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Relationships between Psychological Factors, Disability, Quality of Life and Health in Chronic Pain Disorders

Björn Börsbo

Linköping University
FACULTY OF HEALTH SCIENCES

Rehabilitation Medicine, Department of Clinical and Experimental Medicine,
Faculty of Health Sciences
Linköping University, SE-581 85 Sweden

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To my mother Karin

CONTENTS

ABSTRACT

Chronic pain is a very common condition with a prevalence of 40-65% in the community. The high prevalence of chronic pain causes a lot of human suffering but also high societal costs. The development and maintenance of chronic pain constitutes a complex interplay between neurobiological, psychosocial and genetic factors. A biopsychosocial model of chronic pain has been suggested to make a comprehensive context of the understanding of this issue.

The main aims of this thesis were to analyze the relationships of the different components of the biopsychosocial model of pain and to study the relative importance of pain, stress and different psychological factors on disability and health related quality of life.

The thesis is based on two groups of patients. One group consists of 275 patients with chronic Whiplash Associated Disorder (WAD) and one group comprise 433 patients with WAD, fibromyalgia (FM) and patients with chronic pain related to Spinal Cord Injury (SCI). The patients were investigated by questionnaires assessing different aspects of pain, depression, anxiety, catastrophizing, self-efficacy, disability and Health Related Quality of Life (HRQL).

The main results were that psychological factors (especially depression) correlated relatively strongly with perceived HRQL and disability. The degree of depression appeared to have the most important relationship to perceived HRQL. Despite the fact that the patients rated depression just mild or moderate, depression had a great importance for the outcome of HQRL and disability. Pain intensity and duration played, in the cross-sectional perspective, a minor role for perceived HRQL, whereas pain intensity related more to the outcome of perceived disability.

From a clinical point of view it is important to assess the complex and unique situation of each individual with respect to depression, anxiety, self-efficacy and pain when planning treatment and rehabilitation in order to optimise the outcome of such programmes.

ABBREVIATIONS

ASES	Arthritis self-efficacy scale
ASI	Anxiety Sensitivity Index
BDI	Beck Depression Inventory
CNS	Central Nervous System
CSQ	Coping Strategy Questionnaire
FM	Fibromyalgia
HADS	Hospital Anxiety and Depression Scale
HRQL	Health Related Quality of Life
ICF	International Classification of Functioning, Disability and Health
LiSat-11	Life Satisfaction Questionnaire
MRI	Magnetic Resonance Imaging
NPSI	Non Pain Symptoms Index
PASS-20	Pain Anxiety Symptoms Scale-20
PCA	Principal Component Analysis
PCS	Pain Catastrophizing Scale
PDI	Pain Disability Index
PLS	Partial Least Squares by means of Projection to Latent Structures
PRI	Pain Regions Index
QOLS-S	Quality of Life Scale
SCI	Spinal Cord Injury
VAS	Visual Analogue Scale
VIP	Variable Influence on Projection
WAD	Whiplash Associated Disorders

ORIGINAL PAPERS

The thesis is based on the following studies, which will be referred to by their roman numerals:

I. Peolsson M, Börsbo B, Gerdle B. Generalized pain is associated with more negative consequences than local or regional pain: a study of chronic whiplash-associated disorders. J Rehabil Med. 2007 Apr;39(3):260-8.

II. Börsbo B, Peolsson M, Gerdle B. Catastrophizing, depression, and pain – correlations and influences on quality of life and health: A Study of Chronic Whiplash Associated Disorders (WAD). J Rehabil Med. 2008; 40: 562-569.

III. Börsbo B, Peolsson M, Gerdle B. The complex interplay between pain intensity, depression, anxiety and catastrophizing with respect to quality of life and disability (Submitted to Disability and Rehabilitation).

IV. Börsbo B, Gerdle B, Peolsson M. Impact of the interaction between self-efficacy, symptoms and catastrophizing on disability, quality of life and health in chronic pain patients (Manuscript).

INTRODUCTION

Defining chronic pain

The established definition of pain according to IASP (International Association for the Study of Pain) is: '*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'*. It is noteworthy that pain is always subjective which makes is unquestionable but also limits our ability to assess it with objective methods. It is a sensation in a part or parts of the body, but it is also always unpleasant and therefore as well an emotional experience.

Chronic pain is in turn defined as pains persisting over a certain period of time; often 3 or alternatively 6 month are pragmatically used. The patients studied in this thesis, all qualified by far to be classified as patients with chronic pain.

The extent of the chronic pain problem.

Many studies of the prevalence of chronic pain in the population show that chronic pain is a very common condition. Studies from Sweden found a prevalence of 40 – 65% [1-3] and studies from Great Britain a prevalence of 47 – 51% [4,5].

This high prevalence of chronic pain causes a lot of human suffering but also large society cost. In a Swedish report, the total society cost in Sweden for more serious chronic pain (50-100 mm on the VAS scale) were calculated to 85 billons SEK the year 2003 of which 7% were direct costs for medical care [6].

The Biopsychosocial model of pain

The biopsychosocial approach is now widely accepted as a heuristic perspective to the understanding of chronic pain disorders. The biopsychosocial model of pain, illustrated in **Figure 2,** views physical illnesses such as pain as the result of the dynamic interaction among physiologic, psychological, and social factors, which perpetuates and may even worsen the clinical presentations. Each individual experiences pain uniquely, and a range of psychological and socioeconomic factors can interact with physical pathology to modulate a patient's report of symptoms and subsequent disability [7]. In this thesis the biopsychosocial model of pain is used as a structure when planning the investigations and interpreting the results of the studies. The biopsychosocial model of pain can be regarded as a structure that can comprise and include different models and theories. E.g. gate control theory [8], neuromatrix, the diathesis stress model, ICF and fear avoidance [9]. The biopsychosocial model also includes environmental factors, such as social support, which are of great importance for the individual patients concerning perceived pain and the influence of its consequences [10]. The environmental perspective is however not further investigated in this thesis. The terms *theory* and *model* are used in this thesis as they were originally labelled in the literature.

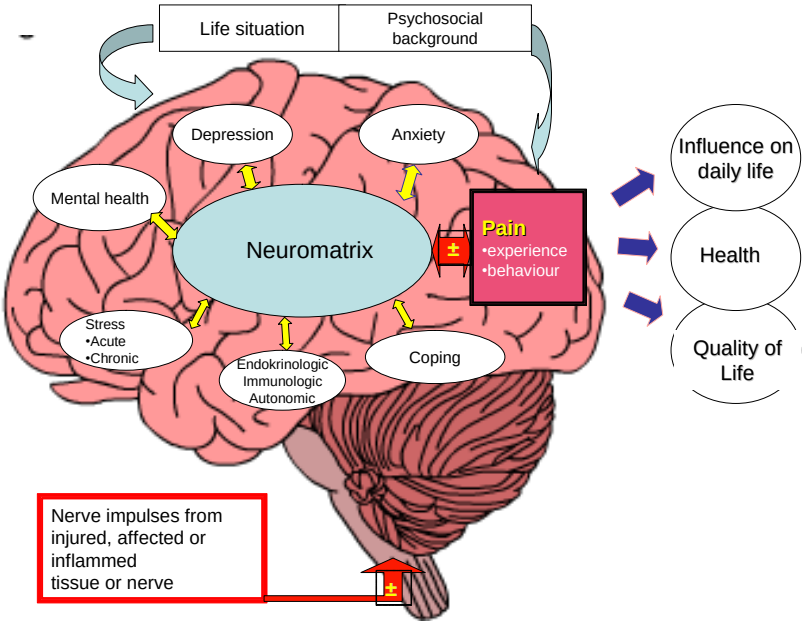

Figure 2: Diagram illustrating the biopsychosocial model of pain.

The neurobiology of chronic pain

The neurobiological systems of nociception and pain are plastic; i.e. when submitted to significant nociception, the function may change in different ways [11]. Chronic pain is a process where both the peripheral and the central nervous system develop an increased sensitivity for different sensory signals (sensitization). Earlier non painful stimuli become painful (allodynia) and/or painful signals are perceived as more painful (hyperalgesia). In acute pain, sensitization is a normal process protecting against more damage. Under certain circumstances this protective mechanism may be over activated and prolonged, i.e. a pathological and noxious sensitization [12]. Several neurobiological processes are involved in the sensitization. In the peripheral nervous system, the nociceptors become more sensitive by pain mediating and pain modulating substances which leads to *peripheral sensitization* [13]. In the central nervous system several different processes interact to create the *central sensitization.* Repetitive stimulation of Aδ-fibers leads to a gradual increase of the nerve cell activity in secondary neurons in the dorsal horn of the spinal cord, called *'Wind up'* [14]. In *heterosynaptic central sensitization*, silent synapses are opened leading to pain produced by low-threshold afferent inputs and the spread of hypersensitivity to regions beyond injured tissue [15]. *Long Term Potentiation* is coincident activity of pre- and post-synaptic elements, bringing about a facilitation of excitatory input to the dorsal horn and is triggered by short high frequented nociceptiv input [16,17]. There are both inhibitory and facilitating *descending pathways* for controlling pain transmission [18]. An altered balance between those two can lead to a net facilitation of pain transmission. For an

overview of pain transmission and modulation se **Figure 1.** This diagram concentrates on the modulation of pain. The pain transmission is far more complicated and includes several other systems and pathways.

Neuromatrix

The neuromatrix theory of pain [19] proposes that pain is a multidimensional experience produced by characteristic 'neurosignature' patterns of nerve impulses generated by a widely distributed neural network—the 'body-self neuromatrix'—in the brain. These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them. Pain is produced by the output of a widely distributed neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology.

The neuromatrix, which is genetically determined and modified by sensory experience, is the primary mechanism that generates the neural pattern that produces pain. Its output pattern is determined by multiple influences, of which the somatic sensory input is only a part, that converge on the neuromatrix [20].

Stress and somatic symptoms

Acute pain activates the HPA (Hypothalamus, Pituary, Adrenal) axis and the sympathetic nerve system. This activation affects the renal and intestinal function as well as the cardiovascular and immune system [21]. Chronic pain is a stressor that will tax the stress system and this prolonged activation of the stress regulation system will ultimately generate breakdowns of muscle, bone, and neural tissue that, in turn, will cause major pain and produce a vicious cycle of pain–stress–reactivity [22].

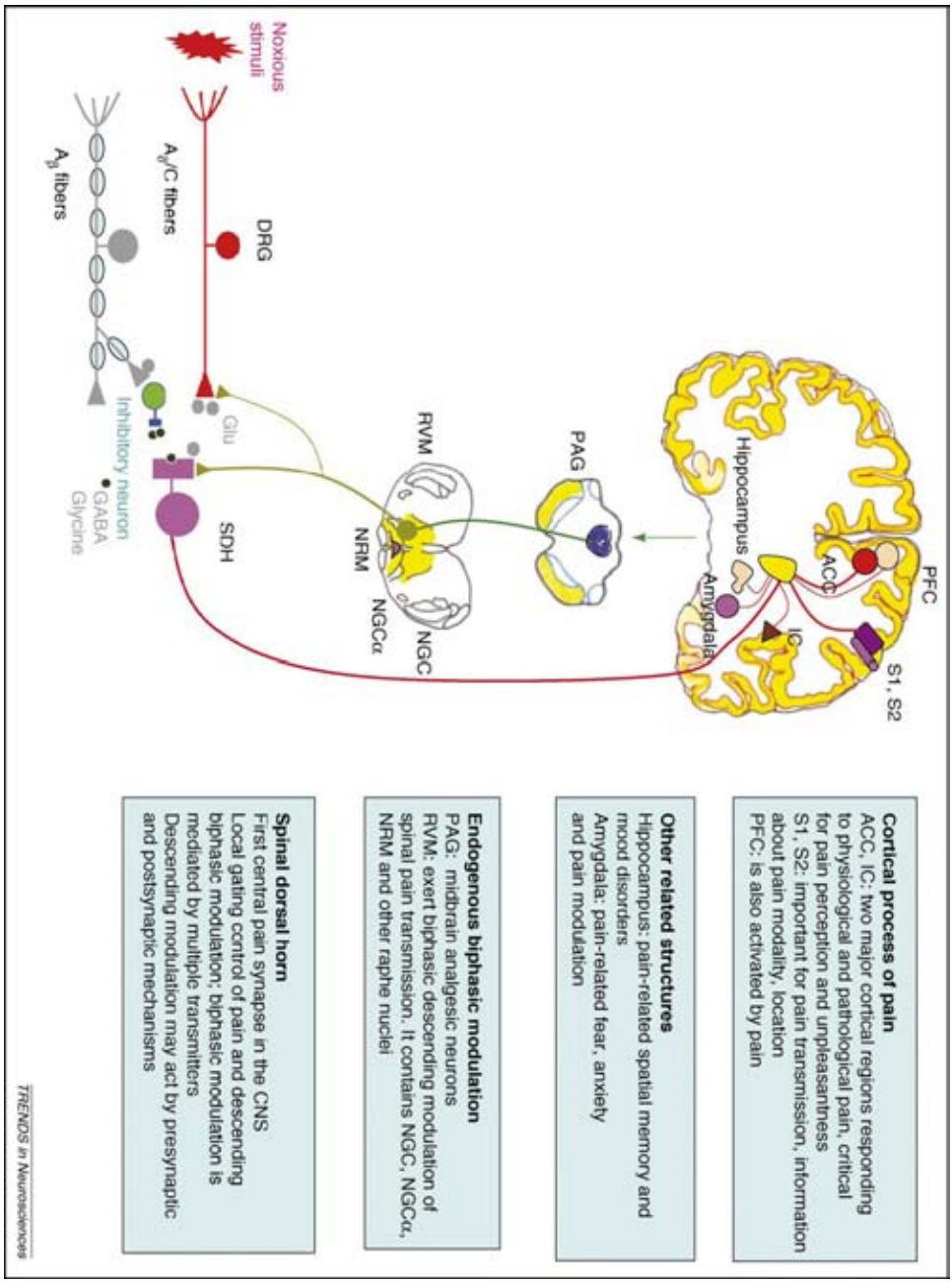

Figure 1. Diagram showing pain transmission and modulation pathways in the central nervous system. (Reprinted from Trends in Neurosciences, Vol. 31(4), Zhou M, Cortical excitation and chronic pain, Page 201, 2008 [23] with permission from Elsevier.)

ICF

It is important to set chronic pain and persons suffering from it into a larger context than the individual perspective. For this purpose the *International classification of functioning, disability and health (ICF)* constitutes a useful tool [24]. ICF offers an integrated biopsychosocial model of human functioning and disability and provides a classification system handling several aspects of health and disability. The structure of ICF contains several levels and parts. **Figure 3** shows the different levels and parts of the structure. Psychological and physiological functions are included in the component *Bodily Function and Structures.*

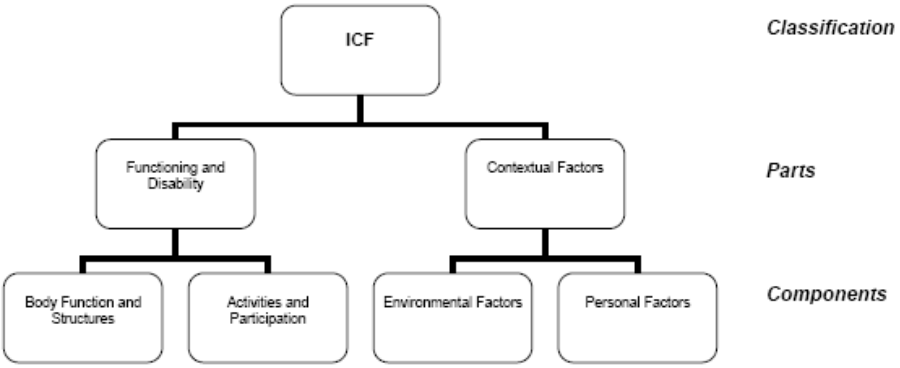

Figure 3. Structure of ICF.

The components in ICF interact with each other **(Figure 4)**. If one component is affected it may modify another component or the health disorder. If body functions and structures are affected, this is referred to as impairment. The reduction of activities is called *activity limitation* and in participation, a *participation restriction*. *Functioning* serves as a sum up term including, body functions, activities and participation. The negative aspect of functioning is *disability* and includes impairments, activity limitations and participation restrictions. If placing a chronic pain disorder as a *health condition* in the diagram, it illustrates clearly the great impact on and the great impact of the different components expressing health and disability, including environmental factors. Further, the concept of ICF fits well with the Biopsychosocial model of pain described earlier.

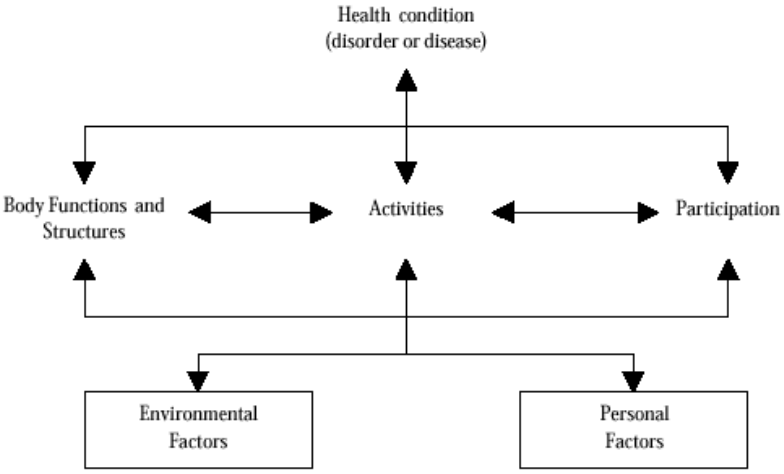

Figure 4. Interactions between the components of ICF.

The diathesis-stress model

There are several models and theories, including psychological factors, describing a theoretical framework of the development and maintenance of chronic pain and chronic pain conditions. In this thesis there are several references to the *diathesis-stress model*. This model was first proposed by Gatchel [25] and developed by Banks and Kerns [26] to describe the relationship between chronic pain and depression. The diatheses are conceptualized as pre-existing, semi dormant characteristics of the individual before the onset of chronic pain that are then activated by the stress of this chronic condition. The stress component of the model refers to the nature of the chronic pain experience. Banks and Kerns suggest that chronic pain is more likely to result in depression than other chronic medical conditions because of the uniquely challenging nature of stressors associated with chronic pain. These stressors include the aversive sensory and distressful emotional aspects of the pain symptoms, impairment and disability, secondary losses that occur across various domains, and perceived invalidating responses from the medical system.

Pincus and Williams [27] describe the model in a way in which the different components are connected by circular loops and some of the connections are of more importance or have stronger effects than others. Thus, diathesis combines with a primary stressor to produce concurrently a state of emotional distress and disability. The effect of diathesis is to increase perception of pain and enhance distress. Pain and distress affect illness behaviour and increase disability. At this stage disability becomes a stressor in its own right **(Figure 5).**

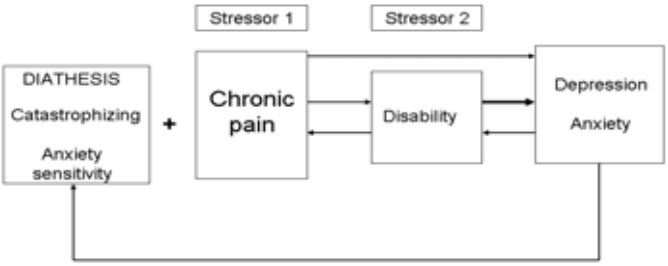

Figure 5. The diathesis-stress model with proposed diatheses and negative affect. (Modified from Pincus and Williams [27]).

The diathesis-stress model is often combined with a epidemiological risk-buffer model or a proactive agentic model. Hence, protective factors, such as self-efficacy can *buffer* the adverse effects of stressors or act as a factor for *proactive shaping* of life circumstances [28].

The chronic pain conditions included in this thesis

Whiplash Associated Disorders (WAD)
A whiplash injury is an injury caused by a whiplash trauma. This trauma implies a strain on the structures of head and neck when a acceleration-deceleration movement transfers forces to those structures without a direct trauma to the head and neck. The majority of subjects with acute WAD will be cured within three months after the trauma [29], but for a minority, the acute neck pain may develop into a chronic pain condition. The prevalence of chronic pain in the community as a consequence of whiplash trauma has been estimated to 1-1.5% [30,31].

Fibromyalgia
Fibromyalgia (FM) is a subgroup of chronic generalized pain disorders. It is diagnosed according to the criteria proposed by American Collage of Rheumatology (ACR) [32]. Long term multifocal muscle pain and widespread allodynia, mainly pressure allodynia, are compulsory symptoms. The prevalence in the population is suggested to 2-4% [33].

Chronic pain associated to Spinal Cord Injury
Chronic pain is an important problem following Spinal Cord Injury (SCI). The reported prevalence varies but averages 65% with around one third rating their pain as severe [34]. A number of specific types of SCI pain can be distinguished based on descriptors, location and response to treatment [34]. Nociceptiv pain can arise from musculoskeletal structures and viscera and neuropathic pain can arise from spinal cord and nerve damage. About 50% of the pain is considered to be neuropathic pain.

Psychological factors related to chronic pain

Depression
The prevalence of depression in the general population is estimated to 4-10% [35]. Depression is not simply a comorbid condition but interacts with chronic pain to increase morbidity and mortality. High frequencies of depressive symptoms e.g. 34.8% in FM, have been found in patients with chronic pain [26,36]. Depressed chronic pain patients report greater pain intensity, greater interference from pain, more pain behaviours, less life control, and more use of passive/avoidance coping strategies than chronic pain patients without depression [37,38]. The temporal relationship between chronic pain and depression is under debate. Fishbain et al. [39] found strong support for the consequence hypothesis: depression is a consequence that follows the development of pain. To describe the relationship between chronic pain and depression, Banks and Kerns [26] suggested a diathesis-stress-model where the diathesis is described as pre-existing, semi-dormant characteristics of the individual before the onset of chronic pain. These characteristics are activated by the stress of the chronic condition and may lead to depression. Qualitative differences between depression as a result of chronic pain and depression as a primary psychiatric disorder have been reported [39,40]. Pincus and Morley suggest that "affective distress", which incorporates wider emotions such as anger, frustration, fear, and sadness, is a better term than depression [41]. Depression is a predictor of disability in chronic pain patients in long-time follow-up studies [7]. There is also a relationship between depression and poorer self-reported functional activity among persons with chronic pain [42].

Anxiety
The prevalence of anxiety disorders in the general population is estimated to 12-17% [43]. *Anxiety* is a co-morbidity to chronic pain with incidence rates between about 15 and 40% [44], co-morbidity also exist between mood and anxiety disorders [45,46]. Several studies have found pain conditions being more strongly associated with several anxiety disorders than with depression [47,48]. Patients with anxiety disorders reported the highest pain intensity and interference and the lowest general activity level in fibromyalgia [36].

Pain related anxiety includes physiological, cognitive, behavioural and affective manifestations of anxiety within the context of pain [49]. Heightened levels of anxiety about pain are believed to contribute to avoidance of activities that are perceived to promote pain, which in turn, often lead to physical deconditioning, secondary behavioural problems and reduced social contact [50]. This pattern of responding is likely to become cyclic in nature, such that emotional responsivity and physical deconditioning lead to greater levels of pain, behavioural

interference, perceived lack of control over life activities and affective distress [51,52]. In this model, anxiety about pain is a critical psychological factor involved with the production of maladaptive responding, behavioural interference, and emotional distress.

Anxiety sensitivity is the fear of arousal-related bodily sensations arising from beliefs that these sensations have harmful consequences, a catastrophically misinterpretation [52,53]. Anxiety sensitivity has been closely associated with negative pain experiences in acute and chronic settings [54,55].

Catastrophizing
Catastrophizing has broadly been defined as an exaggerated negative orientation toward pain stimuli and pain experience [56]. Studies have indentified relationships between catastrophizing and psychological distress [57], physical functioning and disability [58], ratings of pain intensity [59], interference with life activities [60], psychosocial dysfunction [61] and quality of life [62]. Knowledge about whether catastrophizing is a cause or a consequence of chronic pain is still lacking [63]. Studies that can be interpreted in either of these directions do however exist [56,64-67].

Self-efficacy
Perceived self-efficacy is defined as people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives [68]. Self-efficacy beliefs regulate human functioning through cognitive, motivational, affective, and decisional processes [69]. These beliefs affect whether individuals think in self-enhancing or self-debilitating ways, how well they motivate themselves and persevere in the face of difficulties, the quality of their emotional life, and vulnerability to stress and depression. Research verifies the predictive generality of efficacy beliefs as significant contributors to the quality of human functioning [28]. People with a high sense of coping efficacy adopt strategies and courses of action designed to change hazardous environments to benign ones. In this mode of affect regulation, efficacy beliefs alleviate stress and anxiety by enabling individuals to mobilize and sustain coping efforts. Self-efficacy operates as a cognitive regulator of stress and anxiety arousal [70].

Several studies have noted that high scores on self-efficacy are inversely related to pain intensity. This is relevant for different pain conditions such as arthritis [71], musculoskeletal pain [72], cancer pain [73], headache [74], pain in SCI [75], and other chronic pain [76]. Self-efficacy is also inversely connected to depression [77,78] and is a good predictor for pain-related disability [79,80].

Quality of Life and Health
There are several and still evolving definitions of quality of life, health and life satisfaction. It is beyond the scope of this thesis to evaluate and elaborate on those definitions. In the following is accounted for the concepts used in this thesis.

Revicki et al [81] define QOL as '*a broad range of human experiences related to one's overall well-being. It implies value based on subjective functioning in comparison with personal expectations and is defined by subjective experiences,*

states and perceptions. Quality of life, by its very natures, is idiosyncratic to the individual, but intuitively meaningful and understandable to most people' (p. 888). This definition denotes a meaning for QOL that transcends health, and it can be argued that "health" can be included in this definition. Health related Quality of Life (HRQL) is denoted as the subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being [82]. Life satisfaction is often measured within the same domains as QOL, but with the distinction that this concept focuses on the individual's perception of the difference between the subjective reality and needs or wants. Those types of instruments can therefore be considered to be associated with of the HRQL family of instruments [83].

In this thesis all instruments measuring QOL (SF-36, EuroQol, LiSat-11, and QOLS) are used on patients with a chronic health condition, and are therefore considered to evaluate Health Related Quality of Life and in a broader sense the aspect of health. The concept general health is used when evaluating the subscale "general health" in SF-36.

Conclusions of the introduction

There are a great number of studies addressing the importance of isolated psychological factors in chronic pain [77,84] but a much lesser number of studies investigating the interrelationship with psychological factors and pain variables and there relative importance on different outcome variables. Based on the literature it is reasonable to expect that patients with e.g. high pain intensity [85], depression [86] and catastrophizing [62] will perceive health and quality of life considerably worse than those patients rating their situations with respect to these three factors better. Using e.g. certain regression techniques the *mean* influences of these three factors upon health and quality of life can theoretically be determined at group level for each outcome variable separately. However, the clinical question might be more complex; e.g., is the effect of high catastrophizing with respect to health and quality of life similar when e.g. pain intensity is high or low? Or is it from a treatment or rehabilitation perspective important to intervene against high catastrophizing regardless of pain intensity in patients with chronic pain?

AIMS OF THE THESIS

The *overall aims* of this thesis were:

- To analyze how different components of the bio- psycho- social model of pain interacts.
- To study the relative importance of pain, stress and different psychological factors on daily life, disability, health, life satisfaction and quality of life.
- To, from the above mentioned aspects, compare chronic pain conditions of different origin and character.

Specific aims of the different studies where:

Study I

This study was made to answer the following questions:

- Does chronic WAD with widespread pain have more severe consequences with respect to other symptoms, coping strategies, and different aspects of perceived health than chronic WAD patients with local/regional pain?
- Do pain, depression, and not directly pain related symptoms intercorrelate and to what extent do these symptoms correlate with catastrophizing?

Study II

- To classify subgroups according to the degree of pain intensity, depression, and catastrophizing and to investigate the distribution in a group of chronic WAD patients.
- To investigate how these subgroups were distributed and interrelated multivariately with respect to consequences such as health and quality of life outcome measures.

Study III

- To identify subgroups based on the occurrence of depression, anxiety, catastrophizing and the degree of pain intensity and duration and
- To investigate how the subgroups differed with respect to background variables, diagnosis, pain related disability and perceived quality of life.

Study IV

To investigate the interaction between self-efficacy, including subcomponents, and symptoms (pain, depression, and anxiety), catastrophizing, disability, quality of life and health in a population of chronic pain patients.

SUBJECTS AND METHODS

Subjects

This thesis is based on two different groups of patients with chronic pain.

Group 1 (Study I and II)
All patients came from the consecutive flow of patients seeking care at the Pain and Rehabilitation Centre of the University Hospital, Linköping, Sweden and this cross-sectional study is based on 275 patients. Patients fulfilling the criteria of WAD grades II or III according to the Quebec classification [29], were included in the study. Clinical examination and case history established diagnoses of chronic WAD. Radiological evaluation (X-ray, MRI) was only performed when there was a suspicion of skeletal damage or disc herniation.

Group 2 (Study III and IV)
891 patients at the clinical rehabilitation departments at Linköping University Hospital and County Hospital Ryhov in Jönköping from 2002 through 2004 were invited to participate. The inclusion criteria were chronic pain (>3 month), and one of the following diagnoses: Spinal Cord Injury (SCI) related pain, Fibromyalgia (FM), and Chronic Whiplash Associated Disorders (WAD). The patients were selected from the medical records. The diagnoses, settled by experienced clinicians, where obtained from the medical records. Patients with double diagnoses were excluded.

Out of 891 invited patients, we received 434 returned questionnaires after two reminders. One patient did not satisfy the inclusion criteria and was excluded. Thus a total of 433 patients – covering 47 patients with SCI-related pain, 150 with WAD, and 236 with FM – constituted the data material in the second study group.

Methods

Data collection

Group 1
Each patient received a questionnaire shortly before the examination at the centre. The questionnaire was completed at home and was delivered to the physician at the visit to the centre. The questionnaire contained the following items and instruments:

- Age, gender, and background data.
- Number of days on sick-leave during the previous12 months, number of months out of occupation, degree of sick leave (0%, 25%, 50%, 75%, or 100%), degree of disability pension (0%, 25%, 50%, 75% or 100%), and number of visits to physician in the recent 6 months.
- ***Pain intensity ratings*** at 11 predefined anatomical regions. For the rating of pain intensity, a visual analogue scale (VAS) was used; the scale was a 100 mm long with defined end points (‘no pain’ and ‘worst pain imaginable’) but

without marks in between (results in cm). All the questions regarding pain concerned the previous 7 days [87,88].

- ***Pain Regions Index (PRI)***. Number of the above pre-defined anatomical regions associated with pain with a possible range of 0-11.

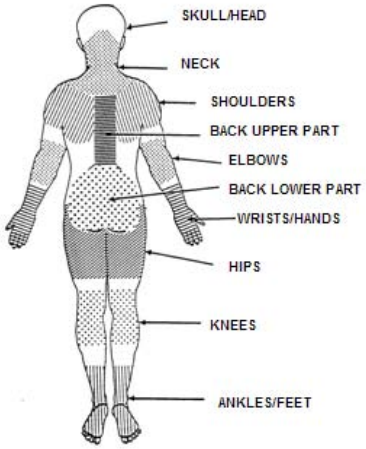

Figure 6. Diagram shown in the questionnaire, to define the anatomical regions

- Presence of other pain related symptoms: radiating pain to the arm(s), radiating pain to the leg(s), headache, perception of heavy head and pain in the throat. For each of these symptoms, the patients chose among the following alternatives: 0 = 'no, never'; 1 = 'no, seldom'; 2 = 'yes, occasionally'; 3 = 'yes, often'. In the analyses and tables these symptoms were dichotomised (0-2 versus 3).
- The ***Beck Depression Inventory* (*BDI*)** evaluates 21 symptoms of depression into a scale ranging between 0 to 63. Scores of less than 10 indicate no or minimal depression, 10-18 indicate mild to moderate depression, 19-29 indicate moderate to severe depression, and scores of 30 or more indicate severe depression. For psychiatric patients, a screening cut-point of 12/13 is suitable, whereas 9/10 is appropriate in screening medical patients (used in the present study) [89].
- Thirty-one different ***symptoms - not directly pain related*** - were registered: sleeping difficulties, tachycardia, bowel problems, gastritis, fatigue-tiredness, weak voice, nausea, anxiousness, difficulties with changes in light intensity, concentration problems, hoarseness, difficulties with swallowing, difficulties with urinating, vertigo, numbness in hands, changed perception hands, blurred vision, defecation problems, sound sensitivity, changes in alcohol sensitivity, light sensitivity, feeling of fullness of ear, irritable, memory problem, diminished field of sight, low mood, changed perception of touch legs, difficulties with control of legs, fatigue in legs, twitches in the legs, and difficulties walking down in stairs. For each symptom the patients chose among the following alternatives: 0 = 'no, never'; 1 = 'no, seldom'; 2 = 'yes,

occasionally'; 3 = 'yes, often'. In the analyses and tables, these symptoms were dichotomised (0-2 versus 3).

- ***Non Pain Symptoms index (NPSI)*** An index that counted the number of the above not directly pain related 31 symptoms (in the dichotomized form) was also computed with a possible range: 0-31).
- ***Coping Strategy Questionnaire* (*CSQ*)** is frequently used to measure how patients cope with pain and includes eight types of coping strategies with the aim to describe how patients cope with pain. These coping strategies are diverting attention, re-interpreting pain sensation, coping self-statements, ignoring pain sensations, praying and hoping, catastrophizing, increased behavioural activities, and pain behaviour. Each strategy is evaluated according to its frequency of use, ranging from never (0) to always (6) with a maximum score of 36. Two additional questions concern the perception of control and possibility to minimize pain (not used in the present study). The Swedish version of the Coping Strategy Questionnaire (CSQ)was used in the present study [90].
- ***Life Satisfaction Questionnaire* (*LiSat-11)*** consisted of estimations of life satisfaction in general as well as 10 specific domains to be estimated: satisfaction with vocational situation, financial situation, leisure situation, contact with friends and acquaintance, sexual life, ADL, family life, and partnership. Two additional variables were added to this list – satisfaction with physical and psychological health. Each item has six possible answers: 1 = very dissatisfying; 2 = dissatisfying; 3 = fairly dissatisfying; 4 = fairly satisfying; 5 = satisfying; 6 = very satisfying [91].
- ***SF-36 Health Survey*** (Swedish version) is an instrument that intends to represent multi-dimensional health concepts and measurements of the full range of health states, including levels of well-being and personal evaluations of health. The instrument covers 36 questions covering 8 dimensions: physical functioning (SF 36pf), role limitations due to physical functioning (SF 36rp), bodily pain (SF 36bp), general health (SF 36gh), vitality (SF 36vit), social functioning (SF 36sf), role limitations due to emotional problems (SF 36re), and mental health (SF 36mh). Each item score is coded, summed, and transformed to a standardized scale calculated from a specific score algorithm (ranging from 0 – 100 with two end points identified as "worst" and "best" possible health state. The transformed score has been used in this study [92].
- ***EuroQol*** instrument captures a patient's perceived state of health. A state of health is defined as combinations of five dimensions and three levels of choice (no problems, some problems, or severe problems) for each dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This descriptive system covers the first part of the instrument. The answers are coded (1-3). The codings are transformed by a table or by using an algorithm to score the findings (EQ-5D). A second part concerns a self-estimation of today's health according to a 100-point scale, a 'thermometer' (EQ-VAS) with defined end points (high value indicates good health and low value indicates bad health). Thus the two parts comprise different aspects related to health as quality of life. In this study the total score (EQ-5D) and the self-estimation scale (EQ-VAS) are reported [93].

Group 2

The patients were asked by a letter to participate and the patients who chose to participate received a postal questionnaire covering background data, psychological and health-related items. Patients who did not return the questionnaire were reminded twice before they were indicated as dropouts. The questionnaire included the following items and instruments. Swedish validated versions were used; references given below present the questionnaires and studies of psychometrical properties:

- Age, gender and background data
- ***Pain intensity ratings*** of 9 predefined anatomical regions. For the rating of pain intensity, a visual analogue scale (VAS) was used; the scale was a 100 mm long with defined end points ("no pain" and "worst pain imaginable"), but without marks in between (results in cm). All the questions regarding pain concerned the previous 7 days. The rating of the most painful region was used (VAS-max) [87,88].
- ***Pain Regions Index (PRI)***. Number of the above pre-defined anatomical regions associated with pain with a possible range of 0-9.
- ***Anxiety Sensitivity Index (ASI)*** is a 16-item self-reported questionnaire. Each item asks about the amount of fear the participant experiences in regard to bodily sensations commonly associated with anxiety. Participants are asked to rate each item on a 5-point Likert-like scale ranging from *very little* (0) to *very much* (4). The ratings on the 16 items are summed for a total ranging from 0 to 64. Studies have found support for test-retest reliability, criterion validity and construct validity (e.g., support for the distinction between AS and trait anxiety) [53,94].
- ***Pain Anxiety Symptoms Scale-20 (PASS-20)*** is a short version of the 40-item PASS that measures fear and anxiety responses specific to pain. The PASS-20 has four 5-item subscales that measure Avoidance, Fearful thinking, Cognitive anxiety and Physiological Responses to Pain. Participants rate each item on a 6-point scale ranging from *never* (0) to *always* (5). Reliability analyses with PASS-20 indicate good internal consistency akin to the PASS-40. Psychometric analyses reveal good convergent, discriminant, predictive and construct validity [95,96].
- ***Hospital Anxiety and Depression Scale (HADS)*** is a self-rating scale in which the severity of anxiety and depression is rated on a 4-point scale. Seven questions are related to anxiety and seven to depression, both with a score range of 0–21. A score of 7 or less indicates a non-case, a score of 8–10 a doubtful case, and 11 or more a definite case. The instrument is widely used in clinical practice and research. Investigations have shown that the HADS is a psychometrically sound instrument. In this study, we used both subscales [97,98].
- ***The Pain Catastrophizing Scale (PCS)*** is a 13-item self-report measure designed to assess catastrophic thoughts or feelings accompanying the experience of pain. Respondents are asked to reflect on past painful experiences and to indicate the degree to which each of the 13 thoughts or feelings are experienced when in pain. The questionnaire uses a 5-point scale ranging from 0 (not at all) to 4 (all the time). Subscales for rumination, magnification and helplessness plus a total score are added up. In this study, we used the total score [56,99].

- ***Quality of Life Scale (QOLS-S)*** is composed of 16 items that together describe the quality of life concept: (i) Material comforts; (ii) Health; (iii) Relationships with parents, sibling and other relatives; (iv) Having and rearing children; (v) Close relationships with spouse or significant others; (vi) Close friends; (vii) Helping and encouraging others, participating in organizations, volunteering; (viii) Participating in political organizations or public affairs; (ix) Learning; (x) Understanding yourself; (xi) Work; (xii) Expressing yourself creatively; (xiii) Socializing; (xiv) Reading, music or watching entertainment; (xv) Participating in active recreation; and (xvi) Independence, being able to do things for yourself. A seven-point satisfaction scale is used. Clients estimated their satisfaction with their current situation. A higher total score shows higher satisfaction. The item scores are added to a total score, ranging from 16 to 112 [100-103].
- ***SF-36 Health Survey*** (Swedish version) see group 1.
- ***The Pain Disability Index (PDI)*** is a 7-item self-report instrument based on a 10-point scale that assesses perception of the specific impact of pain on disability that may preclude normal or desired performance of a wide range of functions, such as family and social activities, sex, work, life-support (sleeping, breathing, eating), and daily living activities. The PDI has shown good reliability and validity in several studies [72,104].
- ***The arthritis self-efficacy scale (ASES)*** is a standardized questionnaire with 20 items which measure an individual's perceived self-efficacy to cope with the consequences of chronic arthritis. In this study a validated Swedish version for chronic pain was used. The only modification made was to change the words ´arthritis pain' and 'arthritis' to 'pain'. The first five-item subscale assesses self-efficacy perception for controlling pain (SE-pain). The second nine-item subscale assesses self-efficacy for performing functions in daily living (SE-function). The six-item subscale measures self-efficacy for controlling other symptoms related to chronic pain (SE-symptom). Each question is followed by a scale for, marking the answer, from 10 to 100. Each subscale is scored separately, by taking the mean of the subscale items [105,106].

Table 1: Summary of variables and instruments used in the different studies.

		Study I	Study II	Study III	Study IV
Variables	***Items/Instrument***				
Pain	VAS	**x**	**x**	**x**	**x**
	Pain duration			**x**	**x**
	PRI	**x**		**x**	**x**
Symptoms	NPSI	**x**			
Depression	BDI	**x**	**x**		
	HADS-D			**x**	**x**
Anxiety	HADS-A			**x**	**x**
	PASS-20			**x**	**x**
	ASI			**x**	**x**
Catastrophizing	CSQ	**x**	**x**		
	PCS			**x**	**x**
Self-efficacy	ASES				**x**
Quality of Life	LiSat-11	**x**	**x**		
	EuroQol	**x**	**x**		
	QOLS-S			**x**	**x**
Health	SF-36	**x**	**x**	**x**	**x**
Disability	PDI			**x**	**x**

Statistical analyses

All statistical evaluations were made using the statistical packages SPSS (versions 12.0 and 15.0) and SIMCA-P+ (versions 10.2 and 11.1). Results in text and tables are generally given as mean values ± one standard deviation (±1SD). In all statistic analyses, $p \leq 0.05$ was regarded as significant. The statistical analyses used in the different studies are given in **Table 2.**

Table 2. Statistical analyses used in studies I-IV.
ANOVA = Analysis of variance; PCA = Principal Component Analysis. PLS = Partial Least Squares by means of Projection to Latent Structures.

Methods/Study	Study I	Study II	Study III	Study IV
Krauskal-Wallis	**x**			
Mann Whitney	**x**			
Spearman´s rho	**x**			
Chi^2	**x**	**x**	**x**	
ANOVA		**x**	**x**	
Cluster analysis			**x**	
PCA	**x**	**x**	**x**	**x**
PLS	**x**	**x**	**x**	**x**

Multivariate analyses

Multivariate projection analyses were made using the software SIMCA P+ 11,5. In all studies *Principal Component Analysis (PCA)* and *Partial Least Squares by means of Projection to Latent Structures (PLS)*were used [107]. The basic analytic questions to which these projection methods can be applied are (a) overview of data, (b) classification and/or discrimination among groups of observations and (c) regression modelling between two blocks of data (X) and (Y). The multivariate methods (using PCA and PLS) are inductive statistical methods where all variables are included. The variables are mean-centred and given the same variance and thus given the same possibility to influence the model. The variables create a model where the interrelationships between the variables, the subjects and between subjects and variables become highlighted. The basic aim applying these projection methods is that data can be reduced to a few latent variables that summarize the original variables.

Other advantages are that they do not require interval scaled data, copes with multicollinearity, copes with missing data, is robust to noise in both X and Y and can be used with small samples, even with more original variables than subjects.

Principal Component Analysis (PCA)

In the PCA the overall pattern of correlations between variables and observations (subjects) may be visualized and at the same time summarised by latent variables. Each variable defines a co-ordinate axis. If the data material has got K variables, exemplifies a K-dimensional space has to be handled. Since a multidimensional space is hard to imagine, figure x illustrates a three-dimensional space with the variables x_1, x_2 and x_3. Each subject is defined by a point in the coordinate system. **(Figure 7)**

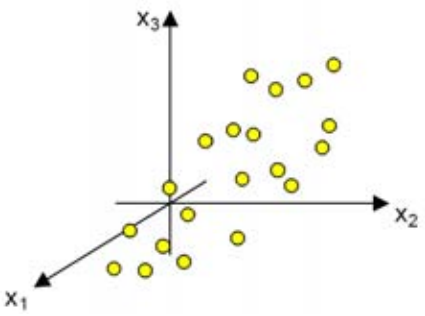

Figure 7: A co-ordinate system with three axes representing variables x_1, x_2 and x_3. Each subject is defined by a point in the three-dimensional space. Modified with permission from Eriksson et al [107].

After mean centering (**Figure 8),** the first principal component is calculated by way of the least square method. It is placed in the direction of the largest variation (**Figure 9).**

The second principal component is orthogonally projected to the first principal component along the second largest variation. The two principal components create a plane on witch the observations are projected **(Figure 10)**.

A component consists of a vector of numerical values between -1 and 1, referred to as loadings and obtained significant components are uncorrelated. Variables that have high loadings (with a positive or negative sign) on the same component are inter-correlated. Items with high loadings (ignoring the sign) are considered to be of large or moderate importance for the component under consideration. Items with high absolute loadings on a component but with different signs are negatively correlated.

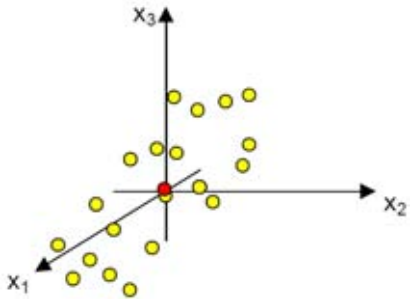

Figure 8: Mean centering.

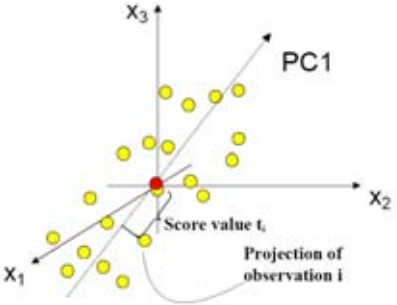

Figure 9: The first principal component calculated.

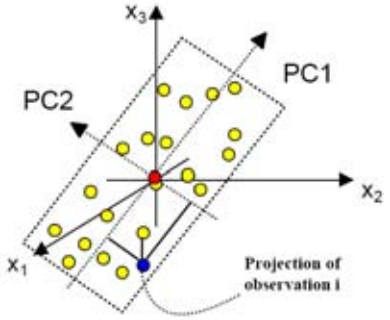

Figure 10: PC 1 and PC 2 in relation to the original variables.

Two plots are generated from the PCA analysis: the *loading plot* **(Figure 11)** describes the correlations between the variables; while the *score plot* **(Figure 12)** describes the correlations between the subjects. Subjects clustered together share similar characteristics, whereas the characteristics of subjects far from each other differ. Since the two plots are complementary, e.g. subjects located far to the right horizontally in the score plot have high values on the variables far to the right in the loading plot.

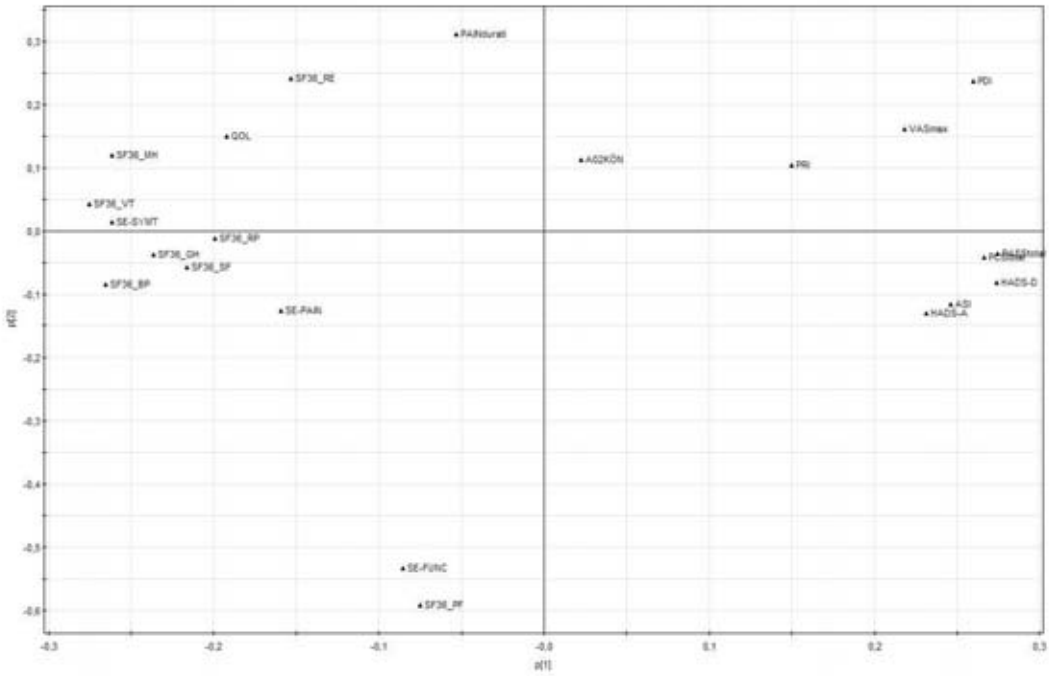

Figure 11: The loading plot shows the relationships between the variables.

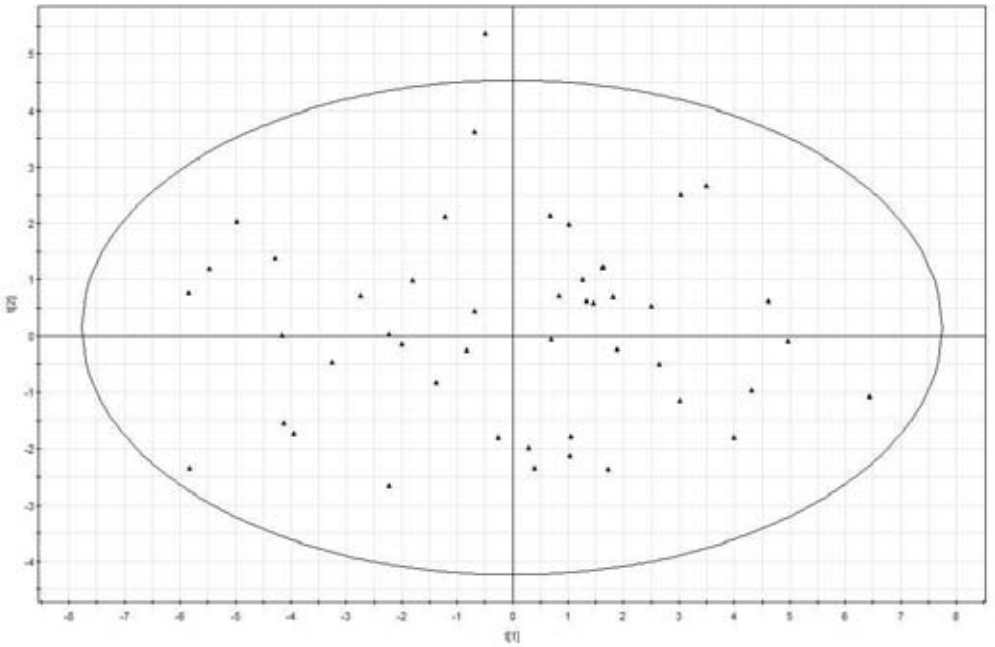

Figure 12: The score plot shows the relationships between the subjects.

Projections to Latent Structures by means of Partial Least Squares (PLS)
PLS is used to regress one or several Y-variables using several other variables (X-variables) [107] and calculates the covariance between a set of X-variables and a set of Y-variables. In PLS the principal components are projected based on the same techniques as in PCA. PLS is useful to predict an outcome.

PLS provides variable-related parameters to facilitate the interpretation of the model. *Regression coefficients* are used to obtain detailed information whether the variable had a significant positive or negative impact as well as the magnitude on the regressed outcome variable (**Figure 13)**. The statistical significance of each coefficient is indicated as 95% confidence interval not including zero. The benefit of this procedure is to provide a single vector of concise model information per response variable. The disadvantage is that the correlation structure among the responses is lost, but this relationship has already been elaborated according to the PCA plot and the PLS table.

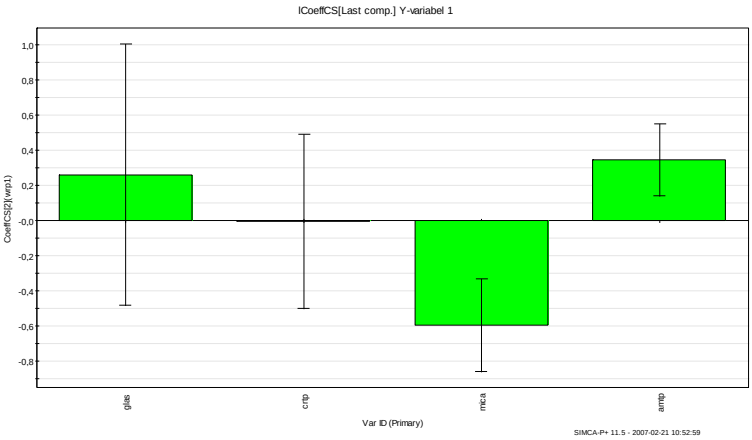

Figure 13: Graphic illustration of regression coefficients in PLS.

The *VIP variable* (variable influence on projection) gives information about the relevance of each X-variable and each Y-variable pooled over all dimensions (**Figure 14)**. VIP is a weighted sum of squares of the PLS weights. Because the weights express the correlation between the X and Y matrices, they summarize the importance of the X-variables. The PLS regression coefficients may be re-expressed as a regression model and express the influence of each X-variable on Y in each single component. The variable of importance for explaining Y is primarily identified by a VIP value ≥ 1.0 and secondary by the regression coefficient in relation to Y.

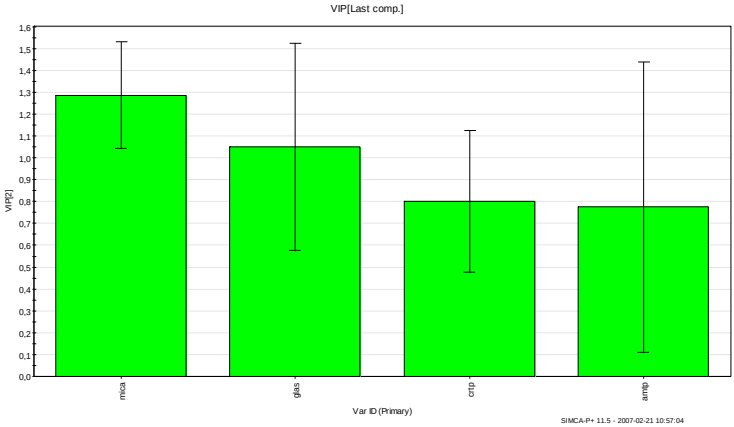

Figure 14: Graphic illustration of the VIP variable in PLS.

Two concepts – R^2 and Q^2 – are further used to describe the results of the modelling procedure in PCA and PLS. R^2 describes the goodness of fit: the fraction of sum of squares of all the variables explained by a principal component as is given both for X-variables and Y-variables, i.e. the degree of the variation in X which is used to explain the variation in Y. Q^2 describes the goodness of prediction: the fraction of the total variation of the variables that can be predicted by a principal component using cross validation methods. Outliers are identified using the two powerful methods available in SIMCA-P: score plots in combination with Hotelling's T^2 (identifies strong outliers) and distance to model in X-space (DModX) (identifies moderate outliers).

RESULTS

Study I

Formation of three subgroups based on number of regions with pain (PRI)
The group of patients with chronic WAD was divided into three subgroups based on PRI (group 1: 0-3 regions (n=45; 17%); group 2: 4-7 regions (n=152; 56%); and group 3: 8-11 regions (n=74; 27%). Very similar results with respect to the different consequences reported below were obtained when cluster analysis was made.

Background data
Somewhat (non-significant) higher proportions of women were found in the group with highest PRI (group 3). There was a significant difference in degree of disability pension between groups (highest prevalence in group 3).

Pain symptoms
Pain intensity in the head, the neck and shoulders, and the low back differed significantly between the three groups. The frequencies of radiation to arms and legs were highest in group 3 and lowest in group 1. No significant differences were found for the other pain related symptoms.

Not directly pain related symptoms including depression
In the whole cohort, the proportion with $\geq$10 on BDI (i.e., at least mild to moderate depression) was 55.9% and with $\geq$19 on BDI (i.e., at least moderate to severe depression) was 23.6%. BDI differed between the three groups ($p<0.001$). The proportion of subjects with $\geq$10 on BDI were 36.4% in group 1, 68.7% in group 2, and 78.1% in group 3. Corresponding figures for $\geq$19 on BDI were 2.3%, 24.7%, and 34.2%.

The NPSI differed significantly between the three groups ($p=0.027$); group 1 had lowest number of symptoms. The individual items that differed between the three groups were sleeping difficulties ($p = 0.020$), fatigue-tiredness ($p = 0.014$), and memory problems ($p = 0.043$).

Coping Strategy Questionnaire (CSQ)
Significant differences were found for two of the subscales of CSQ. Group 3 with high PRI showed highest values both for the catastrophizing ($p = 0.013$) and the reinterpret pain sensation ($p = 0.023$) subscales and group 1 (low PRI) had the lowest values.

Aspects of life satisfaction and generic health
Eight out of 11 scales of the life satisfaction instrument LiSat-11 showed significant differences between the three groups; no significant differences were found for the subscales vocational situation, sexual life, and partnership relations. According to SF-36, all scales except "Role physical" differed between the three groups even though a similar trend for the other scales was found. EQ-5D ($p<0.001$) and EQ-VAS ($p<0.001$) differed between the three groups; i.e., group 1 had the best situation and group 3 the worst situation.

Conclusions with respect to the first aim of study I
Widespread pain in chronic WAD was associated with more negative consequences with respect to pain intensity, prevalence of other symptoms (including depressive symptoms), some aspects of coping, life satisfaction/quality, and general health than local or regional chronic WAD.

Correlations between symptoms and with catastrophizing

Correlations between symptoms
According to the univariate analyses, PRI correlated weakly but significantly with BDI (rho=0.298, p<0.001) and NPSI (rho=0.174, p=0.022). No significant correlations existed between BDI and NPSI (rho=0.128, p=0.098). To understand the multivariate correlation pattern of the different symptoms and related indices, a PCA was made. The obtained significant model (R^2=0.24, Q^2=0.15) consisted of two components (**Table 3**). According to the first component (p1), NPSI and some of the different non-pain symptoms – difficulties with changes in light intensity, concentration problems, fatigue-tiredness, sound sensitivity, and light sensitivity – intercorrelated. Because NPSI and the different not directly pain related symptoms loaded on the first component explaining most of the variation in the data matrix, it can be concluded that subjects differ relatively prominently with respect to the presence of such symptoms. Pain intensity variables, BDI, PRI, and radiation of pain to the arm/arms showed high loadings on the second component (p2) and were thus positively intercorrelated and not correlated with NPSI and its items. To further confirm that BDI showed the strongest correlation with pain symptoms, a PLS regression of BDI was made. The significant regression (R^2=0.16; Q^2=0.05; showed that BDI correlated positively with the pain symptoms (i.e., PRI and pain intensities in different anatomical regions) and not with other not directly pain related symptoms. However, the great majority (84%) of variation in BDI is explained by unknown factors/aspects other than the symptoms investigated in the present study.

The relationships between different symptoms and catastrophizing
When the catastrophizing subscale of CSQ was regressed (R^2=0.31; Q^2=0.22), the following symptoms were most important (in descending order): BDI (VIP =3.25), pain intensity of upper back (VIP=2.70), pain intensity of hands (VIP=2.47), pain intensity of lower back (VIP=2.34), pain intensity of neck (VIP=2.15), pain intensity of head (VIP=1.66), pain intensity of shoulders (VIP=1.63), and PRI (VIP=1.23).

Conclusions with respect to the second aim of study I
NPSI and the not directly pain related symptoms correlated in the multivariate context, but these variables did not correlate with pain intensity variables, PRI, and BDI. The latter group of symptoms showed the strongest correlations with catastrophizing.

Table 3: A principal component analysis (PCA) of the different symptoms and indices related to symptoms. A two-component (p1 and p2) model was obtained (R^2=0.24). Loadings of importance for each component are in bold type. The bottom row shows the variation (R^2) of each component.

Variables	*p[1]*	*p[2]*
Sex	0.01	0.04
Pain intensity –head	-0.04	**-0.33**
Pain intensity - neck	-0.04	**-0.37**
Pain intensity - shoulders	-0.02	**-0.37**
Pain intensity - hands	0.00	**-0.35**
Pain intensity – upper back	-0.06	**-0.33**
Pain intensity – low back	-0.05	**-0.34**
Pain radiation arm	-0.02	**-0.23**
Pain radiation leg	-0.07	**-0.19**
PRI	-0.05	**-0.22**
BDI	-0.03	**-0.17**
NPSI	**-0.35**	0.01
Headache	-0.14	0.03
Sleeping difficulties	-0.16	-0.01
Tachycardia	-0.11	0.00
Bowel problems	-0.06	-0.02
Gastritis	-0.10	0.01
Fatigue-tiredness	**-0.22**	-0.07
Perception of heavy head	**-0.21**	0.00
Weak voice	-0.06	0.07
Nausea	-0.10	0.08
Anxiousness	-0.08	-0.05
Difficulties with changes in light intensity	**-0.23**	0.04
Concentration problems	**-0.23**	-0.01
Hoarseness	-0.14	0.06
Pain in the throat	-0.11	0.06
Difficulties with swallowing	-0.10	0.03
Difficulties with urinating	-0.12	0.05
Vertigo	-0.19	0.04
Numbness in hands	-0.19	0.05
Changed perception hands	-0.19	0.08
Blurred vision	-0.15	0.05
Defecation problems	-0.08	0.01
Sound sensitivity	**-0.22**	-0.02
Changes in alcohol sensitivity	-0.18	0.00
Light sensitivity	**-0.22**	-0.01
Feeling of fullness of ear	-0.16	0.00
Irritable	-0.19	-0.07
Memory problem	**-0.22**	-0.01
Diminished field of sight	-0.17	0.02
Low mood	-0.18	-0.06
Changed perception of touch legs	-0.15	0.14
Difficulties with control of legs	-0.12	0.09
Fatigue in legs	-0.12	0.00
Twitches in the legs	-0.09	0.05
Difficulties walking down in stairs	-0.12	0.11
R^2	*0.15*	*0.09*

Study II

Each subject of the group of patients with chronic WAD was classified on the basis of catastrophizing (*CSQ-cat*), depression (*BDI*), and pain intensity in neck/shoulder (*VAS*). Subjects were classified as 'high' if their value for the variable was higher than or the same as the median value for the whole group and as "low" if it was lower. Hence the following combinations exist: High pain (HP), low pain (LP), high depression (HD), low depression (LD), high catastrophizing (HC), and low catastrophizing (LC). These can be combined into eight possible combinations or subgroups:

Subgroup 1: HP/HD/HC	Subgroup 5: LP/HD/HC
Subgroup 2: HP/HD/LC	Subgroup 6: LP/HD/LC
Subgroup 3: HP/LD/HC	Subgroup 7: LP/LD/HC
Subgroup 4: HP/LD/LC	Subgroup 8: LP/LD/LC

Distributions and characteristics of the eight subgroups

The result of the classification procedure – based on pain intensity, BDI, and CSQ-cat – showed that 24.7% of the WAD patients belonged to subgroup 1 (SG1) and 22.6% to subgroup 8 (SG8) (**Figure 1**). SG1 (i.e., HP/HD/HC) scored high on all scales used in the classification procedure while SG8 scored low according to the three classification variables (i.e., LP/LD/LC). The remaining half (approx. 52%) of the WAD patients were relatively equally distributed among the intermediary subgroups (**Figure 15).**

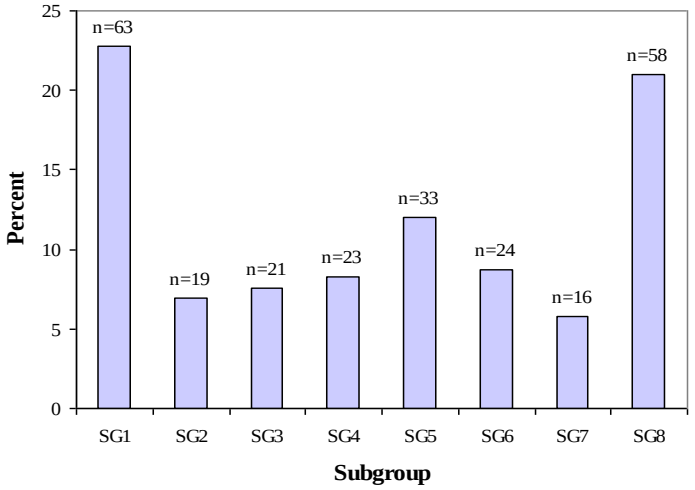

Fig.15: The distribution of the different subgroups based on high or low values of pain intensity, depression, and catastrophizing. SG1 had high values on these three dichotomized variables and SG8 low levels and SG2-7 were intermediary groups.

According to statistical analyses (ANOVA) of the background variables, no significant differences were found with respect to age, gender, or items related to sick leave and disability pension. The only exception was "number of visits to physician" with highest values in SG1 (4.5±3.0 visits) and SG6 (4.5±2.5 visits) and lowest in SG3 (2.6± 2.4 visits) (p=0.048).
In sharp contrast, there were significant differences in almost all variables concerning aspects of life quality and perceived health; i.e., SF-36, LISAT-11 and EuroQol. As expected the group (SG1) with high figures on the three classification variables (i.e., pain intensity, BDI, and CSQ-cat) perceived the situation worst.

The multivariate correlation analysis among the subgroups
For each of the eight subgroups, the mean values of LISAT-11, EuroQol, and SF-36 were used in a PCA analysis (**Figure 16**). The calculated PCA model is based on three principal components (*component 1:* R^2 = 0.68, Eigen value = 5.4; *component 2:* R^2 = 0.14, Eigen value = 1.1; *component 3:* R^2 = 0.08, Eigen value = 0.7); only the first component was significant. The score plot shows the interrelations between the subgroups (**Figure 16a**) and the loading plot (**Figure 16b**) shows the relationships between the items of LISAT-11, EuroQol and SF36. Subgroups clustered together share similar characteristics, whereas subgroups far from each other differ in characteristics; e.g., subgroup 2 (i.e., HP/HD/LC) differed little from SG1 (HP/HD/HC) with respect to LISAT-11, EuroQol, and SF-36. According to the loading plot , it is obvious that high loadings on the first component are associated with a positive situation with respect to life satisfaction and health and negative values with a negative situation. Since, the two plots are complementary; e.g., subgroups located far to the right horizontally in the score plot (**Figure 16a**) have high values on the variables far to the right in the loading plot (**Figure 16b**). As expected, SG1 (i.e., HP/HD/HC) has low (negative) values with respect to life satisfaction and is located to the left in **Figure 16a**, whereas SG8 (i.e., LP/LD/LC) with a good situation is located most to the right in **Figure 16a**. The following multivariate ranking order (from low to high health and life satisfaction) can be revealed from **Figures 16a** and **b**: SG1, SG2, SG5, SG6, SG7, SG3, SG4, and SG8.

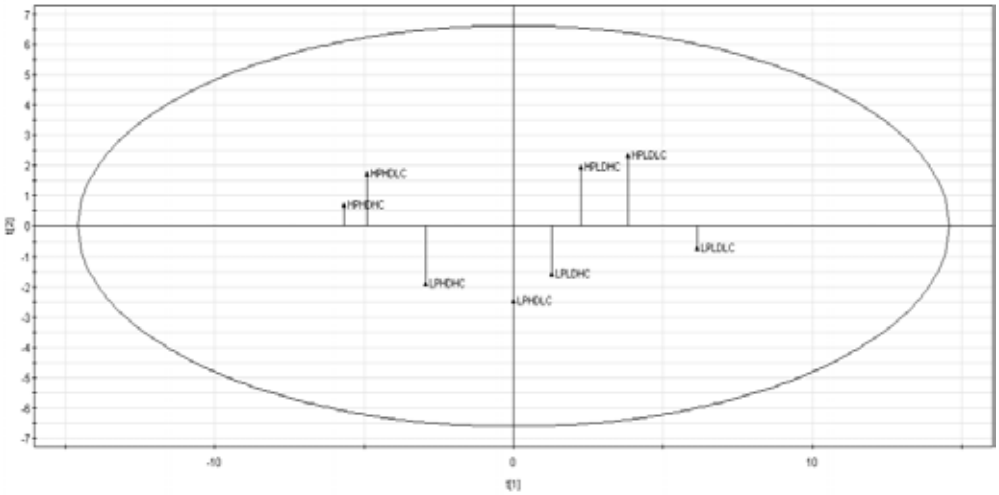

Figure 16a: The PCA score plot illustrates the relationships between the subgroups according to the scores of first versus the scores of second component. The complementary loading plot (Figure 16b) shows the relationships between the items of LISAT-11, EuroQol and SF36. For detailed interpretation of Figure 16 see Results. For an explanation of abbreviations, see text.

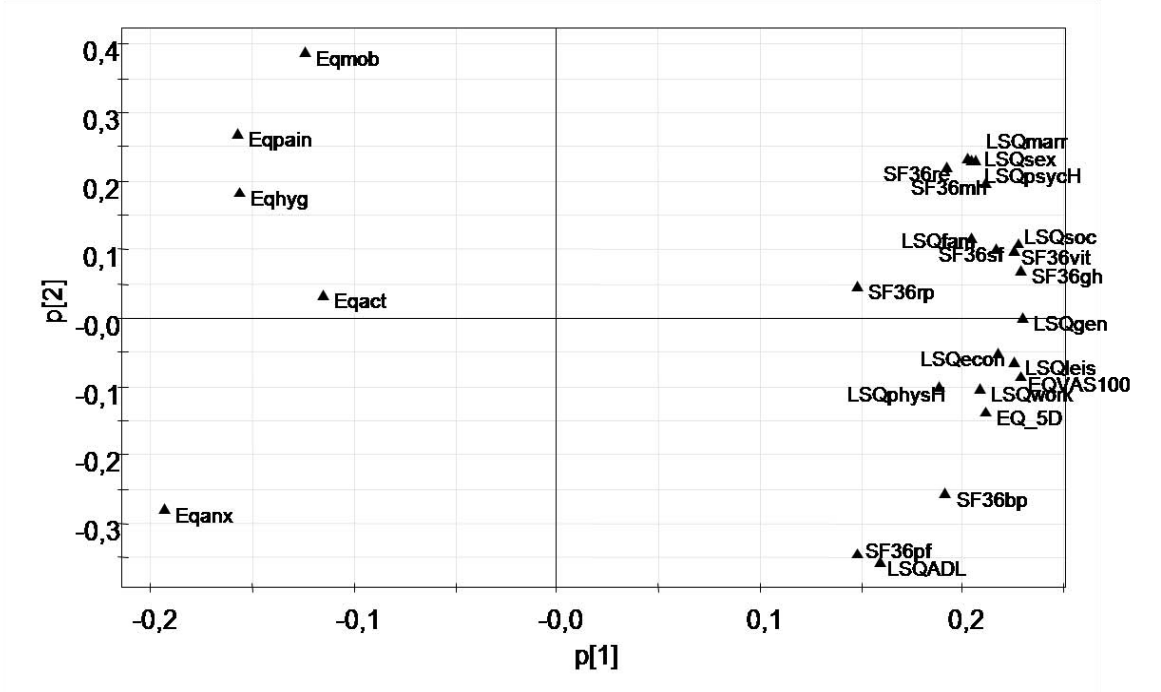

Figure 16b: The PCA loading plot illustrates the relationships between the variables (loadings of first versus loadings of second component). The complementary score plot (Figure 16a) shows the relationships between the subgroups. For detailed interpretation of Figure 16 see Results. For explanation of abbreviations, see text.

Multivariate differences between the subgroups

The analysis can further be refined including the second and third components. The results below show that different patterns of variables are discerned according to the different constellations of pain, depression, and catastrophizing.

High pain intensity versus low pain intensity

The clustering of all groups reporting high pain was compared to all groups reporting low pain. The separating variable pattern is presented in **Figure 17**. Thus subgroups with high pain versus subgroups with low pain mainly differed in functional variables relating to aspects such as ADL, physical functioning, and mobility (i.e., high positive or negative bars in **Figure 17**).

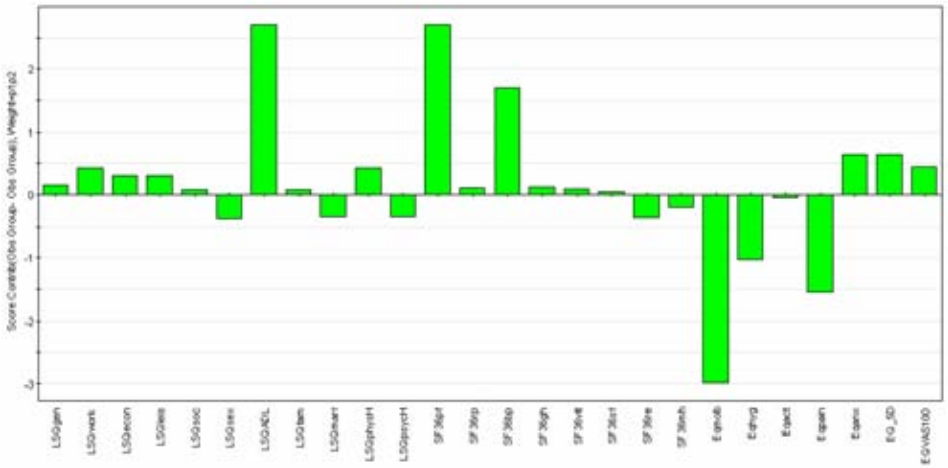

Figure 17: Contribution plot. High absolute bars indicate prominent differences between subgroups with high pain versus subgroups with low pain. For detailed interpretation see Results. For explanation of abbreviations, see text.

High depression versus low depression

When separating all groups scoring high on depression scales (marked with squares in Figure 18) versus all groups scoring low, subgroups with high depression (HD) are all located most far to the left, indicating the worst perceived health and life quality (**Figure 18**). The contribution plot indicated that items concerning psychological, well being, vitality, emotional, and participation aspects were all important and differed between subgroups with high and low depression (data not shown).

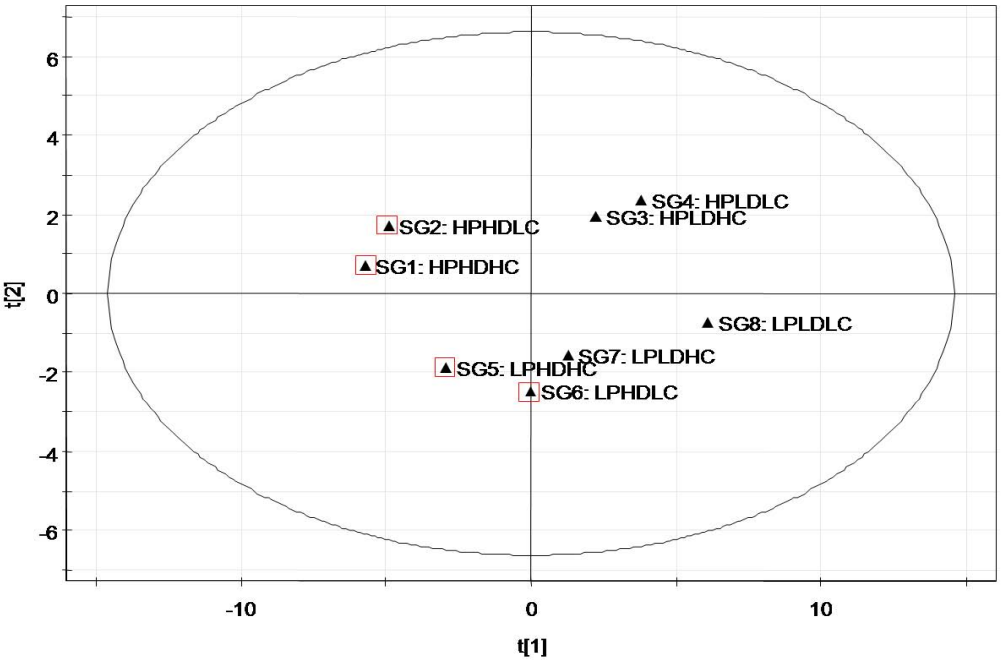

Figure 18: Marked PCA plots highlighting common features (scores of first versus scores of second component). In this plot, subgroups with high depression (denoted with square symbols) versus low depression are shown. The complementary loading plot (Figure 16b) shows the relationships between the items of LISAT-11, EuroQol and SF36. For detailed interpretation see Results. For explanation of abbreviations, see text.

High catastrophizing versus low catastrophizing

Finally, when comparing subgroups scoring high or low on catastrophizing, a more subtle variable profile appeared. The third component captured parts of a new informative structured variance. This third component separated the LP/LD/HC subgroup from all other subgroups, but particularly the remaining subgroups with high catastrophizing. The impact of catastrophizing seems most important when both pain and depression are low. If either pain or depression is high, the catastrophizing parameters seem to have a minor impact on perceived health and well-being. When comparing the subgroups LP/LD/LC and LP/LD/HC, the resulting variable pattern indicates that two items – activity and pain – were most important (**Figure 19**).

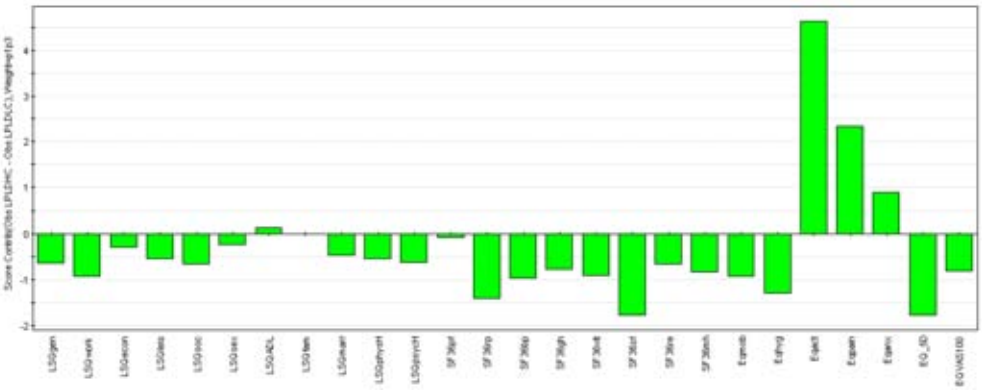

Figure 19: Separating variable profile (contribution plot) between LP/LD/LC and LP/LD/HC. High absolute bars indicate prominent differences between LP/LD/LC and LP/LD/HC. For detailed interpretation see Results. For explanation of abbreviations, see text.

Conclusions with respect to the aim of study II
The 8 subgroups – based on dichotomizing pain, depression, and catastrophizing– showed multivariate differences with respect to health and quality of life. The degree of depression appears to be the most important influencing factor.

Study III

Identification of subgroups and their relations to disability and quality of life
For the group of patients with chronic WAD, fibromyalgia and SCI related pain, a PCA-analysis was performed to identify and exclude different types of outliers. Two outliers were excluded.

The cluster analysis identified four subgroups (**Table 4**, upper part). Standardised input variables were used: depression (HADS-D), anxiety (HADS-A, PASS, ASI), catastrophizing (PCS) and pain (intensity according to VAS and pain duration). As intended, the subgroups differed significantly on all scales.

The first group (n=101), here called the *'most favourable'* group, (favourable here used relatively to the whole group of patients with chronic pain), was characterized by relatively low pain intensity and short pain duration. The scores on depression, anxiety and catastrophizing scales were low. Group 2 (n=85), here called the *'long-time/favourable'* group, had by far the longest pain duration and relatively high pain intensity. They scored relatively low on depression, anxiety, and catastrophizing. Group 3 (n=150), here called the *'short-time/worse'* group, was the group with the shortest duration of pain and with intermediary pain intensity. The scores for depression, anxiety, and catastrophizing were generally relatively high. The fourth group (n=95), here called the *'worst off'* group, scored highest on pain intensity and had a relatively long duration of pain. The scores on the psychological factors were the highest of the four groups.

Table 4. Cluster analysis based on the scales of *depression* (HADS-D), *anxiety* (HADS-A, PASS, ASI), *pain intensity* (VAS) and *pain duration.*
The four identified clusters have been compared with respect to the variables and scales below the dotted line: background data, diagnosis, pain generalisation, disability and quality of life. Mean values (± one standard deviation, SD) are reported. For statistical comparison of the clusters, analysis of variance (ANOVA) was used for all variables except gender and diagnosis, where the Chi^2-test square was used. P-values are given.

Subgroups Variables	Group 1 *'most favourable'* (n=101) Mean (SD)	Group 2 *'long-time/favourable'* (n=85) Mean (SD)	Group 3 *'short-time/worse'* (n=150) Mean (SD)	Group 4 *'worst off'* (n=95) Mean (SD)	Statistics (p-value)
Stand.variables					
HADS-D	3.6 (2.6)	6.8 (3.1)	8.9 (3.4)	11.9 (3.7)	<0.001*
HADS-A	3.3 (2.3)	6.8 (3.1)	8.3 (3.0)	14.3 (2.9)	<0.001*
PCS.total	10.2 (6.4)	16.5 (7.9)	22.0 (6.0)	36.6 (6.6)	<0.001*
PASS.total	28.7 (11.5)	40.8 (11.2)	52.3 (9.1)	70.4 (13.2)	<0.001*
ASI	8.8 (5.9)	16.8 (8.8)	21.6 (8.5)	39.3 (10.5)	<0.001*
Pain duration(months)	96.0 (60.2)	246.4 (66.8)	85.5 (38.8)	116.0 (81.9)	<0.001*
VAS.max	64.6 (22.5)	80.3 (13.8)	77.6 (16.2)	85.6 (13.2)	<0.001*
Background variables					
Gender (% men)	18.8	15.3	18.0	21.1	0.796
Age (years)	41.3 (8.6)	45.9 (6.6)	41.3 (9.1)	41.0 (8.8)	<0.001*
Diagnosis (% within diagnosis)					
WAD	22.0	6.7	44.0	27.3	<0.001*
FM	20.5	26.9	31.2	21.4	<0.001*
SCI	42.6	25.6	23.4	8.5	<0.001*
Diagnosis (% within cluster)					
WAD	32.7	11.8	44.0	43.2	<0.001*
FM	47.5	74.1	48.7	52.6	<0.001*
SCI	19.8	14.1	7.3	4.2	<0.001*
PRI	6.4 (2.5)	7.8 (1.8)	7.4 (1.9)	7.6 (1.9)	<0.001*
Pain disability index (PDI)	27.2 (12.4)	35.0 (10.3)	39.2 (8.7)	45.4 (10.0)	<0.001*
Quality of life (QOLS)	85.2 (14.1)	78.2 (12.6)	70.9 (13.3)	63.1 (15.7)	<0.001*

The identified subgroups were then investigated for possible differences concerning background variables (age and gender), diagnosis (WAD, FM and SCI), spreading of pain (PRI), pain related disability (PDI) and quality of life (QOLS) (table 1, lower part). All subgroups differed significantly on all these variables except with respect for the distribution of gender.

The *'most favourable'* subgroup scored low on disability and the score on perceived quality of life was high. PRI, generalization of pain, was relatively lower than all the other subgroups. This group contained the relatively highest proportion of persons with SCI and pain. The *'long-time/favourable'* group scored relatively low on disability and relatively high on life quality variables. In this group, a large number of people had FM and SCI. The *'short-time/worse'* subgroup showed a relatively high disability score and the perceived quality of life was relatively low. The '*worst off*' group showed the highest disability and the lowest scores on perceived quality of life. The last two subgroups contained a high proportion of persons with WAD.

In conclusion, with respect to the outcome variables disability and quality of life, there is a correlation to the psychological variables depression, anxiety, and catastrophizing. That is, individuals that scored low on psychological items showed a better perceived quality of life and less pain related disability: the higher score on psychological variables, the lower quality of life and higher disability (**Table 4**). For the pain variables (VASmax and pain duration), there is no clear correlation to disability and quality of life, according to the four subgroups, nor is there a correlation between generalisation of pain and psychological factors.

A principal component analysis (PCA) was made to further investigate the multivariate correlation pattern (R^2=0.69; Q^2=0.34). This confirmed the results from the cluster analyses that perceived disability and quality of life correlated to the psychological variables (depression, anxiety and catastrophizing), but not to the pain variables (pain intensity and pain duration).

Regressions of disability and quality of life

In the next step we, using two different analyses, we regressed disability (PDI) and quality of life (QOLS) using the scales HADS, PASS, ASI, pain intensity, and pain duration as regressors. The significant regression (R^2=0.45; Q^2=0.44) of PDI showed that the following variables in descending order were important: HADS-D (VIP=1.30), PASS (VIP=1.10), PCS (VIP=1.06), VAS max (VIP=1.06), HADS-A (VIP=0.96), ASI (VIP=0.94), and Pain duration (VIP=0.18). Hence the most important (VIP $\geq$1.0) variables for the outcome of disability were depression, pain anxiety, catastrophizing, and pain intensity.

When QOLS was regressed (R^2=0.45; Q^2=0.44), the following variables in descending order were important: HADS-D (VIP=1.73), PCS (VIP=0.99), PASS (VIP=0.98), HADS-A (VIP=0.98), ASI (VIP=0.92), VAS max (VIP=0.45) and Pain duration (VIP=0.25). Hence the most important variable for the outcome of quality of life was depression followed by PCS, PASS and HADS-A at the boundary of importance (VIP $\approx$1.0).

Conclusions with respect to the aim of study III

Using cluster analysis based on depression, anxiety, catastrophizing, and pain intensity and duration, it was possible to identify four large subgroups of patients that differed with respect to perceived quality of life, disability and diagnosis. The psychological factors, and especially depression, had a crucial importance for perceived quality of life and disability. Pain intensity and duration play a minor role for quality of life, although pain intensity contributes relatively more to disability. The three pain diagnoses were not symmetrically distributed within the four clusters.

Study IV

Background variables, self-efficacy, symptoms, catastrophizing, disability, quality of life, and health of the investigated cohort

The investigated group of patients, with chronic WAD, FM and SCI related pain, had a majority of women (82%) and a mean age of 42 years. The duration of the pain condition was about 10 years, which with interest fulfill the criteria for chronic pain (i.e., ≥3 or 6 months). The mean pain intensity rating (VAS: 77±18 mm) implicates severe pain. Severe pain can be defined as pain intensity according to VAS in the range 71-100 mm [108].The PRI was 7.3 out
of 9 predefined anatomical regions, which generally imply a prominent spreading of pain. The HADS-D level (7.9±4.3) indicates mildly depressed mood at group level; the range for depressed mood is 7-10. HADS-A (8.1±4.7) indicates mild to moderate anxiety, range 7-10.

Multivariate variable overview - PCA

To give an overview of the correlation pattern of the different variables (except for gender and age), a PCA was made. The significant model obtained (R^2 = 0.55, Q^2 = 0.35) consisted of two significant components (**Table 5** and **Figure 19**). The PCA analysis generated two main plots. The loading plot (**Figure 19**) describes the relations between variables; details concerning the loadings of the first (p1) and the second (p2) component are given in **Table 5**. According to the first component (p1), anxiety (PASS, ASI, and HADS-A), catastrophizing (PCS), disability (PDI), and depression (HADS-D) had high positive loadings (positively intercorrelated) whereas the three self-efficacy variables (SE-PAIN, SE-FUNC, SE-SYMT), quality of life (QOLS-S), and general health (SF36-GH) showed high negative loadings (also intercorrelated). That is, these two groups of variables loading on the first component were negatively intercorrelated. The three pain variables (VASmax, PRI, and Pain duration) were intercorrelated: they had high positive loadings according to the second component (p2). These three variables were negatively correlated with SE-FUNC (i.e., they had a negative loading). From these results (presented in **Figure 19** and **Table 5**), it can also be concluded that subjects differ relatively prominently with respect to the variables with high loadings on the first component (R^2=0.44) unlike the variables with high loadings on the second component (R^2=0.11).

Table 5: Principal component analysis of the different variables. A 2-component (p1 and p2) model was obtained ($R^2 = 0.55$). Loadings of importance for each component are in bold type. The bottom row shows the variation (R^2) of each component.

Variables	**p[1]**	**p[2]**
PASS.	**0.32**	-0.14
PCS	**0.31**	-0.23
PDI	**0.31**	0.15
HADS-D	**0.31**	-0.20
HADS-A	**0.30**	-0.24
ASI	**0.30**	-0.18
VASmax	0.20	**0.33**
PRI	0.14	**0.48**
PAINduration	0.00	**0.51**
SE-FUNC	**-0.21**	**-0.32**
SE-PAIN	**-0.23**	-0.16
SF36_GH	**-0.29**	-0.17
QOLS-S	**-0.29**	0.10
SE-SYMT	**-0.32**	0.00
R^2	*0.44*	*0.11*

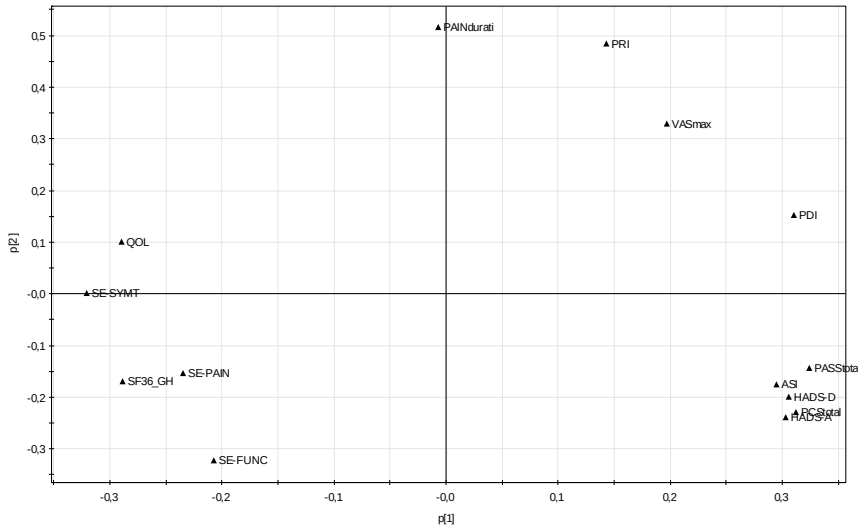

Figure 19: The PCA loading plot illustrates the relationships between the variables (loadings of first versus loadings of second component). For detailed interpretation of Figure1, see Results. For explanation of abbreviations, see text.

A second plot generated from the PCA is the score plot, which describes the relations between the subjects; in addition, the different diagnoses are denoted. The first score plot made, including all variables, showed a minor discrimination between the three diagnoses and mainly identified FM. In the second plot made the variable for spreading of pain (PRI) was excluded because it is a diagnostic criteria for FM. This made it impossible to recognize any diagnosis specific pattern of the subjects; that is, there is no diagnosis specific pattern in the influence of the different variables in the model.

Regression of disability, quality of life and general health
As evident from the PCA (**Figure 19** and **Table 5**), disability, quality of life, and general health were intercorrelated; however, as seen in Figure 1a, they were graphically separated, which indicates moderate correlation. Thus, in the next step, using PLS in three different analyses – disability (PDI) (R^2=0.54; Q^2=0.52), quality of life (QOLS-S) (R^2=0.55; Q^2=0.52), and general health (SF36-GH) (R^2=0.44; Q^2=0.42) – were regressed. These regressions used the scales of depression (HADS-D), anxiety (HADS-A, PASS, ASI), catastrophizing (PCS), self-efficacy (SE-PAIN, SE-FUNC, SE-SYMT), pain intensity (VAS max), duration of pain (PAIN duration), and spreading of pain (PRI) as regressors (**Table 6**).

HADS-D, PASS, PCS, and VASmax correlated positively with PDI, while SE-FUNC and SE-SYMT were negative significant regressors (left column in **Table 6**).

Quality of Life (QOLS-S) was significantly influenced only by two variables, SE-SYMT (positively correlated) and HADS-D (negatively correlated) (middle column in **Table 6**).

For general health (SF-36 GH), there are two promoting variables (i.e., positive regressors): SE-SYMT and SE-PAIN. General health was negatively influenced by, in descending order, PCS, PASS, PRI, HADS-A, ASI, and HADS-D (right column in **Table 6**).

Table 6: Three different PLS analyses – regression of disability (PDI), quality of life (QOLS-S), and general health (SF36-GH) – using the scales for depression (HADS-D), anxiety (HADS-A, PASS, ASI), catastrophizing (PCS), self-efficacy (SE-pain, SE-function, SE-symptoms), pain intensity (VAS max), duration of pain (PAIN duration), and spreading of pain (PRI) as regressors). The VIP-values were calculated to obtain the importance of each variable. VIP ≥1.0 is considered to be a variable of importance and it is also required that the obtained VIP values have 95% CI different from zero. Regression coefficient was calculated to obtain information whether the variable had a significant positive or negative impact on the regressed outcome variable. At the bottom rows are given R^2 for X and Y variables together with Q^2.

Disability (PDI)			**Quality of Life (QOLS-S)**			**General Health (SF-36 GH)**		
X-variables	*VIP*	*Coeff*	*X-variables*	*VIP*	*Coeff*	*X-variables*	*VIP*	*Coeff*
HADS-D	1.27	+0.21	*SE-SYMT*	1.42	+0.31	*SE-SYMT*	1.22	+0.14
PASS	1.14	+0.10	HADS-D	1.72	-0.47	*SE-PAIN*	1.02	+0.13
PCS	1.10	+0.03	PASS	1.07	ns	*SE-FUNC*	0.73	+0.07
VASmax	1.00	+0.19	PCS	1.07	ns	PCS	1.19	-0.09
PRI	0.64	ns	HADS-A	1.04	ns	PASS	1.17	-0.09
SE-FUNC	1.17	-0.24	ASI	0.95	ns	PRI	1.11	-0.21
SE-SYMT	1.16	-0.14	*SE-PAIN*	0.85	ns	HADS-A	1.10	-0.08
SE-PAIN	0.89	-0.10	VASmax	0.60	ns	ASI	1.10	-0.09
HADS-A	1.00	ns	*SE-FUNC*	0.58	ns	HADS-D	1.00	-0.08
ASI	0.97	ns	PRI	0.41	ns	VASmax	0.69	ns
PAINdur	0.02	ns	PAINdur	0.39	ns	PAINdur	0.22	ns
R^2X	0.53		**R^2X**	0.59		**R^2X**	0.54	
R^2Y	0.54		**R^2Y**	0.55		**R^2Y**	0.44	
Q^2	0.52		**Q^2**	0.52		**Q^2**	0.42	

Conclusions with respect to the aim of study IV

In the cross-sectional perspective, self-efficacy had an enhancing influence on perceived quality of life and general health and a reducing influence on disability, whereas pain intensity, spreading of pain, catastrophizing, depression, and anxiety had the opposite influence. The self-efficacy subcomponents had different relative importance regarding disability, quality of life, and general health.

DISCUSSION

Methodological considerations

Data collection

The patients in both Group 1 and Group 2 were selected from clinical departments that specialize in managing severe chronic pain conditions. This means patients with severe pain and very long pain duration. In Group 2, the mean pain intensity was 77 mm on the VAS scale and the mean pain duration was 10 years. This highly selected group of pain patients implicates that the possibility to generalize the results to a broader spectrum of pain patients, e.g. patients with chronic pain in primary health care, is difficult. As a comparison the pain duration in a primary health care sample of chronic pain patients was 12 month [72] and in a study of patients seeking primary health care due to pain, only 37% had pain duration more than 3 month [109].

However the selection of patients in our studies gives us the opportunity to study long term effect of chronic pain states. Among those effects, the associations with psychological factors and the long term effects on disability, health and quality of life. It will also give clinical implications on treating patients with chronic pain in rehabilitation programmes, since this category of patients is often referred to specialised pain management clinics [110].

In Group 1, the questionnaires were completed by the patients before the consultation at the specialized pain clinic. This circumstance may have affected the answers to the questions. One possibility is that the patients, consciously or unconsciously, exaggerated symptoms with the intension that the physician would understand his/hers situation in a better way. This effect should not be mistaken for malingering of symptoms. There is no information about or analysis of drop outs in this group. All patients in this consecutive flow during three years received the questionnaire to return in connection to the visit to the physician. This fact should have improved the response rate.

The response rate of the questionnaires in Group II was low. There was no difference in mean age between the study population (42 years) and the persons who did not respond (41 years). The non-responding individuals exhibited a gender bias: the study group was 18.4% male and the non-responding group was 31.1% male. This may have affected the results. However, in the cluster analysis in study III, there was no significant gender difference between the groups based on psychological and pain variables. The problem with a low return rate for men when using postal questionnaires is known from other studies [3].

The data in this thesis are all collected from questionnaires. Though all with satisfactory psychometrical properties, there is always doubts about if they are measuring what the investigators intend to measure and how well they correspond to the real occurrence of the phenomenon or symptom. Questionnaires are often validated compared to other well established questionnaires [98] but some studies are performed to compare the outcome of self reported measurements and e.g.

physical performance. Alschuler et al. found no differences between self reported disability and actual physical performance [111] and Asante et al. confirmed a high association between functional self-efficacy beliefs and functional capacity evaluation [112]. Another possibility is to compare self reported symptoms e.g. depression and anxiety to clinical evaluation based on established clinical definitions e.g. DSM-IV [113].

Statistics

The statistical methods used must correlate to the type of data and to the area of investigation. In this thesis we collected a great amount of different variables in order to cover a broad area and to find associations in an earlier recognized complex interrelationship of factors. We chose to use multivariate projection methods, PCA (Principal Component Analysis) and PLS (Partial Least Square by means of Projection to Latent Structures) [107]. The advantages of PCA and PLS in health related research is that they do not require interval scale data, are not sensitive to violations of multivariate normality, have no assumptions about independence of cases and are not hampered by co linearity among the variables. The methods are for instance used in clinical psychology research [114]. The authors (Henningsson et al.) discuss *model development* and thereby present a *hard modelling* approach and *soft modelling* approach. *Hard modelling* approach uses well-articulated theories that structure domains on logical or theoretical grounds. Hard models incorporate stringent assumptions about the properties of the variables under investigation, relying on theory and earlier research. In *soft modelling* there is no integrated theory but rather empirically retrieved data. PCA and PLS can be regarded as soft modelling approaches, since they are able to handle great amount of data including many dependent variables. They make a both graphical and quantitative overview of the relationship between variables and patients that are interrelated and compare groups from an amount of variables rather than from a single variable. These methods makes it possible to use empirical, clinical knowledge to identify relevant variables, include a broad range of other variables and use the soft modelling approach to evaluate their unprejudiced complex multivariate relationship [114].

Multiple Linear Regression (MLR) may have been an alternative to PLS as a regression method. However MLR is considered less stable in the presence of co linearity and can be seen as a hard modelling approach considering the separate variables rather than the multivariate correlations among them.

Factor Analysis (FA) has many similarities to, and could have been used instead of PCA. Following the soft modelling approach, PCA reduces the variables to a few components forming new independent variables explaining the maximum possible variation with no assumption about common factors explaining the correlations; this refers to soft modelling approach. There is an important difference to FA concerning the aim of the data reduction since FA finds the factors that explain the inter correlation among the variables.

General discussion of the results

The intention of the following discussion is to analyze the total results of the separate studies in relation to existing knowledge and earlier studies. Further to put the results into the context of existing theoretical models and theories of chronic pain and its consequences and try to link the different models together into a biopsychosocial context. The models and theories are the earlier described *Neuromatrix Theory*, the *Diathesis-Stress model* and *ICF*.

Generalization of chronic pain

Neurobiological mechanisms
Central sensitization is considered to be the neurobiological mechanism of developing generalization of chronic pain. It is associated with increased spontaneous activity of dorsal horn neurons, enhanced responsiveness to nociceptive and nonnociceptive stimuli, and enlarged receptive fields [115]. The consequenses of these neuronal changes include spontaneous pain as well as allodynia/hyperalgesia. A mechanism for these changes includes temporal summation or 'wind-up' of dorsal horn neuron responses to repetitive C-fibre stimulation. Once wind-up occurs, dorsal horn nociceptive neurons maintain a state of increased responsiveness for long periods at much lower stimulus frequencies than would normally be necessary to induce wind-up. This state has been termed windup-maintenance, related to persistent pain conditions, because it is accompanied by expanded receptive fields, enhanced responsiveness to nociceptive and non-nociceptive stimulation [116].

Prevalence of chronic widespread pain
Chronic Widespread Pain (CWP) is usually defined as pain present in at least 2 contra-lateral body quadrants and the axial skeleton that has persisted for at least 3 months [32]. The prevalence in population based studies varies from about 5 – 14% [117]. One possible explanation of the variation of information about prevalence may be different definitions of the concept of CWP [118]. When studying the spreading of pain in our studies we did not use the above definition of CWP. Instead we used an index, PRI, which only outline the number of pain sites, not the location per se and we did not use any cut off value for defining CWP. This fact may make it difficult to compare our results with other studies.

In our study group 2, including different pain disorders, WAD (Whiplash Associated Disorders), Fibromyalgia (FM) and Spinal Cord Injury associated pain (SCI), the mean PRI (pain region index) was 7.3 out of 9 possible predefined regions. This high index may be explained by the great number of FM patients in the group (236/433), FM patients are by definition classified as CWP.

In our study group 1, which included only WAD patients, a relatively prominent proportion, 27%, belonged to the subgroup with 8-11 pre-defined regions of pain out of 11 possible regions. This high frequency of wide spread pain, compared with population based studies, may partly be the result of a selection bias, since the investigated group was referred to a specialised pain clinic, which implies more severe cases. The primary location of the pain to the neck region may also

be a contributing factor to the high number of widespread pain in this group [119,120]. There are also data indicating that WAD per se is associated with an over-representation of widespread pain compared with idiopathic neck disorders, because of the increased association between WAD and widespread hypersensitivity and sensory changes, possible steps towards development of CWP [121,122].

A separating factor between WAD and other neck pain is the occurrence of trauma in WAD. A possible effect of trauma is Post Traumatic Stress Disorder (PTSD) and there is an increased prevalence of PTSD and a number of its symptoms among car crash victims who have WAD [123]. Several studies have demonstrated the association between posttraumatic stress disorder (PTSD) and chronic widespread pain (CWP) [124,125]. PTSD may be a link between WAD and widespread pain that can partly explain our result of the proportionally high occurrence of widespread pain among patients with chronic WAD.

Consequences of widespread pain
Previous studies have shown that people with CWP experience poor subjective health, fatigue, sleep disruption, and physical impairments [126], higher pain intensities [120] and psychological distress [127]. In our study of WAD patients concerning widespread pain (Study I), we were able to confirm that widespread pain was associated with more negative consequences with respect to pain intensity, prevalence of other symptoms including depression, catastrophizing, quality of life and health. In Study III with different pain diagnoses, the relatively '*most favourable*' subgroup (low scores on psychological factors, disability and pain; high score on quality of life and health) showed less widespread pain and differed significantly in this respect to the subgroups with a less favourable situation concerning psychological factors, pain, quality of life and health.

Wide spread pain in a multivariate context
In the more multivariate context, according to PCA-analyses in study I and IV, widespread pain (PRI) is strongly correlated to other pain variables (pain intensity and duration) while there is a much weaker correlation to psychological factors and other symptoms, including depression. In agreement with our findings, earlier studies have shown that the development of sensitization and widespread pain appears to occur independently of psychological variables, but is associated with a higher prevalence of psychological symptoms [121,122].

In the context of the *diathesis-stress model* (see pages 15-16), widespread pain, as a pain component, constitutes a stressor inducing psychological distress. While the different components of the model are connected by circular loops, this process may enhance pain and thereby affect *neuromatrix* and central sensitization processes, leading to further spreading of pain. Pain, in this sense regarded as a stressor, is affecting both psychological and neurobiological systems that thereby get integrated with the pain bridging them together.

Pain intensity and duration

The perception of pain intensity
Pain is per se a subjective experience and in our studies we base our results concerning pain intensity on the self reported VAS scale. Many factors may influence the perception of pain, and the perception of pain is individual for each person. Many studies have pointed out the diverse pain perception and pointed out many factors influencing it. In experimental, *acute pain*, there is an influence of e.g. the perception of pain controllability [128], depression [129], anxiety [130]. In those studies, these influences were associated with functional changes in brain activity. This fact directly associates the cognitive and psychological factors to neurobiological function.

In *chronic pain*, the pain perception is influenced by an amount of factors, interacting in a complex pattern. Plastic changes occur in the neurobiological system including neuromatrix such as, central sensitization [131,132] and altered descending modulation of pain [133,134] resulting in enhanced perception of pain intensity. Long term effects of cognitive [57] and psychological factors [37], as for stress reactions [135] are known to affect the perception of pain intensity.

Pain intensity related to disability, quality of life and health
In studies of both the group of patients with WAD, (Group 1) and the group with WAD, FM and SCI-related pain (Group 2), pain intensity ratings show the same relationship patterns with disability, quality of life and health. Pain intensity shows a weak relationship with quality of life and health, but a stronger relationship with physical functioning and disability.

When comparing subgroups of high vs. low pain in study I, the discriminating variables were found to be variables related to aspects such as ADL, physical functioning and mobility. In study III concerning the cluster analysis, the subgroups rating disability high vs. low, rated the pain intensity high vs. low respectively but with no clear relationship in the intermediate subgroups. When regressing disability, pain intensity showed great impact, whereas pain had a small impact when regressing quality of life. The same pattern is present in Study IV, in which in addition, self-efficacy variables were analysed. Self-efficacy functioning is associated to pain to pain variables, and is a strong regressor lowering disability, opposing the negative impact of pain intensity.

Earlier studies have showed results resembling our findings. Slaboda et al. [136] found that a subgroup of patients with chronic low back pain having lesser ability in lifting capacity, differed from a subgroup performing better in lifting by higher pain intensity, higher pain severity and lower self-efficacy.

If inserting pain intensity as a body function and structure component in the *ICF* context, the direct relationship to activity and functioning becomes evident. In chronic pain it is often not possible to lower pain intensity by e.g. pharmacological treatment. While there is a two way influence between pain intensity and activity in *ICF*, there may be a possibility to lower the perception of pain intensity by optimising the activity level and according to our first study, thereby enhance the perceived health related quality of life. This assumption is

supported by an interventional study comparing active physical treatment, cognitive-behavioural treatment and a treatment combining the two treatments. Although the active treatments were quite different, all 3 treatments were equally effective regarding the reduction of disability, patient-specific complaints, and current pain [67].

Pain duration related to disability, quality of life and health
Considering the complex interplay of pain and its consequences e.g. described in the diathesis-stress model, one could assume that the longer a chronic pain is lasting the worse the consequences regarding pain intensity, comorbid psychological affections, greater influence on disability, perceived quality of life and health. In support for this statement, it has been suggested that the time point in the development of a musculoskeletal pain problem may be an essential aspect of the importance of the relationship between psychological components and function [137]. Gullacksen and Liedbeck, on the other hand, present in a qualitative study a three stage model of adjusting to chronic pain where stage III implicates the constructive use of past experiences, leading to competence and control increased. An increased belief in the own ability enhanced the participation in an active life [138].

In the studies where we had information about duration of pain, i.e. study III and study IV, duration of pain was not associated with disability, quality of life, and health, and it was not a variable of importance when regressing those outcome variables. Time factors are naturally difficult to estimate in these studies with a cross sectional design. A possible explanation of the small importance of pain duration may be that all the patients in our study group all had very long pain durations (only 32/433 patients had duration of pain less than 3 years) and that the time factor had lost its importance since most pain states were consolidated.

An interesting group found in the cluster analysis in study III was the so called *'long-time/favourable'* subgroup. Although the subjects in this group scored high on pain intensity and had by far the longest duration of pain, they scored relatively low on the psychological factors. This group exhibited a relatively good situation according to quality of life and disability. Hence, if psychological factors are kept low, persons with high pain intensity for a long time seems, in this cross-sectional study to have a fair chance to live a life with relatively good quality. This must however be confirmed in prospective studies. Giesecke et al. [139] identified, in a study of patients with fibromyalgia, a subgroup with high tenderness, low depression/anxiety, low catastrophizing and high pain control. However there were no significant differences to other subgroups with regard to self-reported pain or perceived level of physical functioning in their study.

To our knowledge, this subgroup of chronic pain patients (the *'long-time/favourable'*), has not been identified earlier. A possible explanatory mechanism, referring to the diathesis- stress model is that individuals in this subgroup are able to cope with the stress of living with chronic pain and its consequences. They may also be influenced by self-efficacy as protective factors prohibiting the development of negative psychosocial and health effects of chronic pain.

Chronic pain and disability

Assessment of disability
According to *ICF, functioning* serves as a sum up term including, body functions, activities and participation. The negative aspect of functioning is *disability* and includes impairments, activity limitations and participation restrictions.

The Pain Disability Index (PDI), used to assess disability in Study III and IV, asks subjects to rate the degree to which activities in each of seven domains (family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care, and life-supporting activities) are interfered with, due to of chronic pain. This assessment fit well into the theoretical context of ICF. In Studies I and II no questionnaire especially designed for the assessment of disability was used, but subscales of Li-Sat 11 (e.g. contacts with friends, ADL and family life), and of SF-36 (e.g. vitality, physical functioning and social functioning) could be used to get an estimation of the disability dimension.

The relationship between disability and depression
Depression had the outmost strongest relationship with disability throughout the four studies. In Study II, comparing the subgroups with high vs. low depression with respect to perceived quality of life, the separating characteristics were aspects of vitality and participation. When regressing disability in Study III and IV, depression showed the strongest negative impact of the variation of disability. The role of depression for the outcome of disability in chronic pain is well established from earlier studies [39,140]. Studies I-IV are based on self reported disability and depression, not on observed physical functioning. However, Alschuler et al. [111] showed that self reported depression significantly predicted lower levels of observed physical performance.

It should be noted that the degree of depression, measured by HADS-D and BDI, barely reaches the cut off levels for clinical depression at group level in the four studies. The comorbidity and impact of depression in chronic pain conditions have been described earlier. However, qualitative differences between depression, as a result of chronic pain and depression as the primary psychiatric disorder, have been reported and the term 'affective distress' has been suggested [41]. In spite of the relatively low scoring of these depression variables, they seem to have a great impact on the outcome of disability in chronic pain patients. This emphasises the assessing of depression and the importance of considering this psychological factor in the clinical context.

The relationship between disability and anxiety
In Study III and IV, the assessment of levels of anxiety was added. Anxiety was assessed from three different perspectives: General anxiety (HADS-A), pain related anxiety (PASS-20) and anxiety sensitivity (ASI). All of these dimensions of anxiety have earlier been related to disability in chronic pain [36,141,142]. In our studies, pain anxiety contributed more than general anxiety to disability, a finding that agrees with McCracken et al. [143] who showed that disability was most strongly correlated with the more specific pain-related fear measures, compared with a more general measurement of anxiety. The importance of pain-related anxiety on disability could be viewed within the context of the fear

avoidance model. A large number of mainly cross-sectional studies have shown that pain related fear is one of the most potent predictors of observable physical performance and self-reported disability [9].

The relationship between disability and catastrophizing.
Catastrophizing has, in several earlier studies, been associated with disability in patients with chronic pain [63,144]. Catastrophizing has also been considered as a precursor of pain related fear [145]. In a recent study, Buenaver et al. [146] concluded that their study agreed to several other studies that conceptualizes catastrophizing as a diathesis, or risk factor, for deleterious pain-related consequences. This fits with the diathesis-stress model connecting catastrophizing and disability.

In study II, in a comparison between a subgroup of low pain, depression and catastrophizing vs. a subgroup of low pain and depression but with high catastrophizing, the separating items were items with respect to quality of life and health were items concerning pain and activity. This may implicate a role of catastrophizing in the activity level of patients with chronic pain. Catastrophizing was associated to disability in Study III and IV and was a variable of importance of the variance of disability.

The relationship between disability and pain variables
Those relationships are discussed in the section discussing pain intensity and duration (se pages 53 and 54)

The relationship between disability and self-efficacy
Self-efficacy is considered to be a god predictor for pain-related disability [147] and can, according to Turner et al. [78] be regarded as a factor that contributes to disability and depression beyond the role of pain severity.

In Study IV the interest was in the relationships between the subscales of self-efficacy and disability, quality of life and health. Furthermore there was interest in whether certain subscales corresponded to specific variables of psychological factors, pain or cognitive factors.

Concerning disability two subscales were important and had a negative correlation to disability i.e. lowered perceived disability. As expected the subscale self-efficacy function (measuring the perceived ability to perform functions in daily living) was important. However the subscale self-efficacy symptoms (measuring the perceived ability to control other symptoms related to pain) was as important to the variation in perceived disability. This may be seen as a relationship of self-efficacy symptoms to the negative influence of depression, a symptom related to pain, on disability.

Disability and the diathesis stress model
In summary, one may apply the diathesis-stress model that includes disability (**Figure 5**) on relationship between disability and chronic pain. Catastrophizing and anxiety sensitivity may be understood as diathesis (pre-existing, semi-dormant characteristics of the individual). Pain and disability may be understood as stressors leading to depression and/or anxiety and starting a vicious cycle. This

cross-sectional study may also support the role of self-efficacy as protective factors prohibiting the development of negative psychosocial and health effects of chronic pain. This agrees with the theoretical framework of regarding self-efficacy as a factor that can *buffer* the adverse effects of stressors (epidemiological risk-buffer model) or as *proactive shaping* of life circumstances (proactive agentic model) [28]. In this study, we are only able to confirm the presence and relative importance of the different factors; we were unable to express a definite opinion on temporal pathways.

Chronic pain and quality of life and health

Assessment of quality of life and health
As noted in the introduction (see pages 18 and 19) of this thesis, the conceptualization of quality of life as Health related Quality of Life (HRQL) also included aspects of health. General health is only connected to the evaluation of the subscale general health in SF-36.

The relationship between HRQL and depression
The overall conclusion of the four studies with respect to the outcome of HRQL, is the very strong relationship to depression. In study II the 8 subgroups based on dichotomizing pain, depression and catastrophizing were analyzed with respect HRQL variables. All subgroups scoring high on depression scales showed the worst perceived situation concerning HRQL relatively independent of the scores on pain intensity and catastrophizing. In the cluster analysis in Study III, there was a clear relationship between depression and quality of life; the higher the score on depression, the lower perceived HRQL. Regression analysis showed that depression was the outmost dominant variable for the outcome of quality of life. This result was repeated in study IV, where depression was correlated to HQRL, and was the only significant variable with negative influence on the outcome of HRQL. In this study, depression was also correlated to general health (SF-36 GH) but had about the same impact as other psychological variables on the outcome of general health. This mixed pattern of influencing variables may be due to the few and general questions about health.

The relationship between depression and chronic pain is complex and still incompletely understood and the relationship between depression and HRQL in chronic pain patients has been illustrated in only a few studies earlier [86,148]. The studies in this thesis contribute additional knowledge and support findings of earlier studies.

The subgroups in Study II with high depression differed from subgroups with low depression, mostly with respect to items of health and quality of life concerning psychological, well-being, vitality, and emotional as well as participation aspects. Those results agree with Pincus et al. [40] who found that depression in chronic pain corresponds to a more general reduced activity and social withdrawal, and thereby differs in characteristics vs. the primary psychiatric depression disorder.

The fact that depression in chronic pain has a somewhat different appearance, is not characterized by high scoring on depression scales and has a crucial

importance for the outcome of perceived quality of life, makes it very important to assess, recognize and treat depression in the clinical setting.

The relationship between HRQL and anxiety.
In Studies III and IV, the opportunity to study the relationship between different aspects of anxiety to HRQL in patients with chronic pain was given. These studies did not change the impression from Study II that depression had by far the greatest relationship to HRQL despite the addition of anxiety to the analyses. Anxiety was related to HQRL in the cluster analysis in Study III and in the multivariate context in Study IV but had borderline or none significant influence on the outcome of HRQL. There was a significant correlation with the outcome of General Health with about the same level of correlation with pain anxiety, general anxiety and anxiety sensitivity. The latter may correlate to, that the general concept of health, was influenced of different aspects of anxiety, not only the pain related aspect.

There is a lack of studies addressing the relationship of anxiety and HQRL in patients with chronic pain. Früwald et al [149] made a comparative study of post stroke patients, patients with low back pain and myocardial ischemia patients, assessing depression, anxiety and QOL, They demonstrated that QOL was markedly affected in the post stroke patients and in the chronic low back pain and myocardial ischemia patients, and it was rated worst by the most seriously depressed subjects.

The relationship between HRQL and catastrophizing.
There are several earlier studies that have demonstrated a relationship between catastrophizing and low perceived HQRL. Lame et al. [62] concluded that pain catastrophizing showed the strongest association with quality of life, stronger than pain intensity, in patients from a multi-disciplinary university pain clinic. Raak et al. [150] found in a 6 year follow up study of patients with low back pain included in a rehabilitation programme, a decrease in catastrophizing and an improvement in HQRL, and that changes in catastrophizing or in HRQL did not appear to influence self-scored bodily pain.

In studies I-IV was shown a more mixed pattern of the relationship between catastrophizing and HRQL. In the cluster analysis in Study III there was a clear relationship between the level of catastrophizing and HQRL, but when regressing HRQL, the influence of catastrophizing was only of borderline importance. In Study IV, catastrophizing was related to HQRL but no significant influence on the outcome of HQRL where the only significant variable of negative influence was depression.

The results in Study II are interesting since the impact of catastrophizing appeared to be most important on the outcome of HQRL when the scorings of both pain and depression were low. This fact and the result from Study III and IV may implicate that the importance of the relationship between catastrophizing and HQRL may vary, dependent on the presence and level of other psychological factors especially depression. On the contrary, findings from a study of Holroyd et al [151] show that that catastrophizing is associated with impaired QOL,

independent of migraine characteristics and other demographic and psychological variables.

Results of studies I-IV may place the role of catastrophizing as a diathesis in the diathesis-stress model. Its presence in patients with low pain and low depression in Study II, indicates much lower quality of life and, and according to the model, it may lead to depression which has a major influence on HRQL. In a prospective study of patients with rheumatoid arthritis [152], it was found that patients with high pain catastrophizing at baseline showed increases in depression 6 months later, a study that may support the statement.

The relationship between disability and pain variables
Those relationships are discussed in the section discussing pain intensity and duration (see pages 53-54).

The relationship between HRQL and self-efficacy.
Perceived self-efficacy is defined as people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives. Self-efficacy beliefs determine how people feel, think, motivate themselves and behave. A strong sense of self-efficacy enhances human accomplishment and personal well-being in many ways [153]. Therefore it may be concluded that self-efficacy, on a general level, should be related to perceived quality of life. Self-efficacy has also been found to correlate to perceived HRQL. Brekke et al [154] showed in a longitudinal study of patients with rheumatoid arthritis a significant correlation between patients´ baseline level of self-efficacy for pain and other symptoms and the change in perceived HRQL over a 2 year period. Käll et al. [155] evaluated whether psychological factors and personality traits influenced recovery in terms of quality of life in patients with subacute WAD and found that 40% of the variation in the outcome of HRQL was explained by the self-efficacy.

The results of study IV are in accordance with those findings. Self-efficacy correlates multivariately with HRQL. Concerning the outcome of HRQL, the subscale self-efficy symptoms, representing the perceived ability to handle pain related symptoms, was the only positive, significant variable of importance. This may reflect that the only significant negative variable of importance, depression which can be regarded as a symptom related to pain. This agrees with the theoretical framework of regarding self-efficacy as a factor that can *buffer* the adverse effects of stressors (epidemiological risk-buffer model) or as *proactive shaping* of life circumstances (proactive agentic model) [28].

Chronic pain, HRQL and the ICF model
Regarding ICF as an integrated biopsychosocial model of human functioning and disability and providing a classification system handling several aspects of health and disability, our findings about HRQL in chronic pain can easily be interpreted in the theoretical context of this model. Pain, depression and anxiety represent body functions and structures and the diatheses catastrophizing and anxiety sensitivity representing personal factors. All these factors having an influence of the interconnected ICF-system, which represents aspects of health.

Differences in diagnoses

Sometimes there is a clinical impression that patients with a specific pain diagnosis share similar characteristics concerning e.g. type of pain, the level of disability, manifestations of psychological symptoms and the overall way of managing pain and pain related symptoms.

Most studies performed have compared different pain states with healthy subjects, neurobiologically [156] and psychologically [126] and found differences for obvious reasons. Studies comparing different pain states show various results. Zautra et al. [157] found, after controlling for chronic pain levels, little evidence that women with fibromyalgia had greater difficulty in the management of negative emotions than their osteoarthritis counterparts. On the other hand, Cöster et al. [117] concluded that chronic widespread pain with widespread allodynia to pressure pain (FM) was associated with more severe symptoms, higher pain intensity, higher pain severity, fewer pain-free periods, and more pronounced pain-related interference in everyday life and consequences for daily life compared with chronic widespread pain without widespread allodynia. A study from Foss et al. [158] comparing chronic low back pain and post herpetic neuralgia, showed that measures of variability of spontaneous pain differentiate between chronic pain conditions, and thus may have mechanistic and clinical utility.

Diatchenko et al. [159] conclude in their review that there is growing evidence that the onset of idiopathic pain disorders is associated with both physical and psychological triggers that initiate pain amplification and psychological distress. However, each individual will develop these conditions with different probability. This probability is defined by a complex interaction between the individual's genetic background and the extent of exposure to specific environmental events. This may implicate that the outcome of chronic pain mainly depends on individual factors rather than the diagnosis.

One of the over all aims of this thesis was to compare chronic pain conditions of different origins and characters. This was possible to perform in study III and IV. In the cluster analysis in Study III, there was a tendency that the different subgroups of diagnoses were distributed differently in the different clustered subgroups. 43% of the patients with SCI related pain belonged to the *"most favourable"* subgroup, 44% of patients with WAD belonged to the *"short time worse"* subgroup while FM patients were more evenly distributed among the clustered subgroups. Those finding were not scrutinized further in the study.

In Study IV, the score plot generated from the PCA analysis describing the relations between the subjects and, in addition, the different diagnoses denoted, showed a minor discrimination between the three diagnoses and mainly identified FM. When excluding the variable for spreading of pain, because it is a diagnostic criterion for FM, this made it impossible to recognize any diagnosis specific pattern of the subjects; that is, there is no diagnosis specific pattern in the influence of the different variables (depression, anxiety, catastrophizing, self-efficacy, pain variables, disability and quality of life) in the model.

The results may point to the conclusion that the outcome of chronic pain referring to the assessed variables and the assessed patient group, mainly is related to individual factors rather than to a specific pain diagnosis.

SUMMARY AND CONCLUSIONS

- Widespread pain in chronic WAD is associated with negative consequences with respect to pain intensity, prevalence of other symptoms (including depressive symptoms), some aspects of coping, quality of life and health.

- Based on depression, anxiety, catastrophizing, pain intensity and duration we managed to identify subgroups of patients with chronic pain that differed with respect to perceived Health Related Quality of Life (HRQL) and disability.

- The psychological factors (especially depression) showed strong correlation with perceived HRQL and disability.

- The degree of depression appears to have the most important relationship to perceived HRQL.

- Despite the fact that the patients rated depression just mild or moderate, depression had a great correlation with the outcome of HQRL and disability.

- Pain intensity and duration play a minor role for perceived HRQL, whereas pain intensity relates more to the outcome of perceived disability.

- Self-efficacy has a positive relationship, whereas psychological factors (depression, anxiety and catastrophizing) and pain have a negative relationship with the outcome of HRQL and disability.

- There are specific patterns of the subscales of the subscales of self-efficacy and a corresponding pattern of negative factors related to the outcome of HRQL and disability.

- From a clinical point of view it is important to assess each individual in detail with respect to depression, anxiety, self-efficacy and pain when planning treatment and rehabilitation.

FURTHER RESEARCH

This study has a cross section design which makes it impossible to make any statements about temporal processes and causality. There is a need for prospective studies making it possible to follow the process of acute pain developing to chronic pain with respect to psychological factors and pain variables.

Studies including intervention regarding psychological factor and especially their relationship should be an interesting next step based on the results of this study. This should enlighten the temporal process as well as making it possible to scrutinize the effect of influencing different factors of importance emerged from this study.

The issue of why some people develop chronic pain and some not is of crucial importance. Addressing the biopsychosocial model of pain there is complex interplay of both neurobiological psychosocial factors involved. One important factor is the genetics of pain. Some promising studies, Genome Wide Association Studies (GWAS) has shown promising result. It would be very interesting to go further with genetic studies based on the results of our study.

SAMMANFATTNING PÅ SVENSKA

Långvarig smärta är ett mycket vanligt tillstånd med en prevalens på 40-65% i befolkningen. Denna stora förekomst av långvarig smärta förorsakar stort mänskligt lidande men också stora kostnader för samhället. Utvecklingen och upprätthållande av långvarig smärta utgör ett komplext samspel mellan neurobiologiska, psykosociala och genetiska faktorer. Det har förslagits en biopsykosocial smärtmodell för att på ett begripligt sätt beskriva detta problemkomplex.

Det huvudsakliga syftet med denna avhandling var att få en bättre förståelse av hur de olika komponenterna i den biopsykosociala smärtmodellen förhåller sig till varandra och att studera den relativa betydelsen av smärta, stress och olika psykologiska faktorer på upplevd hälsorelaterad livskvalitet och funktionsbegränsning.

Avhandlingen baseras på studiet av två patientgrupper. En grupp av 275 patienter med kronisk whiplashskada (WAD) och en grupp av 433 patienter med de tre olika diagnoserna; WAD, fibromyalgi och smärta relaterad till ryggmärgsskada. Patienterna fick besvara frågeformulär som berörde olika aspekter av smärta, depression, ångest, katastroferande, funktionsbegränsning och hälsorelaterad livskvalitet.

Huvudresultaten var att psykologiska faktorer (fr.a. depression) har en avgörande betydelse för hur patienterna upplever funktionsbegränsning och livskvalitet. Graden av depression förefaller ha den viktigaste relationen till upplevd livskvalitet. Trots att patienterna uppskattade graden av depression som mild eller moderat, är depression av stor betydelse för utfallet av funktionsbegränsning och livskvalitet. Smärtintensitet och smärtduration spelade en mindre roll för upplevd livskvalitet medan smärtintensitet relaterade mer till utfallet av upplevd funktionsbegränsning.

Från klinisk synpunkt är det viktigt att bedöma varje individ i detalj avseende depression, ångest, tilltro till egen förmåga (self-efficacy) och smärta vid planering av behandling och rehabilitering. Det är en nödvändighet att ha fokus på individen och dennes komplexa och unika situation för att optimera resultatet av smärthanteringsprogram.

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The mysterious *lady in red*……

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