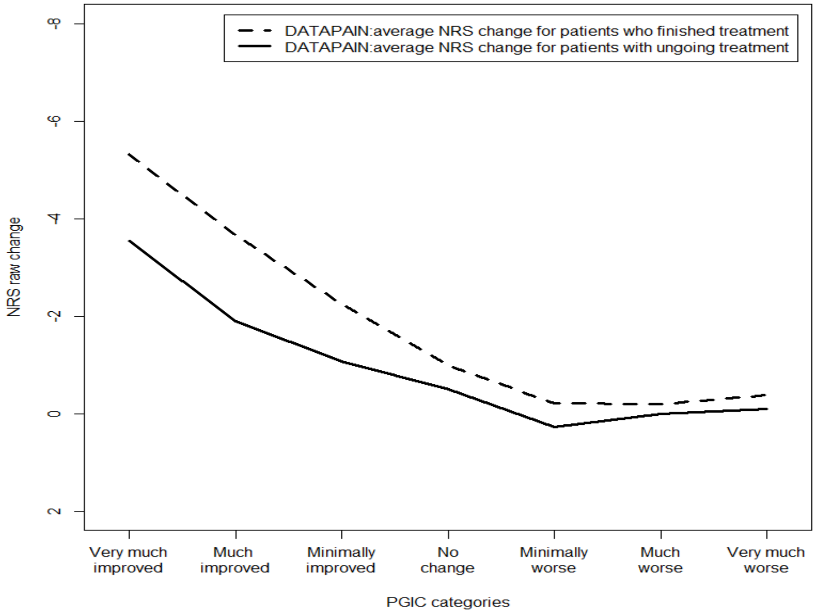

Figure 4, average NRS change score for the PGIC categories in treatment status of the cohort

3.4 Stratification on NRS baseline score

Differences in pain severity at baseline were more prominent in the cohort data than in the RCT's (figure 5 and 6). A clinically important improvement was observed at larger average NRS changes when patients were part of the severe NRS groups; -3.95 (SD:2.62) for the cohort and -4.90 (SD:1.99) for the RCT's, when compared to the modest NRS group; -2.25 (SD:2.33) for the cohort and -4.45 (SD:1.52) for the RCT's, and mild NRS groups; - 1.04 (SD:2.35) for the cohort and -2.76 (SD:0.96) for the RCT's. Suggesting that, independently of study design, an expectation of the amount of pain reduction may be present that depends on the severity of pain at baseline.

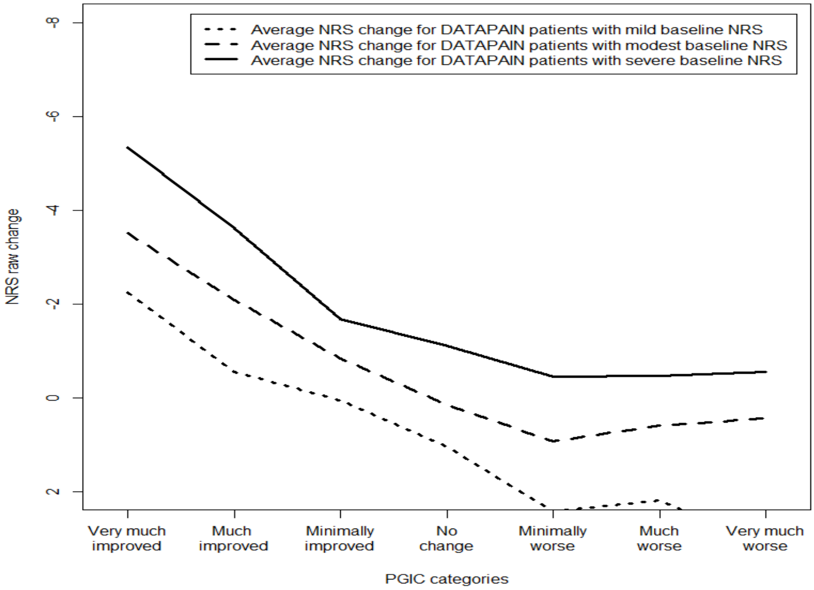

Figure 5, average NRS change score for the PGIC categories stratified on NRS baseline in the cohort

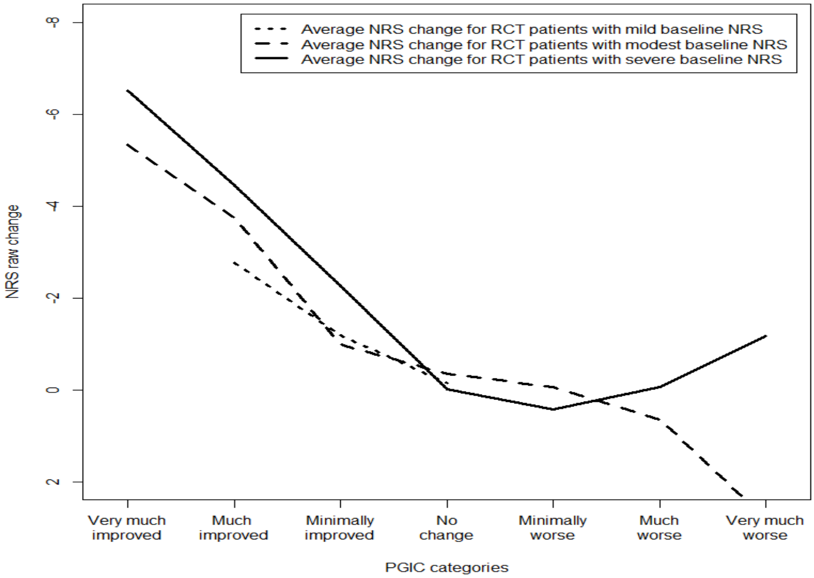

Figure 6, average NRS change score for the PGIC categories stratified on NRS baseline in the RCT's

4. DISCUSSION

The main objective of this study was to assess whether an average decrease of 2 points on the NRS was found to be clinically important, in chronic pain patients who participated in a large observational cohort and in patients included in RCT's of non-pharmaceutical treatments. In this study, patients reported clinically important improvement at a larger pain relief than the average decrease of 2 points on the NRS. The amount of pain relief needed differed substantially between study designs. In both cohort and RCT's, pain severity at baseline modified the amount of pain relief needed for a clinically important improvement. Furthermore within the cohort, considerable differences were found in treatment status.

In the RCT's, strict inclusion criteria's were applied before administering a single intervention, while personalized care was provided to every patient in the cohort, as these patients received care of a multidisciplinary pain team. Therefore, cohort patients may have had more than one intervention, or have been treated intermittently, leading to patients in treatment at 6 months follow up. We believed that this had an influence on the NRS change and the value given to the clinical importance of the improvement. Stratification revealed that the change in pain relief was reduced significantly when observing clinically important improvement for those still being treated. Illustrating that patients in treatment at 6 months were satisfied with their treatment progress at a much lower rate in pain relief. Notwithstanding, the association between the NRS change and clinically important improvement decreased substantially in the AUC, specifying that for these patient other underlying factors may play an important role when answering the PGIC. Therefore, the need for further investigation on factors that contribute in answering the PGIC is warranted.

The stratification on baseline NRS indicated that NRS change is non-uniform across these groups.[4; 15] Care should be taken in the comparison of patients that initiate at different pain intensities at baseline. This may be due to certain expectancy of improvement, hence further research on this specific topic may clarify the motive. The differences in the RCT's were not all significant, plausibly due to the low amount of patients included in the mild NRS baseline group, as per inclusion criteria and hence, low statistical power may have caused us to miss differences.

Stratification on sex revealed no differences at the 2 point raw change representing the two successful categories of the PGIC. Furthermore, a patient characteristic that may play a role as well is age. We have seen on the cross sectional level in our tertiary pain population patients of older age have a lower average pain intensity at presentation.[19] Yet, a longitudinal study on birth cohorts indicate that there is a positive relationship between age and pain intensity within patients over time.[9] Socio-demographic variables that have a negative association with pain are education, employment and wealth.[9; 19] Yet the question remains if these factors have influence on the outcome of the PGIC and are recommended to be further analyzed in future studies.

The results of this study show that a shift has taken place in comparison to the results of Farrar, et al, this may be due to the type of study design or intervention under analysis. Expectations on the effect of treatment on pain decrease seems dependent on many characteristics of patients and the setting they were recruited. It seems that patients are not satisfied with just a two point difference. An option would be to adjust the definition of clinical important improvement. Nevertheless, in clinical practice only a low rate of the pain population obtains a successful intervention. By increasing the clinical importance, to for example a 3 points raw change, this will have a negative impact on our view of their efficacy and it may have implications for future study design, such as necessary sample sizes. Another option could be to analyze the importance and sensitivity of composite scores or quality of life scores as pain outcome measures.

In general, the Spearman correlation coefficient suggested that pain change is an important component measured by the PGIC, yet the lack of strong correlations show that pain relief cannot explain treatment success in full. Moreover, relative changes were omitted in the results as they were interchangeable with the raw changes, making the interpretation easier when only the latter were included. This is due to the high baseline pain scores of the patients we have at the tertiary pain clinic, making the relationship between the raw change and PGIC as stable as the percent changes and PGIC. The questionnaires applied in both methods were validated for the chronic pain population and recommended by the IMMPACT guidelines, reducing the probability of errors in data collection. In both methods, application of stratification controlled for confounding.[8] Overall, consistency in association and performance was found between the change in pain intensity and meaningfulness of the PGIC, regardless of the treatment patients received, sex, treatment status or baseline pain intensity, suggesting a high external validity towards the diverse chronic pain population. Consequently, the application of the results may provide indications on clinically important improvement, contribute in calculating sample size and number needed to treat in future studies, not only in randomized controlled trials, yet also in cohort data for chronic pain patients referred to tertiary pain clinics.

In conclusion, the change in NRS scores associated with clinically important improvement was larger than is stipulated in the literature and the amount of pain relief needed was substantially larger in RCT’s than in cohort data. Stratification on study design and sex showed the presence of heterogeneity in the pain relief and its significance in relation to treatment success, calling for caution in the interpretations as is it may be dependent on study design, NRS at baseline or treatment status.

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Conflict of interest

The authors have no conflicts of interest to declare.

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CHAPTER 7

GENERAL DISCUSSION

General Discussion

This thesis comprises a clinical and methodological part. In the clinical part we describe the findings of sex differences in chronic pain patients that can be encountered in clinical practice. Examples of these sex differences are the representation of the pain experienced by both sexes, specifically on the association of fear avoidance and pain intensity, and the quantification of the impact of the socio-cultural construct. Additionally, specific clusters of pain characteristics are related to treatment outcomes that are found to be relevant for clinical practice. In the second part of this thesis, we report the generalizability of treatment success as it has previously been defined. Furthermore, two specific methods of analyses, the experience sampling method and the intersectional approach, are applied to two samples of chronic pain patients. Than we will summarize the limitations and strengths of this thesis, conclude on the findings and discuss future recommendations on how to move forward.

Part 1: Clinical implications

Sex differences

One important topic of this thesis was the exploration of sex differences in patient-reported outcomes. Sex differences as a research topic has been growing over the past decades, specifically in the experimental and pharmacological settings. Yet, research into clinical sex differences is scarce, and the field of chronic pain is no exception. Three chapters from this thesis have explored sex differences using epidemiological methods. First we identified differences in the biopsychosocial context between both sexes. Second, we demonstrated how differently men and women experience the impact of socio-cultural statuses on their pain experience, assessed by the intersectional approach. Third, we assessed whether the association between fear-avoidance and pain-intensity, which has been established earlier, differed to a clinically meaningful extent between sexes.

Previous epidemiological studies indicate that women have a higher prevalence of the most common types of chronic pain. On average, pain intensity is higher among women than men. Furthermore, the literature concludes that women experience pain more often in combination with cognitive-affective factors like catastrophizing and fear-avoidance, and suffer more psychologically.[6; 30] Chronic pain patients referred to our tertiary clinic differed to some extent from what has been described above. In this thesis we found that women do have higher mean pain intensity at presentation compared to men. Yet, in our large cohort, women showed less pain catastrophizing on average and suffered less psychologically from chronic pain. Moreover, the group we dubbed ‘complex’ because of the combination of high pain intensity, psychological and cognitive-affective factors like pain catastrophizing, depression or anxiety, was represented by 48% of women only, contrary to our expectation based on contemporary literature.

Fear-avoidance

The cross-sectional results on sex differences in fear-avoidance showed that men reported on average more fear-avoidance than women. The higher average of fear-avoidance in men when compared to women is consistent with two studies with small sample size.[10; 66] Why men with chronic pain tend to have more fear-avoidance remains unanswered. Nonetheless, this thesis demonstrated that social-cultural statuses have a substantial impact on men’s pain related complaints, like pain catastrophizing and pain intensity. Therefore, men may show more fear-avoidance due to the impact of social norms or a deeper concern about losing work capacity or productivity.[66] Regardless, men with high levels of fear-avoidance need counseling for the avoidance of activities due to the fear of pain, to reduce physical disuse and interference in daily activities. Moreover, whether this increase in fear-avoidance in men at baseline influences (negatively) pain treatment outcomes is in need of further investigation.

Nonetheless, the longitudinal results of this thesis indicate that the association between fear-avoidance and pain intensity is present in women. A suggestion why women show this association is that they may be sensitive to threat-related stimuli (like anxiety or fear-avoidance), leading to an increased pain perception.[61; 62] This may provide a treatment strategy for the reduction of pain intensity specifically tailored to women with (high) fear-avoidance. Yet previous to this, the causality between fear-avoidance and pain intensity in women needs to be confirmed. In addition, the results of the longitudinal ESM study showed that affect has a moderating effect on pain intensity itself, but not on the relationship between fear-avoidance and pain intensity. The statistically significant effect of positive affective experiences on pain intensity, such as ‘feeling relaxed’ (-0.15, p = <0.001) and ‘satisfied’ (-0.10, p = <0.001) are indicators for patients and healthcare providers when defining positive health.[41; 42] Consequently, there may be a potential role for positive affect in reducing pain intensity. Therefore, we and others recommend to further investigate positive affect and the association to the pain experience in future research.[19; 50]

Even though ‘loneliness’, ‘anxiety’ and ‘anger’ are associated to pain intensity and fear-avoidance, we did not see substantial statistical significance.[18; 80][79] In this thesis, the construct ‘irritability‘ was associated with an increase in pain intensity (0.9, p = <0.001). That may relate to the extent of pain (in)directly interfering with personal values, struggles and goals.[18]

Socio-cultural construct

Until now the impact of the socio-cultural construct on pain experience of chronic pain patients had not been assessed. Let stand alone the impact for both sexes separately. In this thesis, we showed that a positive impact of socio-cultural statuses (education, employment, relationship and age) was present in all patient-reported outcomes but quality of life. Moreover, this impact was, in most cases, larger for men than for women. Some specific results are discussed here below.

One of the most pronounced findings of the impact of socio-cultural factors, was the 2 point increase in pain catastrophizing for women with an advanced age (≥56), while age did not increase catastrophizing of pain in men. In a recent meta-analysis, no effect of age or sex was found on pain catastrophizing.[86] While the study of Dong et al., did find that women above the age of 65 years had an increase in the average pain catastrophizing score when pain intensity increased.[21] Information on the experience of pain at an advanced age is of importance as pain is expected to increase in prevalence due to the elongation of life expectancy. Specifically, an increase in degenerative neck and back disorders is to be expected.[4] Besides, older people experience chronic pain often in combination with comorbid diseases, physical or mental disabilities.[21] Even though women have a longer life expectancy than men (83,1 years for women versus 79,7 years for men of the Netherlands), women also experience less well health with an average of four years of difference compared to men.[63]

This thesis demonstrated an impact of education and employment on chronic pain, that is consistent with the literature on general health.[63; 69] Overall, high levels of education is observed as key in reducing health disparities. It is thought to be one of the most important determinants of maintaining employment despite having chronic pain,[28] and even a slight change in the level of education affects health.[60] In this thesis both sexes experienced a reduction in all average patient-reported outcomes due to high level of education, like lower average of depression. Similarly, the low level of education is related to a more severe pain experience, as in intensity and interference.[8; 17; 38; 52; 72; 82]

Furthermore, employment is an important social determinant of health and well-being, as it provides financial security and opportunity to fulfil a social role.[54; 77] In this thesis, paid employment is associated with lower averages on the outcomes of pain intensity, pain interference, depression, anxiety and pain

catastrophizing, with a larger impact for men suffering from chronic pain. Hence, having a paid job reduces positively the average pain experience of patients with chronic pain that attend the tertiary pain clinic.
Socio-economic status is analyzed by years of education, income and job description or a combination of the aforementioned factors. Yet, mostly education is applied. As indicated previously education provides access to information and the capacity to use this information, besides the fact that education is an important determinant on the level of income and job type.[10; 12; 75] This thesis specifies that within the chronic pain population the socio-economically disadvantaged populations have a more severe pain experience than those who are not socio-economically disadvantaged,[33] [13] despite having a worse general health[23; 26] Indicating a socio-economic influence on pain outcomes introducing health disparities due to levels of education and employment.

A consistent disparity concerning relationship status was found in this thesis. Observed was that being in a relationship is associated with lower mean scores of pain intensity, pain interference, depression, anxiety and pain catastrophizing in men only. Conversely in women, only the BPI affective subscale scores were influenced by relationship status. This average reduction was still smaller (women:β: -0.83; p=0.029) than that in men (men:β: -2.53; p<0.001). The literature of population studies indicate that intimate relationships occurs as a 'protective' factor in men against poorer health, independently whether it is mental or physical health, while women stay 'unaffected' by the negative physical health consequences of divorce, widowhood, or none relational statuses.[39; 64]

Pain Characteristics and Outcomes in clinical practice

This thesis focused on how a specific cluster of biopsychosocial factors, that are viewed as risk factors for chronic pain, influence patient outcomes at 6 months follow-up. The documentation of patients experiencing this combination of symptoms is of importance, as it is assumed that each of these single factors have negative consequences on treatment outcome, deteriorate health states and quality of life.[24; 52; 58; 72; 73] Moreover, a fifth of the chronic pain patients attending our tertiary pain clinic have this combination of symptoms, namely moderate to severe depression or anxiety, high pain catastrophizing and pain severity. The hypothesis was, that the complex group, have a lower likelihood in treatment successes when compared to chronic pain patients regarded as not being complex.
The results of this thesis suggest that although the aforementioned cluster of symptoms is present, the complex group responds alike on pain relief when

compared to the non-complex group. This result relate to the ones found by Farin et al. on the non-predictive role of pain catastrophizing for pain relief in patients with chronic low back pain undergoing inpatient rehabilitation.[28] As well, Poulsen et al.[59] found similar results for pain relief in spinal cord stimulation for chronic neuropathic pain. Yet, most studies do indicate pain catastrophizing as a predictor of pain outcomes such as pain intensity.[2; 3; 34; 35; 84; 85] just like the presence of depression and anxiety at baseline are seen as predictors of worse pain outcome.[2; 3; 16; 34; 35; 46] Furthermore, greater numbers of pain relief is found at 6 months follow-up when patients were categorized into groups of pain intensity at baseline, in drug and interventional RCT's and the DATA*PAIN* registry cohort. In the severe pain group (≥ 7 on the NRS) a larger pain relief is found in comparison with the modest pain group (5 – 7 on the NRS).[29; 83] As the complex group consists among other factors of pain severity (≥ 7 on the NRS) and the non-complex group consists of any value of pain without the combination of psychological or cognitive-affective factors, a larger pain relief could have been expected. Thus the finding of a similar pain relief in both groups, may suggest that the cluster of cognitive-affective and psychological factors in combination with pain severity reduces pain relief after all.

Regarding the similarities in reduction on pain relief and physical interference between the complex and non-complex group, we may imply that the multidisciplinary care provided is adequate. Nonetheless, the follow–up outcomes of the complex group were still higher on average pain and interference than the average baseline scores of the non-complex group. A severe pain outcome on the NRS and high pain interference on active and affective activities in daily life, are indicative for inability of participating in any type of exercise.[51] This pain experience, may reason why the complex pain group has an overall low treatment satisfaction and general perceived health when compared to the non-complex group. A body of evidence does link this combination as responsible for a decrease in treatment satisfaction and general perceived health.[9; 28; 55] Contrariwise, Poulsen et al suggests that baseline pain catastrophizing has no association with PGIC ratings, while Lewis at al suggest that severe baseline pain intensity is a predictor for better pain outcomes such as pain intensity, physical function and depression or anxiety.[46; 59] Besides these risk factors, a high amount of low level of education and absence of employment and/or relationship status were present in the complex groups, that may result in larger difficulties to manage their pain.[7; 20; 47; 48]

Part 2: Methodology

Generalizability of Treatment success

In this thesis, the generalizability of the 2 point difference in NRS change was tested in non-drug interventional RCT’s and cohort data. The overall NRS change needed for a moderate clinically important improvement was larger than the average two points found in the literature.[29] Moreover, this thesis also demonstrates that the average change necessary for treatment success was smaller for patients from the cohort than from those of the RCT’s.[83] These differences may be due to the dissimilarities in the methodology of study design. In case of RCT’s a strict inclusion criteria admit only those patients who fulfill specific criteria to participate in the study. Exclusion criteria(s) filter factors like psychological, psychiatric disorders, and cognitive-affective factors that may (negatively) influence outcomes. RCT’s offer a singular intervention to patients which are followed by the research team to encourage active participation during the intervention and follow-up.[31] Coneversely, in the DATA*PAIN* registry cohort every patient that seeks help is provided with personalized care, giving by a multidisciplinary team. Reflecting real-life pain care and management. This may have lead that some patients receive multiple interventions in time or receive a combination of interventions.[11] We consider that these factors did have influence on the NRS change and the value given to the clinical importance of improvement.
The question remains why differences were found between the RCT’s that applied the drug pregabalin in the landmark paper of Farrar versus the interventional RCT’s of the Pain Medicine department of the MUMC+. The case may be that a different level of expectation on the treatment effect is present. Implying that a plausible larger expectation of treatment is existent in biomedical intervention than by the intake of a pharmaceutical drug.[43; 67]

In general, the Spearman correlation coefficient suggested that the raw change on the NRS is an important component measured by the Patient Global Impression of Change (PGIC). Yet the lack of strong correlations demonstrates that pain relief cannot explain treatment success in full. The overall association observed by the Spearman correlation coefficient is stronger for the data of the RCT’s than that of the registry cohort. This is confirmed by higher values of the area under the receiver operating characteristic curves.[15] Outlining that the dichotomization of success/failure at two points raw change on the NRS is more justified for RCT’s. However, this association and dichotomization may not be accurate enough when patients of the cohort are more than 6 months in treatment. Specifying that for these patients other underlying factors may play an important role when answering the PGIC besides the NRS or that another cut-off score of the NRS may be more suitable for this specific patient group.

Consequently by employing the stratification on treatment status of the cohort, the change in pain relief was reduced significantly. Illustrating that patients in treatment at 6 months (-0.75(CI 95%: -0.91,-0.59)) were satisfied with their treatment progress at a much lower rate in pain relief, than those finished within 6 months (-2.13(CI 95%: -2.39, -1.58)). Additionally, incongruence is displayed when observing pain intensity at baseline. A much larger pain relief was observed for treatment success in both study designs (RCT and cohort) when severe pain was present at baseline than modest and mild pain. Nonetheless, a larger NRS change was needed in the RCT's to specify a successful treatment.[83]

Overall, the results demonstrated that patients are not satisfied with just a two-point difference. An option would be to adjust the definition of clinical important improvement. Nevertheless, only a low rate of the pain population obtains a successful intervention. As well, the number needed to treat are large and obtaining a sufficient samples size is a challenge many settings already.[22; 23]

Application of ESM in the Chronic Pain population

The momentary assessment of ESM allowed us to analyze experiences, symptoms and behaviors in the daily life of the chronic pain patient. This ecological nature of ESM helped us to capture the short term variation of fluctuation in real time reactions to events, like in this thesis factors such as pain, fear-avoidance, and affect.[53; 74; 78] Moreover, the multiple repetition of the same assessment in one day for consecutive days, provided a more reliable association. In our case the association between fear-avoidance and pain intensity in both sexes. One of the most important advantage of ESM is the reduction of recall bias. This bias is present when applying PROM's that study the change over an amount of time like weeks or months.[14; 53] By applying ESM the overestimation of the past experiences or the influence of the current state on past experiences is eliminated.[14] Moreover, the ESM can answer various research questions depending on what level of analysis is searched for, like between or within subject variation, or patient characteristics predicting changes on subject variation.[14] Besides these methodological advantages the ESM might be attractive to apply in clinical studies or treatment trajectories, as it might help to identify patterns explanatory for specific (variation of) symptoms. ESM may help to understand or inform the patient about their own pain by (visual) feedback and assist in the pain management to provide a more personalized care.[14; 70; 74] Besides, the low costs and widespread use of smartphones these days make the ESM more feasible.

On the other hand, this specific ESM study had a few limitations. Only 45 patients actually participated in the study after receiving all information about the study procedure, while 217 patients showed interest to partake. Actual feedback we got from the patients that participated and those interested was that the method is too time-consuming. Moreover, within the 6 days of participation missing data was reported. Although the repeating character of ESM decreases the influence of missing data, missed assessments might be a concern as a sub-group of pain patients might have missed assessments as a consequence of their current mood or level of pain.[81] This may have resulted in overestimation of functioning.[78] All together this could assume that ESM may be (too) burdensome in daily life, at least with the current amount of questions and repeated measures. Concluding that well-reasoned claim needs to be existent when applying this method with chronic pain patients. Some studies have investigated predictors of ESM compliance and indicate that completion rates in younger chronic pain patients is lower than those being older. A decline in completion rates was found over time of the study, indicating study fatigue, loss of interest or difficulties to cope with such an extensive survey while having to sustain the tasks of normal daily life.[56] Moreover, high negative affect and stress may tend to lower completion rates.[1] Concluding that older patients, shorter ESM survey as in length of days yet as well length of items asked per survey moment, participation manuals, and alarm functions indicate to improve higher completion rates.

The Intersectional approach

The intersectional approach is an analytical framework for understanding how certain aspects of a person’s social identity combine to create a position in society, that may be empowering or suppressing. It is found to identify how interlocking systems of power affect those who are most marginalized in society.[25] The intersectional approach opposes to treat factors in isolation and observes how interaction takes place between factors like sex, education and relationship status.[26; 27; 37; 40] Meaning that two or more factors cross each other, yet the crossing itself can happen at different magnitudes or may happen for a specific group of persons yet not for another. The standpoint the intersectional approach receives in this thesis is to observe specific interactions without concluding on interlocking systems of power in society.

First of all, we observed if disparities due to the socio-cultural statuses of chronic pain patients were existent in the pain experience, as this is a novel topic within pain research. Second, to what extent specific interactions were present between sex and the socio-cultural statuses and third how different the impact was on the pain experienced for both sexes individually. For the ease of interpretation a stratification by sex took place, what this analysis revealed was that many disparities remained implicit during the first two steps of the analysis.[37]

This thesis identified disparities in chronic pain due to socio-cultural status and has broadened our understanding of the diversity present in chronic pain, not only between both sexes yet as well within sexes. Implying that socio-cultural statuses are relevant factors, there is a need for clinical research to detect similar interactions, and quantify how they relate to treatment outcome. Additionally, in line with the intersectional approach, a next step would be to quantify the effect of various socio-cultural statuses together for chronic pain patients.[25; 37; 40] This may identify specific profiles of chronic pain patients and improve precision of treatment effect and contribute to the personalization of pain management.[4; 5] As shown by having a specific status, patient groups do better or worse on average. The question remains if subsequent adaptation in pain treatment optimizes treatment response for specific subgroup(s) of the chronic pain population, and to what extend these treatment options will have on the clinical practice.

Limitations

This thesis does not identify underlying (causal) mechanisms as the analyses applied were often cross-sectional in nature and when the study was longitudinal, no intent to determine causal relationships was in mind. Therefore, we need some restraint in drawing mechanistic conclusions from our results. Although for the majority of chapters contained in this thesis had more than sufficient statistical precision and power due to the large sample size of the DATA*PAIN* registry cohort. The sample size of chapter 5 was only modest. However, in this chapter the vast amount of measures taken over the course of a couple of days, although correlated within participants and therefore not representing 100% new information at each measurement, yielded a large amount of observations. The associations we were interested in could be tested using all longitudinal information available, without omitting participants from the analysis with intermittent missing data due to questionnaires that couldn’t be completed at the time of the *beep*. Even then, we call for caution of the interpretation of the results, as we do not know to what extent the parameter estimates may be distorted due to confounding. Moreover, an unfavorable ratio of men to women of the longitudinal cohort was present, hampering the precision of estimates of differences between the sexes.

The largest and most challenging limitation of this thesis was that other characteristics of importance for this study were not routinely collected, due to the limitations of the registry cohort. The analyses could have profited from confounders such as the classification of disease, interventions that had been given, and current medication intake. However, we have adjusted our findings for many potential confounding variables in the multivariable analyses, although residual confounding may remain. The sample used for a large part of this thesis was derived from a heterogeneous population, and multiple PROM's were administered to cover many aspects of chronic pain, making cross sectional and longitudinal analyses possible. Additionally, only 25% of patients who completed the questionnaires at baseline also completed the follow-up questionnaire, introducing selection bias. Observing larger percentage of the complex patient in the longitudinal analyses.

Strengths

The major strength of this thesis is the application of the prospective DATA*PAIN* registry cohort. With no more than two measurement moments of 15.000 chronic pain patients. Making longitudinal assessment of patient groups and patient experience possible within the chronic patient population. For this thesis no exclusion criteria's were applied, besides the presence of adulthood and chronic pain, ensuring high external validity and generalizability of the results [36]Additionally, a smaller specific cohort on the experience sampling method and various peer-reviewed RCT's of the department of Anesthesiology and Pain Medicine were combined with (partial) data of the pain registry cohort. This thesis introduced new standpoints of inspection of chronic pain, such as the intersectional approach of sociocultural statuses, the observation of sex differences by the ESM, and the inspection of group differences in well-known (cross-sectional and longitudinal) study designs.

Conclusion

Independently from the chosen standpoint or study design, all the results of this thesis encountered the presence of heterogeneity. First of all, the pain experience differs greatly when observing the biopsychosocial context of the chronic pain patient. Especially when combinations of risk factors of chronic pain are combined. Second, heterogeneity is found when analyzing both sexes separately on fear avoidance. Third, disparities are identified by the sociocultural statuses of men and women suffering from chronic pain. Showing that men seem to benefit (more) of favorable life statuses, like being in a relationship. Fourth, in the pain clinic heterogeneity was identified by clustering pain patients. Indicating lower likelihood of treatment successes when a cluster of risk factors are present at intake. In which a disadvantaged socio-cultural statuses may play a role. Fifth, no generalizability of the clinical important improvement on pain relief is found for chronic pain patients of this thesis.

Future recommendations

Multidisciplinary pain care is recognized as the treatment for patients with chronic pain.[32; 71] Aiming to target pain, and optimize daily life functioning,

increase social, physical and psychological wellbeing.[44; 57] By coordinating treatment activities and aligning them to patient-specific goals. Despite the biopsychosocial perspective on chronic pain, there is no one size fits all approach for multidisciplinary pain care. This is observed in the substantial variation in content of care provided, duration of the care needed per patient, pain condition, pain mechanisms or patient group.[45; 68]
To improve personalized pain care the thoughts are twofold. One is that the personalized tailored care at multidisciplinary pain clinics may not be fully compatible with the needs of the (complex) patient when it comes down to quality of life. Topics that may improve societal participation are lacking in multidisciplinary tertiary pain clinics. A suggestion would be to combine the personalized multidisciplinary approach together with a societal approach. Including social workers can provide help on topics such as financial aid and work reintegration. Moreover, interventions as pain education, self-management, and specific information for family and caregiver(s) may improve patient outcome and the overall treatment satisfaction.

Nonetheless, even though an introduction of social workers to multidisciplinary pain teams is made, we still lack specified information on predictors of treatment outcome to promote the precision of personalized pain care. Identifying particular predictors for individuals or groups of pain patients based on their pain experience and biomedical profile, enables the improvement of treatment response.[5] This favors a change in pain management that requires a more holistic approach with a patient oriented vision.[4] Wherein, medical specialists united in multidisciplinary teams work together with stakeholders, to promote both physical and digital care networks, focusing on outcome indicators of the patient.

A visionary goal would be to have the ability to provide interventions to patients, based on the impact the interventions has on relevant individual patient outcome(s). To realize this, precise understanding is needed of how biomedical data and biopsychosocial factors interact with the intervention and how these altogether influence patient outcome(s). This goal can be achieved by developing a data driven Value Based HealthCare (VBHC) approach.[4] Gaining insight in patient profiles and relevant health statuses, based upon available biomedical data, patient reported outcomes of relevant health domains, patient reported experiences, such as value based healthcare questionnaires, quality of care, and health care processes of the University Pain Center Maastricht into one large dataset. The objective of this VBHC approach is to visualize the copious relations existent between these determinants, that due to the complexity of pain are invisible to the human eye and mind. With the aim that the VBHC approach will provide insight in the accessibility and performance of care by mapping clinical processes, reduce registration burden through the reuse of data (data efficiency) and expose bottlenecks that patients may experience in receiving care.[65; 76]

This unique project is a strong combination of stakeholders, research academics, clinical specialists on chronic pain, patients (experience experts), and experts on integrated health solutions, that all have the same objective; deliver the right care to the right patient. This project, as aforementioned, provides insight into health statuses of patients suffering from chronic pain, most important expose health inequality between groups. Additionally, by applying the VBHC approach, the utilization of resources in pain management can be optimized and provide insight into care paths for particular subgroups of patients. Hereby, this project contributes in reshaping healthcare services in a way that is rightfully appropriate for the patient, reduces workload of the clinicians and is economically resourceful for our healthcare system.[49; 65; 76]

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CHAPTER 8

SUMMARY

The research in this thesis has been performed to improve our understanding of the way pain is experienced by chronic pain patients, and to unravel the vast heterogeneity between patients. Exemplified by substantial differences in patient-reported outcomes and by likelihood of treatment success. Therefore, we have analyzed the large MUMC$^+$ DATA*PAIN* registry cohort, a smaller chronic pain cohort measured using the experience sampling method, and data of multiple randomized controlled trials performed at the department of Anesthesiology and Pain Medicine of the MUMC+. This thesis starts by creating an overview of the biopsychosocial context of chronic pain patients. Subsequently, the heterogeneity within and between sexes is presented, by quantifying the impact of the socio-cultural construct on patient outcomes and by analyzing sex differences in the association of fear-avoidance and pain intensity. Furthermore, chronic pain patients were clustered and compared to observe differences in the likelihood of treatment success. Along this line, the last chapter presents the generalizability of the clinical importance of improvement in different types of study design and patient groups.

Chapter 2 describes 11,214 chronic pain patients included in the DATA*PAIN* registry cohort. Patient’s (socio) demographics, pain characteristics, quality of life values and psychological values were described. This provided us a cross-sectional overview of the average composition of the cohort and variance of the chronic pain patient before the first consultation with the specialist. Almost 60% of the DATA*PAIN* registry cohort patients were female, the unemployment rate was 35.9%, and a low level of education was the most common (59%). Seventy-two percent reported severe pain (NRS 7-10), and when pain severity increased the psychological and quality of life values deteriorated. Approximately 36% of patients showed severe signs of depression or anxiety, and 39% displayed high pain catastrophizing. The combination of risk factors, like pain severity, pain catastrophizing, and anxiety or depression was reported by 17.8% of the cohort. This study showed consistency with earlier findings of the literature that higher pain intensity is among women. However inconsistent with the literature, that female patients had better averages than men for factors like pain catastrophizing, depression and anxiety.

In **chapter 3,** the impact of the socio-cultural construct on the association between sex and pain outcomes was investigated for chronic pain patients. Differences in pain reporting within the sexes are often larger than those between sexes. An explanation may be that the socio-cultural construct generates responses that differ substantially for both sexes. The socio-cultural

construct observed in this chapter consisted of age (18-55 years versus 56-96 years), relationship status (being in a relationships versus not being in a relationship), employment status (having a paid job versus no paid job) and level of education (low versus high level of education). Because of the novelty of the topic, we first needed to establish the impact of sex and socio-cultural characteristics on patient outcomes in general. This was realized by applying multiple linear regression, with a stepwise backward elimination procedure in combination with clinical expertise to only select strong independent determinants for each patient outcome. The PROM's that we measured were: numeric rating scale (NRS) for pain intensity, RAND-36 Health Survey subdivided into a mental and physical subscale for quality of life, Brief Pain inventory (BPI) divided into an affective and active subscale for pain interference in daily activities, Hospital Anxiety and Depression scale (HADS) divided into a subscale for anxiety and depression, and the Pain Catastrophizing Scale (PCS) for pain catastrophizing.
Overall, the results showed that both the socio-cultural construct and sex were associated with the patient outcomes, except for the RAND-36 on quality of life. Subsequently, we stratified on sex to illustrate the differences for both sexes. In which it was observed that men's social positions have a significantly more positive influence on how they perceive pain and associated complaints. On average, higher age (≥ 56) led to a lower pain intensity, interference in physical daily activities and depression for both sexes. Yet, this impact was larger for men than for women. Contrariwise, the average of pain catastrophizing increased with 2 points only in women with a higher age. Being in a relationship had a positive impact on all the patient reported outcomes for men. Conversely, women in a relationship only had a lower average on the BPI affective subscale. Meaning less impact of pain interference on affective activities such as enjoyment in life. Having a high education and paid employment reduced the averages for every patient reported outcome and varied in impact for men and women. The reasoning for these sex disparities remains unrevealed. Nonetheless, our results add to the existing literature by suggesting that the heterogeneity found in chronic pain may be partly explained by patients' socio-cultural characteristics rather than by biological sex characteristics only.

In **chapter 4**, chronic pain patients of the DATA*PAIN* registry cohort were classified into complex or non-complex patient groups. Those with high pain severity (≥ 7 on the NRS), moderate or severe depression or anxiety (>10 on the HADS subscale depression or anxiety) and high pain catastrophizing (>31 on the PCS) were clustered into the complex group. This combination was assumed to have negative consequences pain relief, on treatment outcome, deteriorate health states and quality of life over a 6-month period. The complex group was compared with the non-complex group and the likelihood of treatment outcomes were assessed. The specific patient reported outcomes observed were treatment satisfaction on the Patient Global Impression of Change (PGIC), the NRS for pain relief, the BPI with the active and affective subscale for pain interference and quality of life indicator for health status by the General Perceived Health (GPH). Cross-sectional and longitudinal data of 1637 chronic pain patients were analyzed, of which 345 (21.08%) were regarded as complex. Logistic regression was used to analyze if belonging to the complex group modified the possibility of having a successful treatment on the PGIC or a positive health status on the GPH. Subsequently, linear regression was used to assess if the complex group differed in average reduction in pain relief and interference compared to non-complex patients.

The complex group had only 0.59 times the odds of treatment satisfaction compared to non-complex patients. The odds ratio for GPH was 0.28 indicating even larger differences. The BPI affective subscale had a statistically significantly different change score, while the change scores of pain relief and BPI active subscale were not significantly different. The results of this study suggests that although high pain severity and psychological values were present, the complex patient does not respond differently on pain relief when compared to the non-complex group. Though, greater numbers of pain relief were thought to be found, because the literature indicates that when subdividing pain at baseline into severe (≥ 7 on the NRS), modest (5 – 7 on the NRS) and mild (0-5 on the NRS) pain groups, a larger NRS change is found in the severe groups when compared to the modest group. Indicating that the combination of risk factors present in the complex group influences pain relief after all. Moreover, on baseline the complex group shows high pain interference on active and affective activities of daily life, that remains present at follow-up. This may be due to the negative cognitive-emotional reaction to pain in complex patients, in which catastrophical thoughts about activity may overwhelm and limit those patients in daily activities.

This study has provided opportunities for a prospect of plausible successes on clinically relevant patient outcomes. These result suggest that when treating complex patients, the desired treatment outcome(s) should be recognized by specialist and patients before initiating treatment, as these may be less likely to occur than for non-complex patients and thus may guide treatment decision.

In **chapter 5**, the association between fear-avoidance and chronic pain intensity was further analyzed, as it remained unclear whether this association depends on sex. Additionally, the potential confounding effect of affective experiences on the association between fear-avoidance and pain intensity was analyzed. The patients participating in this experience sampling cohort, a total of 45 chronic pain patients, were recruited at intake of the DATA*PAIN* registry cohort. The experience sampling method is a structured digital diary technique to appraise subjective experiences in daily life. Short momentary assessment questions were used to repeatedly assess patients' pain intensity, level of fear-avoidance and positive as well as negative affect during their daily life. Linear mixed-effects models were applied to estimate measures of association. Both an unadjusted and adjusted model was made, in which the latter corrected for statistically significant affective experiences.

To our knowledge, this was the first study using the experience sampling method to investigate sex differences in the association between fear-avoidance and pain intensity in chronic pain patients. Cross-sectional results demonstrated that men had on average more fear-avoidance than women. However, results from the longitudinal data suggest that no association between fear-avoidance and pain intensity was found in men, whereas in women, an increase in fear-avoidance was associated with an increase in pain intensity. The statistically significant affective experiences 'relaxed', 'irritated' and 'satisfied' did not confound the above mentioned findings.
Why male chronic pain patients tend to have more fear-avoidance than female patients, but unrelated to pain intensity is unknown. Moreover, whether high values of fear-avoidance in men at baseline influences (negatively) pain treatment outcomes remains unanswered. However, having more fear-avoidance does have influence on pain intensity in women, perhaps due to those with low fear-avoiding being more active, which subsequently may decrease pain.

In the **sixth chapter** the clinical importance of improvement for patients was analyzed. What is already known is that the change on the NRS is constructed on a subjective pain experience, which hampers establishment of a definition of the clinical importance of improvement. Hence, by combining the results of the Patients Global Impression of Change (PGIC) with the NRS (named an anchor-based method) the clinical importance of improvement can be determined. A 2-point change on the NRS has been shown to be equivalent to a moderate clinically important improvement in data of randomized controlled trials (RCT's), when treating chronic pain patients with medication. In this chapter, we assessed whether these findings could be generalized to patients from the DATA*PAIN* registry cohort and to patients who had been included in non-drug interventional RCT's of our pain medicine department. The NRS change was quantified by subtracting the baseline NRS from the NRS at 6-months follow-up.

Categorization of success/failure was applied on the PGIC by calculating the raw and percent average NRS changes. The Spearman correlation coefficient was used to quantify the overall linear relationship. Moreover, the discriminative ability of the NRS change for determining self-perceived treatment success was explored through the area under the receiver operating characteristic curve. Data was stratified separately on study design (observational versus experimental), sex, and pain intensity at baseline for both the cohort and RCT's. In addition, the cohort was stratified on treatment status at follow-up (being in treatment versus finalized treatment).
The records of 1661 chronic pain patients were examined. Overall, the observed NRS change needed for moderate clinically important improvement was larger than the average two points found in the literature. Yet, the average changes necessary in patients from the cohort were smaller compared to the RCT's. This may be due to the differences in treatment protocol, or because active participation in a randomized experiment may affect expectations. Strict inclusion criteria with singular interventions were applied in the RCT's, while personalized care was provided to all chronic pain patients of the cohort. We believe that this may also have had an influence on the NRS change and the value given to the clinical importance of improvement.

The stratification indicated that the clinical importance of improvement is non-uniform across the groups of pain intensity at baseline and treatment status. The average change necessary was larger for the severe pain intensity group at baseline than modest and mild pain intensity groups at baseline. This finding represents both the cohort and RCT's, suggesting that independently of study design, an expectation of the amount of pain reduction may be due to the severity of pain at baseline. Moreover, the mean NRS change needed for treatment satisfaction was smaller when treatment was still ongoing than when finalized within 6-months. Altogether, these results indicate that the clinical importance of improvement varied substantially, representing heterogeneity in pain relief and its relation to treatment success in chronic pain patients. Calling for caution in the interpretation as it may depend on study design, NRS at baseline, or treatment status.

SAMENVATTING

Het onderzoek in dit proefschrift is uitgevoerd om meer inzicht te krijgen in de manier waarop pijn door chronische pijnpatiënten wordt ervaren, en om de heterogeniteit tussen patiënten te analyseren. De heterogeniteit blijkt uit de verschillen in de patiënten gerapporteerde uitkomsten en in de kans op succes van de behandeling. Voor dit onderzoek zijn meerdere cohorten en studies gebruikt. Het gaat om het grote MUMC+ DATA*PAIN* registratie cohort, een klein chronisch pijn cohort gemeten met de experience sampling methode, en data van gerandomiseerde gecontroleerde studies, allen uitgevoerd op de afdeling Anesthesiologie en Pijngeneeskunde van het MUMC+.
Dit proefschrift begint met een overzicht van het biopsychosociale context van chronische pijnpatiënten. Vervolgens wordt de heterogeniteit binnen seksen gepresenteerd, door de impact van het sociaal-culturele construct op pijnuitkomsten te kwantificeren. Verschillen tussen beide sekse wordt geanalyseerd in de associatie van angst-vermijding en pijnintensiteit. Verder zijn chronische pijnpatiënten geclusterd en vergeleken om verschillen in de kans op succes van de behandeling te observeren. In verlenging van deze analyse, presenteert het laatste hoofdstuk de generaliseerbaarheid van het klinisch betekenisvolle verbetering in verschillende soorten onderzoeksopzetten en patiëntengroepen.

Hoofdstuk 2 beschrijft 11.214 chronische pijn patiënten van het DATA*PAIN* registratie cohort, en hun (socio)demografische gegevens, pijnkenmerken, kwaliteit van leven en psychologische waarden. Dit gaf ons een cross-sectioneel overzicht van de gemiddelde samenstelling en variantie in het cohort. Bijna 60% is vrouw, het cohort heeft een werkloosheidspercentage van 36% en een laag opleidingsniveau kwam het meest voor (59%). Tweeënzeventig procent rapporteerde ernstige pijn (NRS 7-10) en wanneer de ernst van de pijn toenam verslechterden de psychologische waarden en die van het kwaliteit van leven. Ongeveer 36% van de patiënten vertoonde tekenen van depressie of angst, en 39% vertoonde hoge waarden in pijn catastroferen. De combinatie van risicofactoren, zoals de ernst van de pijn, pijn catastroferen en angst of depressie werd gerapporteerd door 17,8% van het cohort. Deels van de bevindingen van deze studie komen overeen met eerdere conclusies uit de literatuur, over dat vrouwen een hogere pijnintensiteit hebben. Echter waren er ook bevindingen die niet consistent zijn, bijvoorbeeld dat vrouwen hogere gemiddelden hebben dan mannen voor factoren zoals pijn catastroferen, depressie en angst.

In **hoofdstuk 3** is de invloed van het sociaal-culturele construct op de associatie tussen sekse en pijnuitkomsten onderzocht. Verschillen in pijnrapportage binnen de seksen zijn vaak groter dan die tussen mannen en vrouwen, en een verklaring kan zijn dat het sociaal-culturele construct verandering genereert die voor beide seksen aanzienlijk verschillen. Het waargenomen sociaal-culturele construct bestond uit leeftijd (18-55 jaar versus 56-96 jaar), relatiestatus (wel of geen relatie), werkstatus (wel of geen betaalde baan) en opleidingsniveau (laag versus hoog opleidingsniveau). Vanwege de innoverende visie van het onderwerp, is eerst de invloed van geslacht en de sociaal-culturele kenmerken op de patiënt gerapporteerde uitkomsten (PROM' s) in het algemeen vastgesteld. Dit werd geanalyseerd door lineaire regressie met een stapsgewijze achterwaartse eliminatieprocedure, in combinatie met klinische expertise van de pijnspecialisten, om zo alleen sterk onafhankelijke determinanten voor elke PROM te selecteren. De door ons gemeten PROM 's waren de numerieke beoordelingsschaal voor pijnintensiteit (NRS), de RAND-36 Health Survey verdeeld in een mentale en fysieke subschaal voor kwaliteit van leven, de Brief Pain Inventory (BPI) verdeeld in een affectieve en actieve subschaal voor pijninterferentie in dagelijkse activiteiten, de Hospital Anxiety and Depression Scale (HADS) verdeeld in een subschaal voor angst en één voor depressie, en de Pain Catastrophizing Scale (PCS) voor pijn catastroferen.

Uit de resultaten bleek dat zowel het sociaal-culturele construct als het geslacht verband hielden met de PROM' s, behalve voor de RAND-36 over levenskwaliteit. Vervolgens is er gestratificeerd op geslacht om de verschillen voor beide seksen apart te illustreren. Hierbij werd geconstateerd dat sociale posities van mannen een significant positievere impact hebben op pijn en bijbehorende klachten. Gemiddeld leidde een hogere leeftijd (≥ 56) voor beide seksen tot een lagere pijnintensiteit, minder hinder bij lichamelijke dagelijkse activiteiten en minder depressie. Dit effect was echter groter bij mannen dan bij vrouwen. Daarentegen steeg het gemiddelde van het pijn catastroferen met 2 punten alleen bij vrouwen met een hogere leeftijd. Het hebben van een relatie had een positieve invloed op alle PROM' s voor mannen. In tegenoverstelling hadden vrouwen met een relatie alleen een lager gemiddelde op de BPI affectieve subschaal. Dit betekent minder invloed van pijninterferentie op affectieve activiteiten zoals plezier in het leven. Het hebben van een hoge opleiding en betaald werk verminderde het gemiddelden voor elke door de patiënt gerapporteerde uitkomst en varieerden in impact voor mannen en vrouwen. De reden voor deze verschillen tussen mannen en vrouwen blijft onbekend. Niettemin voegen onze resultaten toe aan de bestaande literatuur door te suggereren dat de heterogeniteit die bij chronische pijn wordt gevonden, gedeeltelijk kan worden verklaard door sociaal-culturele kenmerken van patiënten in plaats van alleen door biologische geslachtskenmerken.

In **hoofdstuk 4** werden chronische pijnpatiënten van het DATA*PAIN* registratie cohort ingedeeld in complexe of niet-complexe patiëntengroepen. Degenen met een hoge pijnintensiteit (≥ 7 op de NRS), matige en ernstige depressie of angst (>10 op de HADS subschaal depressie of angst) en hoog pijn catastroferen (>31 op de PCS) werden geclusterd in de complexe groep. Aangenomen werd dat deze combinatie van factoren negatieve gevolgen hebben voor pijnverlichting, tevredenheid van de behandeling en kwaliteit van leven over een tijdsspanne van 6 maanden. De specifieke patiënt gerapporteerde uitkomsten die werden waargenomen waren de tevredenheid over de behandeling op de Patient Global Impression of Change (PGIC), de NRS voor pijnverlichting, de BPI met de actieve en affectieve subschaal voor pijninterferentie en de indicator voor kwaliteit van leven op de General Perceived Health (GPH). Cross-sectionele en longitudinale gegevens van 1637 chronische pijnpatiënten werden geanalyseerd, waarvan 345 (21,08%) als complex werden beschouwd. Logistische regressie werd gebruikt, om te analyseren of de complexe groep de kans op een succesvolle behandeling op de PGIC en positieve gezondheidsstatus op de GPH reduceerde. Ook werd lineaire regressie toegepast om te beoordelen, of de complexe patiënten verschilde met de niet-complexe patiënten, in de gemiddelde pijnvermindering en reductie in pijninterferentie bij 6 maanden na het ondergaan van behandeling.

De complexe groep had slechts 0.59 maal kans op behandeltevredenheid in vergelijking met niet-complexe groep. De odds ratio voor GPH was 0.28, wat duidt op nog grotere verschillen. Voor de complexe groep, de BPI affectieve subschaal had een statistisch significant verschil in de score tussen baseline en 6 maanden (veranderscore), terwijl de veranderscores van pijnverlichting en BPI actieve subschaal niet significant verschilden. De resultaten van deze studie suggereren dat, hoewel er sprake was van hoge pijnintensiteit en psychologische waarden, de complexe patiënt niet anders reageert op pijnverlichting in vergelijking met de niet-complexe patiënt. Wel werd gedacht een grotere pijnverlichting te vinden, omdat uit de literatuur blijkt dat bij een onderverdeling van pijn op baseline in ernstige (≥ 7 op de NRS), matige (5-7 op de NRS) en milde (0-5 op de NRS) pijngroepen, een grotere verandering op de NRS wordt gevonden in de ernstige groep in vergelijking met de matige groep. Dit zou kunnen wijzen dat de combinatie van risicofactoren in de complexe groep toch van invloed zijn op de pijnverlichting. Bovendien vertoont de complexe groep op baseline een hoge pijninterferentie op actieve en affectieve activiteiten van het dagelijks leven, die bij de follow-up aanwezig blijven. Dit kan het gevolg zijn van de negatieve cognitief-emotionele reactie op pijn bij complexe patiënten, waarbij catastrofale gedachten over activiteiten de patiënten overweldigen en beperken in dagelijkse activiteiten.

Deze studie biedt een vooruitzicht aan mogelijke behandeluitkomsten. De gewenste behandeluitkomst(en) van de complexe pijn patiënt, zal door specialist en patiënt moeten worden erkent voordat de behandeling wordt gestart. Aangezien deze zich wellicht minder snel zal voordoen dan bij niet-complexe patiënten.

In **hoofdstuk 5** werd de associatie tussen angstvermijding en chronische pijnintensiteit geanalyseerd. Aangezien onduidelijkheid in de literatuur heerst of deze associatie beïnvloed wordt door geslacht, hebben wij specifiek gekeken naar sekse verschillen. Maar ook is het effect van affectieve ervaringen op de associatie tussen angst-vermijding en pijnintensiteit geanalyseerd. De 45 chronische pijnpatiënten die deelnamen werden geworven bij de intake van het DATA*PAIN* registratie cohort. De toegepaste methode, experience sampling methode, is een gestructureerde digitale dagboektechniek om subjectieve ervaringen in het dagelijks leven te beoordelen. Korte momentane beoordelingsvragen werden gebruikt om herhaaldelijk de pijnintensiteit, niveau van angst-vermijding en affectieve ervaringen van de patiënten tijdens hun dagelijks leven te beoordelen. Lineaire mixed-effects modellen werden toegepast om associatiematen te schatten. Er werd zowel een ongecorrigeerd als een gecorrigeerd model gemaakt, waarbij in het laatste werd gecorrigeerd voor statistisch significante affectieve ervaringen.

Voor zover wij weten, was dit de eerste studie waarbij de experience sampling methode werd gebruikt om sekseverschillen te onderzoeken in de associatie tussen angst-vermijding en pijnintensiteit bij chronische pijnpatiënten. De cross-sectionele resultaten toonden aan dat mannen gemiddeld meer angst-vermijding hadden dan vrouwen. De resultaten van de longitudinale data suggereerden echter dat bij mannen geen associatie tussen angst-vermijding en pijnintensiteit werd gevonden, terwijl bij vrouwen een toename in angst-vermijding samenhing met een toename in pijnintensiteit. De statistisch significante affectieve ervaringen 'ontspannen', 'geïrriteerd' en 'tevreden' waren niet van invloed op de bovengenoemde bevindingen. Waarom mannelijke chronische pijnpatiënten meer angst-vermijding tonen dan vrouwelijke patiënten, maar niet gerelateerd is aan de pijnintensiteit, is vooralsnog onbekend. Bovendien blijft onbeantwoord of hoge waarden van angst-vermijding bij mannen op baseline een (negatief) invloed hebben op de uitkomsten van de pijnbehandeling. Het hebben van meer angst-vermijding heeft echter wel invloed op de pijnintensiteit bij vrouwen, wellicht doordat degenen met een lage angst-vermijding actiever zijn, wat vervolgens de pijn kan doen verminderen.

In het **zesde hoofdstuk** werd de klinisch betekenisvolle verbetering voor patiënten geanalyseerd. Het is reeds bekend dat de verandering op de NRS wordt geconstrueerd op basis van een subjectieve pijnervaring, hetgeen het opstellen van de definitie van klinisch betekenisvolle verbetering bemoeilijkt. Door de resultaten van PGIC te combineren met de NRS (ook wel anker gebaseerde methode genoemd) kan de klinisch betekenisvolle verbetering worden bepaald. Een verandering van 2 punten op de NRS is in gerandomiseerde gecontroleerde onderzoeken (RCT' s) bij de behandeling van chronische pijnpatiënten met medicatie, gelijkgesteld aan een matige klinisch betekenisvolle verbetering. In dit hoofdstuk gingen wij na of deze bevindingen konden worden gegeneraliseerd naar patiënten van het DATA*PAIN* registratie cohort en naar patiënten die waren geïncludeerd in niet-medicamenteuze interventionele RCT' s van de afdeling pijngeneeskunde in het MUMC+. De NRS verandering werd gekwantificeerd door de NRS bij baseline af te trekken van de NRS bij 6 maanden follow-up. Categorisering van succes/falen werd toegepast op de PGIC door de ruwe en procentuele gemiddelde NRS veranderingen te berekenen. De Spearman correlatiecoëfficiënt werd gebruikt om de algemene lineaire relatie te kwantificeren. Bovendien werd het discriminerend vermogen van de NRS verandering voor het bepalen van het ervaren behandelsucces onderzocht, door middel van de oppervlakte onder de receiver operating characteristic curve (ROC curve) te berekenen. Stratificatie vond plaats op geslacht en pijnintensiteit bij baseline voor zowel in het cohort als in de RCT' s. Alsmede werd het cohort gestratificeerd op behandelstatus bij follow-up (in behandeling versus afgeronde behandeling).

De dossiers van 1661 chronische pijnpatiënten werden onderzocht. In het algemeen was de waargenomen NRS verandering, die nodig was voor een klinisch betekenisvolle verbetering, groter dan de gemiddelde twee punten die in de literatuur werden gevonden. Toch waren de gemiddelde veranderingen bij patiënten uit het cohort kleiner dan bij de RCT' s. Dit kan het gevolg zijn van de verschillen in behandelingsprotocol, of omdat actieve deelname aan een gerandomiseerd experiment de verwachtingen kan beïnvloeden. In de RCT' s werden strikte inclusiecriteria met enkelvoudige interventies toegepast, terwijl gepersonaliseerde zorg werd verleend aan alle chronische pijnpatiënten van het cohort. Wij denken dat dit ook van invloed is geweest op de NRS verandering en de waarde die aan het klinisch belang werd toegekend.
De stratificatie gaf aan dat de klinisch betekenisvolle verbetering niet uniform is in relatie tot de groepen van pijnintensiteit op baseline. De gemiddelde

betekenisvolle verandering was groter voor de groep met ernstige pijnintensiteit dan voor de groepen met matige en lichte pijnintensiteit. Deze bevinding geldt zowel voor de cohort als voor de RCT' s, hetgeen suggereert dat onafhankelijk van de studieopzet een verwachting van de hoeveelheid pijnvermindering kan voortvloeien uit de ernst van de pijn op baseline. Bovendien, was de gemiddelde NRS verandering nodig voor een tevreden behandeling, kleiner wanneer de behandeling nog gaande was dan wanneer deze binnen 6 maanden werd afgerond. Al met al, geven deze resultaten aan dat het klinisch betekenisvolle verbetering aanzienlijk varieerde, hetgeen duidt op heterogeniteit in pijnverlichting en de relatie daarvan met het behandelsucces bij chronische pijnpatiënten. Het vraagt om voorzichtigheid bij de interpretatie, aangezien deze kan afhangen van de studieopzet, de pijnintensiteit of behandelstatus.

RESUMEN

La investigación de esta tesis se ha llevado a cabo para mejorar nuestra comprensión sobre la experiencia del dolor crónico, examinado desde el punto de vista de los pacientes. Además, investigamos la heterogeneidad, que se refleja en los Resultados Percibidos por los Pacientes (RPP) y la probabilidad de éxito del tratamiento. Consecuentemente, hemos analizado dos cohortes: la gran cohorte del registro del MUMC+ DATA*PAIN* y una cohorte de pacientes de dolor crónico de menor medida. Esta última, fue medida mediante el método de muestreo de experiencias. Además de las cohortes, se utilizó datos de varios ensayos controlados aleatorios realizados en el departamento de Anestesiología y Medicina del Dolor del MUMC+.
En los capítulos de esta tesis, comenzamos a crear una visión general del contexto biopsicosocial de los pacientes con dolor crónico. Posteriormente, se presenta la heterogeneidad dentro de los sexos y entre estos, cuantificado por el impacto del entorno sociocultural y además por analizar las diferencias de sexo en la asociación de miedo-evitación e intensidad del dolor. Además, se agruparon y compararon los grupos de pacientes con dolor crónico para observar diferencias en la probabilidad de éxito del tratamiento. En esta línea, el último capítulo presenta la generalización de una mejoría clínicamente importante en diferentes tipos de diseño de estudio y grupos de pacientes.

El **segundo capítulo** describe a 11.214 pacientes con dolor crónico incluidos en la cohorte del registro DATA*PAIN*. Se describieron los datos (socio)demográficos de los pacientes, las características del dolor, los valores de la calidad de vida y los valores psicológicos. Esto nos proporcionó una visión transversal de la composición media y la varianza del paciente con dolor crónico, antes de la primera consulta con el especialista. Casi el 60% de los pacientes de la cohorte del registro DATA*PAIN* eran mujeres, la tasa de desempleo era de un 36% y el nivel de estudios bajo era el más común (59%). El 72% informó de dolor severo (NRS 7-10), y cuando la gravedad del dolor aumentaba los valores psicológicos y de calidad de vida se deterioraban. Aproximadamente el 36% de los pacientes mostraba signos graves de depresión o ansiedad, y el 39% mostraba un elevado catastrofismo ante el dolor. La combinación de factores de riesgo, como el dolor severo, el catastrofismo ante el dolor y la ansiedad o la depresión, fue señalada por el 17,8% de la cohorte. Este estudio mostró consistencia con los hallazgos anteriores de la literatura, como la intensidad del dolor, que es más elevado para mujeres. Sin embargo esta tesis, no concuerda con la literatura en que las mujeres obtienen promedios más altos que los hombres en factores como el catastrofismo ante el dolor, la depresión y la ansiedad.

En el **tercer capítulo**, se investigó el impacto del entorno sociocultural en la asociación entre el sexo y los Resultados Percibidos por los Pacientes (RPP) en pacientes con dolor crónico. Las diferencias del dolor dentro de los sexos suelen ser mayores que las que existen entre los sexos. Una explicación puede ser que el entorno sociocultural genera respuestas que difieren sustancialmente para ambos sexos. El entorno sociocultural observado en este capítulo consistió en la edad (18-55 años frente a 56-96 años), la relación sentimental (tener una relación sentimental frente a no tenerla), la situación laboral (tener un trabajo remunerado frente a no tenerlo) y el nivel de estudios (nivel de estudios bajo frente a un nivel alto). Debido a la novedad del tema, primero era necesario establecer el impacto del sexo y las características socioculturales sobre los RPP' s en general. Esto se llevó a cabo aplicando regresiones lineal múltiples, con un procedimiento de eliminación retrogrado en combinación con la experiencia clínica de las especialistas, para seleccionar únicamente los determinantes independientes fuertes e importantes para cada RPP. Aquel medidas fueron: la Escala Numérica de Clasificación para el Dolor (NRS), la encuesta de salud RAND-36 subdividida en una escala mental y física para la calidad de vida, el inventario Brief Pain Inventory (BPI) subdividido en una escala afectiva y activa para la interferencia del dolor en las actividades diarias, la escala hospitalaria de ansiedad y depresión (HADS) dividida en una escala para la ansiedad y una para la depresión, y la escala del catastrofismo ante el dolor (PCS).

En general, los resultados mostraron que tanto el entorno sociocultural como el sexo se asociaron con los RPP' s, excepto el RAND-36 sobre la calidad de vida. Posteriormente, se estratificó en función del sexo para ilustrar las diferencias para ambos. En ella se observó que las posiciones sociales de los hombres influyen de forma significativamente más positiva en cómo perciben el dolor y las enfermedades asociadas. Por término medio, una mayor edad (≥ 56 años) condujo a una menor intensidad del dolor, interferencia en las actividades físicas diarias y depresión para ambos sexos. Sin embargo, este impacto positivo fue mayor para los hombres que para las mujeres. Por lo contrario, la media del catastrofismo ante el dolor aumentó en 2 puntos sólo en las mujeres de mayor edad. Estar en una relación sentimental tuvo un impacto positivo en todos los resultados reportados por los hombres. Por lo contrario, las mujeres que tenían una relación sentimental sólo tenían una media más baja en la escala afectiva del BPI. Esto significa un menor impacto en la interferencia del dolor en las actividades afectivas, como el disfrute de la vida. Tener una educación alta y un empleo remunerado, redujo los promedios de todos los resultados comunicados por los pacientes y varió en el impacto para hombres y mujeres. La razón de estas discrepancias entre los sexos sigue sin revelarse. No obstante, nuestros resultados se suman a la literatura existente al sugerir que la heterogeneidad encontrada en el dolor crónico puede explicarse en parte por las características socioculturales de los pacientes y no sólo por las características biológicas del sexo.

En el **cuarto capítulo**, en la cohorte del registro DATA*PAIN* clasificamos los pacientes con dolor crónico en dos grupos; complejos o no complejos. Los que presentaban una elevada gravedad del dolor (≥ 7 en la NRS), depresión o ansiedad moderada o grave (>10 en la escala de depresión o ansiedad de la HADS) y un elevado catastrofismo ante el dolor (>31 en la PCS) se agruparon en el grupo complejo. Se presumió que esta combinación tenía consecuencias negativas para el resultado del tratamiento, como el deterioro de la calidad de vida. Los RPP’ s observados fueron, la satisfacción con el tratamiento por la Impresión Global del Cambio del Paciente (PGIC), la NRS para el alivio del dolor, el BPI con la escala activa y afectiva para la interferencia del dolor y el indicador de calidad de vida para el estado de salud mediante la Salud General Percibida (GPH). Se analizaron los datos transversales y longitudinales de 1637 pacientes con dolor crónico, de los cuales 345 (21,08%) se consideraron complejos. Se utilizó la regresión logística para analizar si la pertenencia al grupo complejo modificaba la posibilidad de tener un tratamiento exitoso en el PGIC o un estado de salud en el GPH. También, se utilizó una regresión lineal para evaluar si el grupo complejo difería en la reducción media del alivio del dolor y de las interferencias en comparación con los pacientes no complejos.

El grupo complejo tenía una probabilidad de solo 0.59, de estar satisfecho con el tratamiento en comparación con los pacientes no complejos. La relación de probabilidades (OR) para el GPH fue de 0.28, lo que indica diferencias aún mayores. La escala afectiva del BPI vario estadísticamente significativa entre grupos, mientras el cambio en el alivio del dolor y la escala activa del BPI no fueron significativamente diferentes para los dos grupos. Los resultados de este estudio sugieren que, aunque la gravedad del dolor y los valores psicológicos eran elevados, los pacientes complejos no responden de forma diferente, al alivio del dolor en comparación con el grupo no complejo. Sin embargo, se pensó que se encontrarían mayores cifras de alivio del dolor, porque la literatura indica que cuando se subdivide el dolor al inicio en grupos de dolor severo (≥ 7 en la NRS), medio (5 - 7 en la NRS) y leve (0-5 en la NRS), se encuentra un mayor cambio en el grupo severo en comparación con el grupo medio. Esto podría indicar ,que la combinación de factores de riesgo presentes en el grupo complejo, si influyen en el alivio del dolor. Además, en el inicio de estudio, el grupo complejo muestra una elevada interferencia del dolor en las actividades activas y afectivas de la vida diaria, que sigue estando presente en el seguimiento. Esto puede deberse a la reacción cognitivo-emocional negativa al dolor en pacientes complejos, en los que los pensamientos catastróficos sobre la actividad pueden abrumar y limitar a los pacientes en las actividades diarias.

Este estudio ha proporcionado una perspectiva de éxitos plausibles en resultados clínicamente relevantes. Estos resultados sugieren que, al tratar a los pacientes complejos, el especialista y los pacientes deben reconocer los resultados deseados antes de iniciar un tratamiento, ya que es menos probable que se produzcan en los pacientes complejos y por tanto, pueden guiar la decisión del tratamiento.

En el **quinto capítulo**, se analizó con más detalle la asociación entre el miedo-evitación y la intensidad del dolor crónico, ya que en la literatura, no estaba claro si esta asociación podría depender del sexo. Además, se analizó el posible efecto de las experiencias afectivas en la asociación mismo. Un total de 45 pacientes que participaron en la cohorte con el método de muestreo de experiencias y fueron reclutados en la admisión de la cohorte del registro DATA*PAIN*. El método de muestreo de experiencias, es una técnica de diario digital estructurado para valorar las experiencias subjetivas en la vida diaria. Se utilizaron preguntas cortas de evaluación momentánea para evaluar repetidamente la intensidad del dolor de los pacientes, el nivel del miedo-evitación y el afecto positivo y negativo durante la vida diaria. Se aplicaron modelos lineales de efectos mixtos para estimar las medidas de asociación. Se realizó un modelo no ajustado y ajustado, en el que este último corrigió las experiencias afectivas estadísticamente significativas.

Hasta donde sabemos, éste fue el primer estudio que utilizó el método de muestreo de experiencias para investigar las diferencias de sexo en la asociación entre el miedo-evitación y la intensidad del dolor en pacientes con dolor crónico. Los resultados transversales demostraron que los hombres tenían de media más miedo-evitación que las mujeres. Sin embargo, los resultados de los datos longitudinales sugieren que no se encontró ninguna asociación entre el miedo-evitación y la intensidad del dolor en los hombres. Mientras que en las mujeres, un aumento del miedo-evitación se asoció con un aumento de la intensidad del dolor. Las experiencias afectivas estadísticamente significativas "relajado", "irritado" y "satisfecho", no confundieron los hallazgos mencionados. Se desconoce el por qué los pacientes masculinos con dolor crónico tienden a tener más miedo-evitación que las mujeres, pero sin relación con la intensidad del dolor. Además, aún no se sabe si los valores elevados de miedo-evitación en los hombres al inicio del estudio influyen (negativamente) en los resultados del tratamiento del dolor. Sin embargo, tener más miedo-evitación sí influye en la intensidad del dolor en las mujeres. Esto, quizás es debido a que las que tienen poco miedo-evitación son más activas, lo que posteriormente puede disminuir el dolor.

En el **sexto capítulo** se analizó una mejoría clínicamente importante para los pacientes con dolor crónico. Lo que sabemos, es que el cambio en la NRS se construye sobre una experiencia subjetiva del dolor, lo que dificulta el establecimiento de la definición de una mejoría clínicamente importante. Por lo tanto, combinando los resultados de la Impresión Global del Cambio de los Pacientes (PGIC) con la NRS (denominada método basado en anclaje) se puede determinar la mejoría clínicamente importante. Se ha demostrado que un cambio de 2 puntos en la NRS equivale a una mejoría clínicamente importante de forma moderada en los datos de los Ensayos Controlados Aleatorios (ECA), cuando se trata a pacientes con dolor crónico con medicación. En este capítulo, se evaluó si estos hallazgos podían generalizarse a los pacientes de la cohorte del registro DATA*PAIN* y a los pacientes que habían sido incluidos en ECA' s no farmacológicos de nuestro departamento de medicina del dolor del MUMC+. El cambio en la NRS, se cuantificó restando la NRS inicial, de la NRS a los 6 meses de seguimiento. La categorización de éxito/fracaso se aplicó en el PGIC, calculando los cambios brutos y porcentuales de la NRS media. Se utilizó el coeficiente de correlación de Spearman para cuantificar la relación lineal global. Además, se exploró la capacidad discriminativa del cambio de la NRS, para determinar el éxito del tratamiento percibido, mediante el área bajo la curva de características operativas del receptor. Para analizar los datos, se estratificaron según el diseño del estudio (observacional o experimental), el sexo y la intensidad del dolor al inicio del estudio, tanto para la cohorte como para los ECA' s. Simultáneamente, la cohorte se estratificó en función del estado del tratamiento durante el seguimiento (estar en tratamiento frente a finalizado).

Se examinaron los registros de 1661 pacientes con dolor crónico. En general, el cambio observado en la NRS necesario para una mejoría clínicamente importante de forma moderada, fue mayor que la media de dos puntos encontrada en la literatura. Sin embargo, los cambios medios necesarios, en los pacientes de la cohorte fueron menores en comparación con los ECA' s. Esto puede deberse, a las diferencias en el protocolo del tratamiento, o que la participación activa en un experimento aleatorio puede afectar a las expectativas. En los ECA' s, se aplicaron criterios de inclusión estrictos con intervenciones singulares, mientras una atención personalizada se proporcionó a todos los pacientes de la cohorte. Creemos que esto también puede haber influido en el cambio de la NRS y en el valor otorgado a la mejoría de la importancia clínica.

La estratificación indicó que la mejoría de la importancia clínica no es uniforme entre los grupos de intensidad del dolor al inicio del estudio. El cambio medio necesario fue mayor para el grupo de intensidad de dolor grave al inicio del estudio, que para los grupos de intensidad de dolor moderada y leve. Este hallazgo se representó tanto en la cohorte como en los ECA' s, lo que sugiere que, independientemente del diseño del estudio, una expectativa de la cantidad de reducción del dolor puede deberse a la intensidad del dolor al inicio del estudio. Además, el cambio medio de la NRS necesario, fue menor cuando el tratamiento aún estaba en curso que cuando finalizó a los 6 meses. En conjunto, estos resultados indican que la mejoría clínicamente importante varió sustancialmente, lo que representa la heterogeneidad en el alivio del dolor y su relación con el éxito del tratamiento en los pacientes con dolor crónico. Se pide precaución en la interpretación, ya que puede depender del diseño del estudio, de la NRS al inicio o del estado del tratamiento.

CHAPTER 9

IMPACT PARAGRAPH

This chapter describes how to create an impact on society by utilizing the knowledge gained from this thesis. This can be achieved by applying multiple approaches to transfer knowledge to a wide audience, not only through peer-reviewed journals, but also through conferences and presentations. Moreover, the knowledge can be taken into account by hospital services and processes in order to implant them in society. This chapter discusses a couple of options.

The prevalence of chronic pain is estimated at 18% of the Dutch population and will increase in the upcoming years due to aging.[4] The complexity of chronic pain transcends medical and therapeutic disciplines accentuating the urge of multidisciplinary care for patients. On the individual level, a decrease in physical, psychological and societal abilities reduces the quality of life.[1; 15; 16] Chronic pain negatively impacts patients and their nearby relatives, imposing financial burden on multiple levels. For example, patients show an increased use of healthcare services, but are also at risk of work incapacity, a decrease in income, and early retirement.[15] All considered, this leads to total (in)direct cost in the Netherlands alone of 20 billion euros per year, exceeding many times the cost of diabetes, heart failure and cancer combined.[14]

Clinical implications

The objective of this thesis was to improve our understanding of the way pain is experienced by chronic pain patients and to unravel the diversity present between pain patients. The results of this thesis may help healthcare professionals take more patient characteristics into account for clinical decision making. Our understanding of differences between the sexes in their experience of chronic pain improved substantially. This thesis showed consistency with earlier findings of the literature that average higher pain intensity is among women, but our thesis also showed female patients having lower averages than men for factors like pain catastrophizing, depression and anxiety, indicating better scores.[2; 5; 8] When observing sex differences in fear avoidance, we have found that men have higher scores of fear avoidance on average, yet their scores are not related to pain intensity, while the contrary happens in women: when fear avoidance increases, so does pain intensity. However, the causality between fear-avoidance and pain intensity in women needs to be established. Then, these findings may give indication that treating fear avoidance in women may help reduce pain intensity, while this may not be the case in men. Regardless of causality, men with high levels of fear-avoidance need counseling for the avoidance of activities due to the fear of pain, as fear-avoidance may lead to physical disuse and interference in daily activities. Moreover, whether high fear-avoidance in men at baseline influences (negatively) pain treatment outcomes is also unclear as of yet. Therefore, this information is of relevance to clinicians and to researchers. The implementation of these results will take place by peer reviewed publishing and by sharing the knowledge on pain conferences like the International Association for the Study of Pain in Toronto upcoming September. Moreover, presentations for pain specialist has been given on symposia like the Science Café of the department of Anesthesiology and Pain Medicine of the MUMC+. Besides, this thesis will help to disseminate these findings to a wider (lay) public, bringing fear-avoidance to the attention of the multidisciplinary team of the MUMC+ will be done by participating in the meetings set for the multidisciplinary team. There, a proposition for referral to the rehabilitation department can be made when high levels of fear avoidances are encountered in chronic pain patients.

In this thesis, the impact assessment of the socio-cultural construct (education, employment, relationship and age) on patient reported outcomes revealed in pain intensity, depression, anxiety, pain catastrophizing and pain interference. These disparities were in most cases larger for men than for women, for instance, we have shown a larger average decrease in pain intensity for men than for women, with an increase in level of education.[18] Moreover, this thesis specifies that within the chronic pain population the more vulnerable populations, like the low educated and unemployed, have a more severe pain experience than the overall chronic pain population, besides the fact of being men or women.[5; 6; 9; 13; 18] Even though the reasoning for these results remain unrevealed, this thesis suggests that the heterogeneity found in the chronic pain population may be partly explained by a patients' socio-cultural status in combination with their sex.

The clinical implication of these findings are of great importance, as these vulnerable groups may experience greater difficulties in accessing and understanding information about pain, yet as well in self-management, making health decisions and the use of the health care system, due to presence of low health literacy.[3; 7; 10; 11] In clinical practice and in pain management, attention needs to be given to this bottleneck as it can hinder treatment success. Hence, in the clinical decision making process, clinicians may emphasize the information provided to the patient.[1] Moreover, referral to supplementing services such as medical social work may help the (vulnerable) patient in their pain management and develop themselves to the fullest extent possible. Informing the chronic pain patient of these supplementary services can be achieved through clinician referral, by pamphlets in the waiting room and online advertising of the pain center website. Moreover, to give prominence to the services of the medical social workers, they will be invited to a chronic pain team meeting held every Tuesday, to inform about their services and assess which chronic pain patient can profit most.

Furthermore, this thesis shows that the pain reduction necessary to be satisfactory about an intervention varies according to study design and baseline pain intensity. Thus, it is difficult to generalize at what amount of pain relief a patient with chronic pain is satisfied with, and thus when an intervention can be labeled as successful.[19] This may even be more difficult for a fifth of the chronic pain patients attending our tertiary pain clinic that have a combination of depression or anxiety, pain catastrophizing and pain severity. These chronic pain patients have a lower chance of attaining treatment success like patient satisfaction, pain relief and a decrease in pain interference. This combination of pain symptoms that we labeled ‘complex’ should be recognized by specialist and patients before initiating treatment, as the combination of these symptoms may guide treatment decision and is therefore relevant for pain physicians, other healthcare professionals, and patients.

Dissemination of the results will be conducted by peer reviewed publishing, pain congresses like the European Pain Federation in Dublin 2022, as well, the information was shared on the Spring symposium of the department of chronic pain of the MUMC+. Moreover, this thesis will help to disseminate all the results aforementioned among chronic pain patients, families, caregivers and associations of chronic pain patients.

Pain management

The mission of chronic pain care is to pursue and ensure that as many chronic pain patients as possible are in control and retain, promote or regain ownership of their own functioning.[1] To promote this, certain transformation is necessary within pain management strategies, and this thesis provides knowledge for this change. The first feature needed is a more personalized care path, by identifying (risk) factors that a specific pain patient has. Second, care should be guided and based on the likelihood of success on patients outcomes, thus an assessment should be made of predictors of those pain outcomes and the effect of interventions. Insights into these two features can be gained by the application of a Value-based Healthcare Approach and applied as an instrument to support clinical decision making.[12; 17] Consequently, the knowledge on how pain experience differs for pain patients is of importance, like the knowledge gained in this thesis on sex differences, the impact of the socio-cultural construct and possibilities of treatment successes.

The first step in dissemination is to gather all relevant stakeholders, like patient, clinician, hospital, IT and private companies that have knowledge on the approach. With the aim to provide insight in the accessibility and performance of care by mapping clinical processes, reduce registration burden through the reuse of data (data efficiency) and expose bottlenecks that patients may experience in receiving care.

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Research under review:

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About the author

Sophie Waardenburg was born in Hilversum 1983. In 2000 she graduated high school at Morna Valley International College in Ibiza, Spain and perused two years of education in Arts. In 2009 she graduated in Osteopathy (Valencia, Spain) and in 2016 in Physiotherapy (NCOI, Netherlands). Whilst, coordinating her therapeutic clinic in Spain, she was involved in the non-profit organisation Apneef, treating people with physical and/or mental disabilities. For her physiotherapy thesis, she conducted a Delphi study with 19 international experts to reach a consensus on the characteristics and items of a questionnaire for central sensitization in headache patients. This research was supervised by Dr. Eric Bakker.

To translate knowledge of the human musculoskeletal system to scientific research, she obtained a Master in Health Science Research at the Maastricht University in the Netherlands in 2020. To extend her expertise, she pursued a PhD under supervision of Dr. Sander van Kuijk, Dr. Nelleke de Meij and promotor Pr. Dr. Jan van Zundert, at the department of Anesthesiology and Pain Medicine and the department of Clinical Epidemiology and Medical Technology Assessment (KEMTA) at Maastricht UMC+. She focused her career on chronic pain, assessing sex differences and biopsychosocial factors in the pain experience. In addition to her PhD, she is a consultant in epidemiologically related research.

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