Health-related quality of life in patients with chronic pain

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ACADEMIC DISSERTATION

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One man, when he has done a service to another, is ready to set it down to his account as a favour conferred. Another is not ready to do so, but still thinks of the man as his debtor, and he knows what he has done. A third in a manner does not even know what he has done, but he is like a vine that has produced grapes and seeks for nothing more after it has once produced its proper fruit. As a horse when he has run, a dog when he has tracked the game, a bee when it has made the honey, so a man when he has done a good act, does not call out for others to come and see, but he goes on to another act, as a vine goes on to produce again the grapes in season.

Marcus Aurelius, 121-180 A.D.
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Abstract

Chronic pain impairs health and both physical and cognitive function, and is associated with considerable psychosocial problems. The management of chronic pain is challenging, and multidisciplinary pain management (MPM) is considered the most efficacious method of treating chronic pain. However, treatment outcomes vary greatly, and it is not possible to predict which patients will benefit from MPM.

Health-related quality of life (HRQoL) measurement aims to capture the comprehensive, subjective health state of a patient. Generic HRQoL enables comparison across all patient populations and is an integral component of cost-utility studies. Several instruments can measure HRQoL. However, they may produce differing results. Although measuring HRQoL is considered essential for treatment effectiveness, and it is also recommended in trials of chronic pain management, the validity of different instruments has not previously been compared.

The aim of this thesis is:

• To assess the validity of two HRQoL instruments, the 15D and the EQ-5D, in chronic pain patients treated at a tertiary pain centre.
• To describe the HRQoL in a large sample of severe chronic pain patients; to analyse the association between HRQoL, socioeconomic background and different aspects of chronic pain.
• To describe the long-term HRQoL changes after outpatient MPM at a tertiary pain centre
• To identify possible associations between good or bad HRQoL outcomes and the background variables.

The thesis consists of three publications, and reports on two patient populations. The validity of the two HRQoL instruments, the EQ-5D and the 15D was studied using a sample of 391 patients attending secondary or tertiary multidisciplinary pain clinics. At the beginning of their treatment episode, the patients responded to the two HRQoL instruments’ questionnaires, as well as another set of questionnaires measuring socioeconomic factors, self-rated health, pain intensity and interference, depression, pain acceptance, pain-related anxiety, and sleep. The second study sample consisted of 1528 patients with chronic non-cancer pain, treated at a tertiary multidisciplinary pain clinic of the Helsinki University Hospital. These patients filled in the 15D HRQoL questionnaire at baseline and again after a 12-month follow-up. They also filled in the pre-admission questionnaire of the pain clinic, which contained questions on pain, related psychosocial disability and socioeconomic background. The structure of the treatment episode was extracted from the hospital’s electronic archives. We compared the baseline HRQoL results with those of an age- and gender-matched sample of the general population, and studied the association between HRQoL and background variables using stepwise linear regression. We examined the mean and individual changes in HRQoL and studied the association between the background variables and
the HRQoL change using linear and logistic regression methods.

The EQ-5D and the 15D showed moderate agreement, but the scores had considerable differences. Both HRQoL instruments were strongly associated with the pain-related factors, but the 15D appeared slightly more sensitive than the EQ-5D in relation to the psychosocial factors of chronic pain, and had better discriminatory power in better health states. The mean HRQoL of chronic pain patients in tertiary care was very low, much below that of the general population sample, and one of the lowest reported by the 15D instrument. The 15D HRQoL score was associated with measures of psychosocial burden of chronic pain, but pain intensity had no independent predictive value in HRQoL.

There was a clinically and statistically significant mean improvement (+0.017) in the 15D score 12 months after the beginning of MPM. Fifty-three per cent of patients reported a clinically significant improvement, and 43% a major improvement in their 15D HRQoL score. However, the HRQoL changes varied considerably, and the mean HRQoL of the patients remained below that of the general population and most other patient populations. Being employed, having a higher education, and shorter pain duration as the only pain-related variable were associated with a higher probability of improvement.

The results demonstrate the validity of the two HRQoL instruments in patients with chronic pain; the widely-used EQ-5D and the 15D. However, the scores that the two instruments produced differed considerably, the results slightly favouring the 15D. The very low observed HRQoL underlines the considerable burden of disease among patients with chronic pain, and the psychosocial aspects of pain were important in determining the overall quality of life. The large variations in the changes in HRQoL after MPM imply a need to better recognize patients who will or will not benefit from the treatment.
Tiivistelmä

Krooninen kipu heikentää terveyttä sekä toimintakykyä ja siihen liittyy huomattavia psykososiaalisia ongelmia. Kroonisen kipun hoito on haastavaa, ja hoitotuloksissa on suurta vaihtelua. Moniammatillinen kivunhoito (multidisciplinary pain management, MPM) on nykykäsityksen mukaan tehokas kroonisen kipun hoitomenetelmä, mutta hoidosta hyötyvää potilaita ei pystytä tunnistamaan.

Terveyteen liittyvää elämänlaatu kuvaavat potilaan kokonaisuutta ja sen vaikutuksia terveyteen ja toimintaan sekä sosioekonomisiin taustatekijöihin. Kroonisen kipun hoito on monimutkainen ja sen tuloksissa on suuria vaihteluita. Monimutkainen kivunhoito (multidisciplinary pain management, MPM) on nykykäsityksen mukaan tehokkain kroonisen kipun hoitomenetelmä, mutta hoidosta hyötyvää potilaita ei pystytä tunnistamaan.

Tämän väitöskirjan tavoitteet olivat seuraavat:

- Arvioida kahden elämänlaatumatkinnan, EQ-5D:n ja 15D:n validiteettia erikoissairaanhoidon kivuklinikalla hoidetulla kroonisilla kipupotilailla
- Kuvailla terveyteen liittyvää elämänlaatua suurikokoisessa, vaikeahoitoisessa kroonista kipua sairastavien potilaiden aineistossa sekä tutkia sosioekonomisten tekijöiden ja kroonisen kipun eri piirteiden yhteyttä elämänlaatuun
- Kuvaile elämänlaadun muutokset polikliinisesti yliopistosaaralassa toteutetun moniammatillisen kivunhoitohakson jälkeen
- Tunnistaa mahdollisia yhteyksiä hyvän tai huonon elämänlaatumuutokseen ja potilaiden taustatekijöiden välillä.


Elämänlaadussa havaittiin kliinisesti ja tilastollisesti merkitsevää keskimääräinen parantuminen (15D-elämänlaadun muutos +0,017) 12 kuukautta hoitojakson alamisen jälkeen. 53%:lla potilaista elämänlaadun paraneminen ylitti kliinisesti merkittävän rajan (+0,015), ja 43%:lla elämänlaadussa tapahtui suuri parantuminen (+0,035). 35%:lla elämänlaatu kuitenkin laski kliinisesti merkittävästi, ja potilaiden keskimääräinen elämänlaatu jäi yhä paljon alhaisemmaksi kuin verrokkiväestöllä ja suurimmalla osalla muista potilasryhmistä. Töissä olo, korkeampi koulutus ja lyhyempi kivun kesto ennakoivat hieman suurempaa elämänlaadun kohentumista.

List of original publications

This thesis is based on the following original publications (Studies I-III) and some unpublished data.


III. Vartiainen Pekka, Heiskanen Tarja, Sintonen Harri, Roine Risto P., Kalso Eija. Health-related quality of life change in patients managed at an outpatient multidisciplinary pain clinic. *Submitted in 10.5.2018*

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List of abbreviations

15D  The 15-dimensional health-related quality of life instrument
AAPT  ACCTION-APS Pain Taxonomy
AQoL  Australian Quality of Life Instrument
BDI  Beck Depression Inventory
BNSQ  Basic Nordic Sleep Questionnaire
BPI  Brief Pain Inventory
CBT  Cognitive-Behavioural Therapy
CI  Confidence Interval
CPAQ  Chronic Pain Acceptance Questionnaire
DALY  Disability-Adjusted Life Year
EQ-5D  Euro-QoL 5-dimensional health-related quality of life instrument
EQ-5D-3L  EQ-5D questionnaire with three levels of severity in each dimension
EQ-5D-5L  EQ-5D questionnaire with five levels of severity in each dimension
EQA-VAS  Visual analogue scale on quality of life, used as a reference for the EQ-5D
ES  Effect Size
FM  Fibromyalgia
HRQoL  Health-Related Quality of Life
IASP  International Association for the Study of Pain
IBS  Irritable Bowel Syndrome
ICD  International Statistical Classification of Diseases and Related Health Problems
IMMPACT  Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
ISOQOL  International Society for Quality of Life Research
LBP  Low Back Pain
MID/MIC  Minimum Important Difference/Minimum Important Change
MPM  Multidisciplinary Pain Management
MRI  Magnetic Resonance Imaging
NICE  National Institute for Health and Care Excellence
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>NRS</td>
<td>Numeric Rating Scale</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PAG</td>
<td>Periaqueductal Gray</td>
</tr>
<tr>
<td>PASS</td>
<td>Pain Anxiety Symptoms Scale</td>
</tr>
<tr>
<td>PB</td>
<td>Parabrachial nucleus</td>
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<tr>
<td>PTSD</td>
<td>Post-Traumatic Stress Disorder</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Years</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>RVM</td>
<td>Rostral Ventral Medulla</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SEM</td>
<td>Standard Error of Mean</td>
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<tr>
<td>SF-12</td>
<td>Shortened, 12-item version of the SF-36</td>
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<tr>
<td>SF-36</td>
<td>The 36-Item Short Form Health Survey</td>
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<td>SG</td>
<td>Standard Gamble</td>
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<tr>
<td>TMD</td>
<td>Temporomandibular Disorder</td>
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<td>TTO</td>
<td>Time Trade-Off</td>
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<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
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<tr>
<td>VRS</td>
<td>Verbal Rating Scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WTP</td>
<td>Willingness-to-Pay</td>
</tr>
<tr>
<td>YLD</td>
<td>Years Lived with Disability</td>
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<tr>
<td>YLL</td>
<td>Years of Life Lost</td>
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Introduction

Chronic pain poses a great burden on individuals and is a serious problem to modern society. It is associated with impaired health and functioning. Its pathogenesis is poorly understood, and consequently, its treatment often symptomatic. Many treatment modalities have emerged, but their efficacy remains modest at best.

The gold standard of chronic pain treatment is multidisciplinary pain management (MPM). However, trials of chronic pain management usually suffer from extensive heterogeneity in their study designs and outcomes. Thus, these studies are generally not comparable with each other, and our knowledge of the efficacy of pain management programmes remains limited (Scascighini et al., 2008). Moreover, the treatment outcomes observed in chronic pain management trials vary greatly, most patients achieving either a major benefit or no benefit at all (Heiskanen et al., 2012; Moore et al., 2014). We still do not know what makes MPM superior to other forms of treatment, or which patients benefit from it.

Health care interventions must be proven effective. The gold standard of evidence-based medicine, the randomized controlled trial (RCT) study setting, is not without limitations, and it may not be applicable to all research questions. For example, the external validity of RCT results can sometimes be questioned, as the real-world clinical environment in which the treatments are provided is not necessarily an ideal study setting. (Frieden, 2017; Rothwell, 2005) It is important that we also critically assess the efficacy of health care interventions in this real-world setting.

Health-related quality of life (HRQoL) measurement aims to capture the comprehensive, subjective health of patients. It encompasses various aspects of health and combines them into an index that reflects the patient’s health state against the preferences of a healthy population. It has many advantages that make it an appealing outcome measure for chronic pain management. It is subjective, comparable across all patient groups and treatments, and it facilitates cost-effectiveness studies. The measurement of HRQoL is recommended in trials of chronic pain management (Turk et al., 2003) as well as in trials assessing MPM (Kaiser et al., 2018). However, different HRQoL instruments have produced differing results among chronic pain patients (Lillegraven et al., 2010; Torrance et al., 2014), as well as among other patient groups (Haw thorne et al., 2001; Richardson et al., 2011). This has brought to attention the fact that the properties of different HRQoL instruments, such as validity, have not been studied among chronic pain patients (Schofield, 2014).

We conducted the present study to acquire information on the properties of HRQoL instruments in treating chronic pain patients, to study the effect of pain on HRQoL, and to estimate changes in HRQoL after MPM.
Review of the literature

Definition of pain

Pain is the flagship of unpleasantness. The sensation has evolved to teach us to avoid harmful situations; for example, not to use a broken limb in order to give it time to heal. To make us remember the lesson, pain sensation is accompanied by strong, negative emotions. Physiologically, pain signals tissue injury or a threat of such and encourages withdrawal from painful situations. Another function of pain is to facilitate the healing of a tissue injury, by making us avoid the use of the injured site. The International Association of the Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (1994). In other words, the experience of pain is our brain’s meaningful reaction to signals of tissue damage.

Normal pain sensation

The typical pathway from painful stimulus to pain experience can be divided into transduction, transmission, modulation, and perception. Transduction implies the activation of peripheral primary afferent nerve fibres. The activation of these nociceptors can be caused by mechanical or chemical energy (such as pressure or heat), or by inflammation-signalling molecules released by injured cells. The nociceptors discharge action potentials in response to these stimuli, the rate of which correlates to the intensity and duration of the noxious stimulus. Nociceptors have a certain threshold of activation, and normally only produce action potentials when the intensity of a potentially noxious stimulus crosses this threshold. Nociceptors are classified into two major groups, A-delta fibres and C fibres. A-delta fibres are myelinated, and transmit signals of acute, well localized pain sensation. C fibres are unmyelinated, and they convey poorly localized, slow pain signals.

The nociceptors synapse in the dorsal horn of the spinal cord. There, the secondary neurons transmit the pain signal towards the thalamus and somatosensory cortex, but in the central nervous system the pain signal is subject to significant modulation and interpretation. A classic example of this modulation is the gate-control theory (originally proposed by Melzack and Wall, 1965), which suggests that the transmission from the primary afferent neurons to the spinal cord is modulated at the spinal cord level, more accurately, in the substantia gelatinosa of the dorsal horn. This gating mechanism is controlled by, for example, the activity of somatosensory fibres: nociceptive fibre activity opening the gate, and non-nociceptive fibre activity closing it. In practice, the theory implies that a non-nociceptive stimulus, such as touch, can inhibit pain sensation. This modulation can be produced by a multitude of pathways, and can be either inhibitory or excitatory.

The role of modulation of the pain signal has been studied by functional imaging of the brain (e.g. positron emission tomography, PET) and simultaneous pain stimulation. The number of neurons activated in areas processing the affective component of pain
after pain stimulus has shown to be smaller among subjects who know to expect a painful stimulus than among those who are unaware of it. If the attention of a subject is focused on something, the number of neurons activated in these areas is smaller.

In laboratory experiments on acute pain, the intensity of stimulus has correlated fairly well with experienced pain intensity. Outside experimental laboratories, the mechanism that causes pain (e.g. a surgical procedure) and the experienced pain intensity varies substantially among individuals. In chronic pain, this difference in intensity among individuals is even more pronounced. Even everyday experience shows that psychological factors such as intense concentration in a competitive situation, or fear, can profoundly affect pain perception.

The brain areas identified in the descending modulation include periaqueductal grey matter (PAG), the nucleus raphe magnus and the nearby formatio reticularis, and locus coeruleus in the tegmentum. Endogenous opioids, serotonin, noradrenalin and gamma-aminobutyric acid (GABA) are involved in the neurotransmission of the descending modulatory signals (Millan, 2002). For a review on the modulation mechanisms at the spinal level, see (Todd, 2010), and for supraspinal mechanisms, see (Apkarian et al., 2005).

Painful stimuli, such as trauma or surgery, also trigger various autonomic and endocrine responses, which include the activation of the sympathetic nervous system, and the release of e.g. catecholamines and cortisol. This produces well-recognized responses such as an increase in blood pressure and heart rate, and they may affect the recovery from the trauma or surgery. These mechanisms, and the effect of anaesthesia on them, are reviewed by (Desborough et al., 2000). However, the magnitude of these mechanisms does not necessarily correlate with the intensity ratings of postsurgical pain (Ledowski, 2012).

The interpretation of pain experience involves many brain regions and pathways. The spinothalamic tract conveys signals of nociception from the spinal cord to the thalamus. This is especially relevant in the perception of acute pain and its sensory-discriminative component. The somatosensory cortex is mainly responsible for the sensory-discriminative component. Pain experience also has many other components: for example, acute pain evokes negative emotions and possibly results in behavioural changes in the organism experiencing pain. The concept of the pain matrix refers to the several interconnected neural networks involved in pain processing. This involves several levels of processing: the nociceptive matrix is responsible for nociception and receives input from spinothalamic projections. Second-order processing is not nociceptive-specific, but involves a conscious perception of pain, attentional modulation and control of vegetative reactions, involving areas such as the posterior parietal, prefrontal and anterior insular cortices. Third-order areas, such as the orbitofrontal and perigenual/limbic networks can further mediate the effect of one’s beliefs, emotions and expectations concerning the pain experience (Garcia-Larrea and Peyron, 2013).
Some brain areas and connections involved in the processing of a pain signal. It must be noted that the image is a gross simplification, and in reality many more connections and areas are involved in the pain experience.

Blue signal indicates an incoming pain signal from the spinal cord via the spinothalamic tract that is transmitted to the somatosensory cortex, and contributes to the sensory-discriminative component of the pain experience. Green indicates the brain areas and networks involved in the secondary processing of pain signal, such as behavioural changes or attentional modulation, that are not nociceptive-specific. Red indicates the signals of descending modulation of pain, that can be either facilitative or inhibitory.

RVM = Rostral Ventral Medulla; PB = Parabrachial Nucleus; PAG = Periaqueductal grey; S1, S2 = Primary & secondary somatosensory cortices

The image is based on the illustration “Skull and brain sagittalsvg” by Patrick J. Lynch and C. Carl Jaffe (https://commons.wikimedia.org/wiki/File:Skull_and_brain_sagittalsvg). The original image is licensed under CC BY-SA 2.5
**Definition of chronic pain**

The role of the pain experience in facilitating an organism's survival is clear - pain should teach us to avoid harmful situations. However, chronic pain seems to provide no benefit at all for an organism's survival or adaptation. Generally, pain is considered chronic when it persists for more than the normal time for tissue healing. For the new ICD-11 coding tool for diagnoses, the Task Force for the Classification of Chronic Pain, set up by the IASP, has defined pain as chronic if it lasts for over three months (Treede et al., 2015).

**Classification of chronic pain**

A 'Chronic pain' category has been proposed for the new ICD-11 classification. This category is divided into seven major groups: (1) chronic primary pain, (2) chronic cancer pain, (3) chronic post-traumatic and post-surgical pain, (4) chronic neuropathic pain, (5) chronic headache and orofacial pain, (6) chronic visceral pain, and (7) chronic musculoskeletal pain (Treede et al., 2015).

Other approaches to classification have also been proposed. The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the US Food and Drug Administration and the American Pain Society (APS) have published the ACTTION-APS Pain Taxonomy (AAPT). The aim of AAPT is to create an evidence-based approach to classifying and diagnosing major chronic pain conditions (Dworkin et al., 2016).

The AAPT suggests the following classification for chronic pain conditions. Listed are the specific chronic pain conditions for which the AAPT has diagnostic criteria. They do not cover all the chronic pain conditions that occur within the categories:
### Peripheral nervous system
- Complex regional pain syndrome
- Painful peripheral neuropathies
- Postherpetic neuralgia
- Post-traumatic neuropathic pain, including pain after surgery
- Trigeminal neuralgia

### Central nervous system
- Pain associated with multiple sclerosis (MS)
- Post-stroke pain
- Spinal cord injury pain

### Spine pain
- Chronic axial musculoskeletal low back pain
- Chronic lumbosacral radiculopathy

### Musculoskeletal pain
- Fibromyalgia and chronic myofascial and widespread pain
- Gout
- Osteoarthritis
- Rheumatoid arthritis
- Spondyloarthropathies

### Orofacial and head pain
- Headache disorders (See *International Classification of Headache Disorders*)
- Temporomandibular disorders

### Abdominal, pelvic and urogenital pain
- Interstitial cystitis
- Irritable bowel syndrome
- Vulvodynia

### Disease-associated pain not classified elsewhere
- Pain associated with sickle-cell disease
- Pain associated with cancer: cancer-induced bone pain, chemotherapy-induced peripheral neuropathy, and pancreatic cancer pain

*Table modified from Dworkin et al., 2016.*

The AAPT has also developed a multidimensional framework that can be assessed in all chronic pain conditions (Dworkin et al., 2016). The dimensions are:

- Core diagnostic criteria
- Common features (that are not included in the core diagnostic criteria)
- Common medical and psychiatric comorbidities
- Neurobiological, psychosocial and functional consequences
- Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors

It has been increasingly noted that many common chronic pain conditions do not manifest alone; they frequently coexist in patients. These conditions include, but are not limited to, temporomandibular disorder (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia, chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain (Maixner et al., 2016). Although these conditions have multifactorial aetiologies and diverse clinical manifestations, they share many...
characteristics, such as a high prevalence of comorbid symptoms including fatigue, sleep impairment, problems with cognition, physical dysfunction, and disturbances in affect (e.g. anxiety, anger, depression). The definitions of these syndromes also overlap, and many patients may fulfil the criteria for several conditions. Traditionally, the significant overlap in chronic pain conditions has not been paid sufficient attention during patient recruitment for clinical trials. Maixner and colleagues have summarized the theory, mechanisms and implications of chronic overlapping pain conditions (Maixner et al., 2016).

**Biopsychosocial model**

Historically, chronic pain was seen as a simple pathological process, the intensity of which was linearly dependent on the extent of tissue damage, and which could be fixed with medication or surgery (Jensen and Turk, 2014). If pain was not ‘organic’, it was deemed ‘psychogenic’ or ‘functional’. Any psychological factors assessed were regarded as underlying mechanisms or causal factors, i.e., something that caused psychogenic pain. The prevailing view, however, is that chronic pain is a complex, multidimensional problem, and the biopsychosocial model of chronic pain describes chronic pain as a dynamic interaction of related biological, psychological and social processes.

Pain experience and its impact is a combination of somatic input (e.g. pain stimulus), psychological processes (e.g. beliefs, coping strategies and mood), and environmental factors (i.e., social contexts associated with significant others, community or cultural rules and expectations, occupational aspects). All these aspects also interact with each other. Rather than direct causative agents, cognitive, psychological, and social factors are also seen as mediators that influence pain experience and behaviour (Fillingim et al., 2016; Gatchel et al., 2007; Turk et al., 2016).

The biopsychosocial model is widely accepted and supported, although not without criticism. It has been criticized as being rather vague and wide-ranging, and as failing to provide concrete concepts of the connections between the biological, psychological and social aspects (Blyth et al., 2007; Edwards et al., 2016). Weiner argues that the model may place too much emphasis on psychological factors, especially when the underlying pathology is not clearly defined (Weiner, 2008). Also, according to Blyth et al., the social aspects and the interaction of social, psychological and behavioural factors have been paid little attention (Blyth et al., 2007). It should also be noted that psychological factors such as fear and anxiety caused by pain are often normal reactions, also observable in healthy populations. These various psychological factors in chronic pain are outlined later.
The graph lists factors that are associated with chronic pain and pain-related disability. According to current understanding and the biopsychosocial model, all of these factors are in interaction with each other in contributing to chronic pain problem.

Overview of biological mechanisms of chronic pain

The mechanisms and functions of acute pain are rather well understood in comparison to those that cause chronic pain. The pathology behind chronic pain may be everywhere in the sensorineural pathway, and various sensory mechanisms contribute to the development of chronic pain, depending on the underlying cause or disease. Many of the pathological mechanisms that cause chronic pain are unknown.
Peripheral mechanisms

When tissue injury or inflammation occurs, chemical signalling molecules released by the damaged cells sensitize and activate the peripheral nociceptors. The sensation of pain is heightened, and pain threshold is lowered by this sensory change called \textit{hyperalgesia}. In \textit{allodynia}, normally non-painful stimuli, such as soft touch or mild heat, can be interpreted as painful. These changes in pain signalling and perception can be caused by prolonged inflammation, and inflammatory diseases such as rheumatoid arthritis are a common cause of chronic pain. Allodynia can also occur with damage to peripheral nerves, either mechanical or biochemical. Often but not always, sensory abnormalities follow the anatomical pattern of the injured nerves.

There are many possible aetiologies for chronic pain from peripheral nerve injury. Peripheral nerve injury may occur as a result of metabolic changes or diseases. One of the most common peripheral neuropathies is diabetic peripheral neuropathy. When the elevation of blood glucose levels is prolonged, nerve cells suffer and die. A high blood glucose level is directly toxic to nerve cells, but this toxicity is also mediated via microvascular changes in the capillaries that nurture the nerve cells. Manual workers’ prolonged exposure to hand-transmitted strong vibrations may also cause neuropathic changes. Prolonged compression of a nerve may in turn cause local ischemia and demyelination and death of the axons. Toxins such as alcohol or certain chemotherapy agents, can also cause polyneuropathy.

However, not all patients with damaged nerves develop chronic pain. The incidence of disabling chronic pain after an operation is estimated to be 2–10%, depending on the operation, and nerve injury alone is not sufficient for the development of a chronic pain condition (Kehlet et al., 2006). More intense pre-amputation pain increases the risk for severe phantom limb pain (Jensen et al., 1985), and the intensity of acute postoperative pain is associated with a risk of severe chronic postoperative pain (Katz et al., 1996; Tasmuth et al., 1996). The risk factors for chronic pain after nerve injury have been identified, and many are psychosocial in nature (Katz et al., 2009; Kehlet et al., 2006). Meretoja et al. have developed a prognostic model for predicting the risk of persistent pain after a breast cancer operation. Pain in the operative area prior to operation, high body mass index, axillary lymph node dissection, and more severe acute postoperative pain intensity on the seventh postoperative day were independently associated with the risk of persistent pain (Meretoja et al., 2017).

Central mechanisms

Hyperalgesia and allodynia can also be caused by processes involving the central nervous system, and such changes are part of normal pain perception. In a burn injury, for example, primary hyperalgesia occurs in the damaged area, but the sensation surrounding the immediate, injured site also becomes sensitized. The development of a neuropathic pain condition involves changes in peripheral and central pathways, even though it may have originated from a purely peripheral process. Primary
hyperalgesia in the affected area is mainly mediated by C fibres, and secondary hyperalgesia by sensitized A-delta and A-beta fibres.

Many chronic pain conditions are described according to their anatomical location, but certain syndromes present pain in multiple body locations. FM is a condition in which the primary complaint is widespread chronic pain in various parts of the body. It is often accompanied by chronic fatigue, psychological disorders, sleep problems, and impaired cognitive processes. FM is also included in the list of frequently coexisting pain conditions. Local musculoskeletal pain is the most significant risk for developing widespread pain (Markkula et al., 2016).

Chronic pain may also be central in origin. A striking example of this is central post-stroke pain, occurring in approximately 10% of stroke patients. Stroke in the spinothalamic cortical network predisposes to post-stroke pain. It may manifest months after the initial stroke, and is accompanied by diverse sensory abnormalities (Kumar et al., 2009).

Most often, no clear known neurologic pathology can be demonstrated in chronic pain conditions. The descending modulatory mechanisms of pain sensation have shown to function differently in chronic pain states. For example, the activation of descending pain facilitator networks is accepted as a contributor to chronic pain (Heinricher et al., 2009). Central sensitization refers to the activation of the neurons responsible for pain experience as a result of a previous subthreshold stimulus, and is a contributor to pain hypersensitivity and alterations in pain perception in chronic pain states (Latremoliere and Woolf, 2009). In other words, central sensitization represents an increased gain of the pain perception system. It is a normal physiological change after injury, but the same mechanisms have also shown to be activated in chronic pain states (Latremoliere and Woolf, 2009), and they contribute to the development of chronic widespread pain (Meeus and Nijs, 2007). The mechanisms of central sensitization are described in a review by Latremoliere and Woolf (Latremoliere and Woolf, 2009).

In a follow-up study of patients with subacute low back pain (LBP), those still in pain after six months had stronger connections between nucleus accumbens and the frontal cortex already in the subacute phase, indicating the involvement of learning and reward systems in the development of chronic pain (Baliki et al., 2012). Functional MRI studies have also shown that the representation of pain shifts from sensory to emotional circuits as LBP becomes chronic (Hashmi et al., 2013). The psychosocial factors in the development of chronic pain are important, and will be covered in more detail in the following sections.

**Immunological mechanisms**

Immunological mechanisms appear to play a role in the development of many chronic pain states. Perhaps the best-known example is postherpetic neuralgia. In this condition, the Varicella Zoster Virus (VZV), which resides in the dorsal root ganglion, reactivates, and the infection or the resulting immunological response
leads to damage in the nerve cells. Clinical presentation includes persisting pain and altered sensory perception in the respective dermatome area (Kinchington and Goins, 2011). Autoantibodies against voltage-gated potassium channels have shown to associate with an increased excitability of the nerves involved in pain signalling, increasing pain sensitivity. Prolonged local inflammation is a significant contributor to chronic pain in, for example, rheumatoid arthritis. Recent research has explored the role of inflammatory mechanisms in the CNS in the development of chronic pain. A higher concentration of inflammatory proteins in cerebrospinal fluid and plasma has been measured in patients with FM than in healthy controls (Bäckryd et al., 2017a). Similarly, patients with neuropathic pain had higher levels of several inflammatory chemokines and proteins than healthy controls (Bäckryd et al., 2017b). High body mass index (BMI) is associated with many chronic pain conditions, and one proposed mechanism is the systemic low-grade inflammation observed in those with high BMI (Oddy et al., 2018).

The role of the central nervous system’s glial cells (astrocytes, microglia) in chronic pain has also been studied. These cells are known to, for example, release inflammatory cytokines, and glial activation is associated with pathological inflammatory changes such as neuronal hyperexcitability, neurotoxicity and chronic inflammation. However, the role of glial cells can also be protective, releasing anti-inflammatory molecules or clearing out debris and facilitating recovery. Glial conditioning, as well as the type of stimulus, has been suspected to mediate in whether the response of these support cells is beneficial or harmful (Milligan and Watkins, 2009).

*Psychosocial factors associated with chronic pain*

Although the pathogenesis of chronic pain may vary substantially, and not all pathophysiological mechanisms are understood, many risk factors for developing a chronic pain condition have been identified.

The term ‘yellow flags’ was originally invented by Kendall et al. (Kendall et al., 1997). It refers to the psychological, social and environmental factors that raise the risk for increased or prolonged disability after musculoskeletal symptoms. Originally, the term referred to all risk factors deemed to be of a psychosocial nature, but the risk factors may also be divided into psychological and social/environmental factors (Main and Burton, 2000). Targeting these yellow flags in interventions seems to predict better outcomes than not taking them into account when directing interventions (Nicholas et al., 2011).

In their review article, Blyth et al. also discuss the use of the term ‘psychosocial risk factors’ (Blyth et al., 2007). They imply that the current use of this term in the literature is extensive and heterogeneous, and that the precise factors and mechanisms that contribute to these risks are not very consistent. They also suggest that interventions targeting psychosocial factors are not systematic across studies, and that social aspects...
have perhaps been overlooked. They call for a more rigorous definition of psychosocial risk factors, so that testable hypotheses can be created, and the factors can be measured more accurately.

However, a plethora of research has underlined the significance of psychological and social factors in chronic pain. In general, psychosocial measures predict pain-related disability or impaired quality of life better than pain intensity (Edwards et al., 2016; Lamé et al., 2005). Depressive symptoms, as well as catastrophizing, are associated with various outcomes of pain and its treatment. A variety of pathways, from cognitive to behavioural to neurophysiological, seem to mediate these negative effects (Edwards et al., 2011). Psychosocial factors are also important in the development of chronic pain; for example, after a motor vehicle collision, psychological factors predict a new onset of chronic widespread pain (Wynne-Jones et al., 2006). Psychosocial factors are also important for the comprehensive welfare of patients, as changes in pain beliefs and coping have been associated with concurrent changes in their functioning, when pain intensity levels have stayed the same (Jensen et al., 2007).

**Fear-avoidance model**

How does pain become chronic? The fear-avoidance model describes the process in individuals who, after the onset of acute pain, develop chronic pain via a vicious cycle of disability and related psychosocial processes. It was originally presented by Vlaeyen et al., (1995), and has since been reviewed and updated. (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen and Linton, 2000).

The starting point of the cycle is the pain experience rather than an attempt to specify what causes the pain - a pain stimulus is only one possible aetiology. A key step is how the patient interprets the pain. The experience might involve a disproportional emotional response, such as fear. Fear in turn leads to avoidance of activity. This makes sense in acute pain, but in prolonged pain the fear may not represent a real danger of tissue damage. Because avoidance limits the accumulation and confrontation of new experiences, these patients may overestimate their future pain and its negative consequences. In this vicious cycle, a concept of hypervigilance plays a role - having experienced fearful pain, patients scan their bodies for signals of pain, automatically filtering out information other than that which is pain-related. They become sensitive to future signals of pain or its possibility. Reactive disability, depression or other negative affects worsen the situation.
Several studies have proven the model's validity, and it has become popular in guiding research on pain-related disability and pain management. Crombez et al. reviewed the current state of evidence of the model, and listed key challenges that the model does not address (Crombez et al., 2012). Summarizing the challenges, the model defines fear and avoidance as primarily psychopathologic processes, although these emotions are normal and prevalent responses to pain in a healthy population. Second, the model does not describe how individuals might try to maintain their functioning despite disabling or even fearful pain experiences. Third, it assumes that fear-avoidance is the only motivation for an individual’s actions, and ignores other motivations and goals that they may have. The concepts of the model, as well as its limitations, are reviewed later.

In their review, Keefe et al. grouped the psychosocial factors associated with chronic pain into two categories: those associated with increased pain and related disability, and those associated with decreased pain and related disability (Keefe et al., 2004). The factors associated with increased pain and poor adjustment to persistent pain were emotional distress (depression and anxiety), pain catastrophizing, and fear and helplessness. The factors associated with decreased pain and better adjustment to persistent pain were self-efficacy, pain coping strategies, readiness to change, and acceptance.
Depression and distress

Mood disturbances due to pain are perhaps the most studied and measured psychological constructs in chronic pain. Depressive, anxious and other related emotions can also be termed ‘negative affects’ (Edwards et al., 2016). It is well known that emotional distress is common among chronic pain patients (e.g. Burke et al., 2015). Depression, as well as depressive symptoms, are frequently associated with pain (see previous section, and e.g. (Bair et al., 2003)), and are important determinants of pain-related disability (Tripp et al., 2006).

Often considered a consequence of chronic pain, these negative affects may also precede chronic pain (e.g. Fillingim et al., 2013). Pain-related distress is sometimes associated with transition from acute to chronic pain (Linton, 2000). The relationship of pain with depressive and anxiety disorders is complex and, according to the biopsychosocial model of pain, works both ways – one does not necessarily cause the other. However, although depression and anxiety are associated with chronic pain, they are not necessarily a direct consequence of it (Rudy et al., 1988). After trauma, anxiety predicts pain better than pain predicts anxiety (Castillo et al., 2013). In longitudinal studies of chronic pain and mood disorders, most anxiety disorders satisfying the diagnostic criteria have been already present before the onset of pain, and a slight majority of depressive disorders have been diagnosed after the onset of pain (Knaster et al., 2012).

Extensive evidence shows that pain-related emotional distress predicts (better than pain intensity) various pain-related outcomes such as physical disability, work disability and health care costs (Edwards et al., 2016). Pain-related anxiety is associated with, for example, maladaptive pain coping mechanisms such as the avoidance of physical activity, and those with high anxiety overpredict the amount of pain they will experience during a physical examination (Keefe et al., 2004). In a two-year prospective study of patients undergoing back surgery (transforaminal lumbar interbody fusion), preoperative depressive symptoms were the only factor predicting return to work. The models accounted for the effect of pain intensity, disability and quality of life pre- and post-operatively. More depressed patients were less likely to return to work or took longer to return to work (Parker et al., 2015). Of tertiary pain clinic patients, those who fulfilled the criteria for depression were more likely to be unable to work or to report work absence; in addition, they reported higher disability (Rayner et al., 2016).

The fear of pain is closely related to emotional distress. Conceptually it is distinct from pain-related anxiety, as anxiety is targeted towards the future, whereas fear is targeted towards something present and concrete, but strongly overlaps with pain-related anxiety. Similarly to the mentioned negative effects, pain-related fear predicts higher disability, pain chronicity and participation avoidance (Picavet et al., 2002; Swinkels-Meewisse et al., 2003).

Depressive symptoms can be measured with the widely-used Beck Depression instrument (BDI) (Beck et al., 1961, 1996). A commonly used pain-related anxiety measurement tool is the Pain Anxiety Symptoms Scale (PASS) questionnaire
Coping strategies are associated with pain (de Rooij et al., 2014). Beneficial coping mechanisms has shown to be related to pain management outcome (Keefe et al., 2004; Turk et al., 2016). Improvements in coping skills are mediated by self-efficacy (Edwards et al., 2016; Turner et al., 2007). A tool for measuring self-efficacy in all chronic pain conditions has been developed and validated (Anderson et al., 1995), and disease-specific instruments also exist (Turk et al., 2016).

Several studies show that self-efficacy mediates the association between chronic pain and disability (Arnstein et al., 1999; Costa et al., 2011; Edwards et al., 2011). The mediating effect of self-efficacy has also been noted in the association between change in pain intensity and change in pain-related disability (Costa et al., 2011). There is also evidence that improvements in self-efficacy result in improvements in coping skills (Keefe et al., 2004).

**Self-efficacy**

Self-efficacy refers to an individual’s belief in their ability to perform and work to achieve desired outcomes. Self-efficacy is the determinant of how we think, feel and act in difficult and stressful situations (Bandura, 1982; Keefe and Somers, 2010). For people in chronic pain, high self-efficacy means that they can perform a task, and have confidence in their ability to accomplish this task, despite their chronic pain (Turk et al., 2016). A closely related term is resilience, which is defined as the capacity to adapt in the face of adversities (Stewart and Yuen, 2011).

In general, greater self-efficacy is associated with lower pain intensity, whereas unpleasantness and functional impairment from pain, and lower self-efficacy are associated with greater pain and disability ratings in several chronic pain conditions (Keefe et al., 2004; Turk et al., 2016). It has also been suggested that self-efficacy is a mediator and predictor of pain intervention outcomes (Edwards et al., 2016; Turner et al., 2007). A tool for measuring self-efficacy in all chronic pain conditions has been developed and validated (Anderson et al., 1995), and disease-specific instruments also exist (Turk et al., 2016).

Several studies show that self-efficacy mediates the association between chronic pain and disability (Arnstein et al., 1999; Costa et al., 2011; Edwards et al., 2011). The mediating effect of self-efficacy has also been noted in the association between change in pain intensity and change in pain-related disability (Costa et al., 2011). There is also evidence that improvements in self-efficacy result in improvements in coping skills (Keefe et al., 2004).

**Pain coping strategies**

Different individuals have different strategies and methods for dealing with persistent pain, and these are of varying efficacy. Coping strategies can be behavioural (e.g. relaxation) or cognitive (e.g. positive thinking); they can be active (information-seeking, engaging) or passive (help-seeking, withdrawal). Based on the results that they produce, different methods can be seen as adaptive (good results) or maladaptive (bad results). Different coping strategies are associated with pain perception, control over pain, emotional distress, and functional disability (Evers et al., 2003; Haythornthwaite et al., 1998; Jensen et al., 2002). These coping strategies can be measured using various structured instruments, some of which have been outlined in two reviews (Keefe et al., 2004; Turk et al., 2016). Coping strategies are often also the focus of non-pharmacological pain management (Edwards et al., 2016). An increase in beneficial coping mechanisms has shown to be related to pain management outcome (de Rooij et al., 2014).

Coping strategies are associated with pain-related beliefs and, for example, catastrophizing and self-efficacy. An example of this is how patients with acute LBP and
high levels of negative affect and catastrophizing are more likely to rest in bed for long periods and become physically deconditioned, and are the least likely to exercise (Bousema et al., 2007; Verbunt et al., 2008). In contrast, protective factors (such as social support) are associated with greater engagement in physical exercise and activity (Stewart and Yuen, 2011). Catastrophizing is also associated with various negative cognitive processes related to pain (Edwards et al., 2016).

Acceptance

Acceptance can be defined as the ability to embrace experiences when trying to deny or change them would be ineffective or harmful. In chronic pain, this means that an individual accepts a certain amount of pain and, instead of focusing all effort on abolishing this pain, focuses on more important aspects of life. In other words, there may be occasions when helpful change in the quality of a patient's life can only occur when some aspects of the pain problem are accepted (McCracken et al., 2004a). The alternative option would be that the (perhaps futile) struggle of controlling pain becomes so central that other aspects of one's life suffer. Acceptance is also closely related to the ability to pursue a meaningful life despite chronic pain. The broader term for this is psychological flexibility. This concept and its relation to chronic pain has been further reviewed by McCracken and colleagues (McCracken et al., 2004a; Thompson and McCracken, 2011). Several studies show an association between acceptance and related factors and the functioning of chronic pain patients (Edwards et al., 2011).

Several treatment methods that target acceptance and related constructs have emerged. One method called the Acceptance and Commitment Therapy (ACT) is a process-oriented intervention which, instead of active efforts to control pain, encourages acceptance, psychological flexibility, and values-based actions as the most productive response to chronic pain (McCracken and Vowles, 2014). Another method is known as mindfulness-based stress reduction (MBSR) and is based on mindfulness techniques. These treatment methods and their effectiveness have been reviewed by Veehof et al. (Veehof et al., 2011).

The most frequently used instrument for measuring acceptance is the Chronic Pain Acceptance Questionnaire (McCracken et al., 2004b; Vowles et al., 2008).

Catastrophizing

The tendency to negatively evaluate one's ability to deal with pain, and to exaggerate the negative consequences of pain, is described as pain catastrophizing. This consists of cognitive and emotional aspects such as helplessness, pessimism, rumination about pain-related symptoms, and magnification of pain reports (Edwards et al., 2011; Turk et al., 2016). Catastrophizing can bias perceptions and expectations, and lead to the development of passive coping styles (Sullivan et al., 2001; Turk et al., 2016). Sullivan and colleagues defined catastrophizing as a response to persistent pain, designed to deal with negative emotions by eliciting proximity to and support from others, bringing into perspective social aspects (Sullivan et al., 2001).
Catastrophizing has shown to be associated with many negative consequences of chronic pain – patients who catastrophize have higher levels of disability when adjusted for other pain-related variables such as pain intensity (Martin et al., 1996), higher rates of health care usage (Gil et al., 1992), increased use of analgesics (Jacobsen and Butler, 1996), and they take longer to recover from surgery (Kendell et al., 2001).

Although most research has been conducted in highly selective pain populations such as those treated in pain clinics, there is also population-based evidence that pain catastrophizing is associated with various aspects of impaired general health (Severeijns et al., 2002).

Catastrophizing significantly overlaps with other behavioural and mood disturbances (such as anxiety, depression and avoidance) (Edwards et al., 2011). However, it appears to be independently related to low general health and negative pain outcomes after controlling for other possible explanatory variables (e.g. pain intensity, variables measuring sociodemographic status and condition severity) (Edwards et al., 2011; Severeijns et al., 2002; Turner et al., 2002).

Concerning causality, catastrophizing predicts pain onset and disability (Jarvik et al., 2005). It also predicts postoperative pain, poor quality of life, and transition to chronic pain among people undergoing surgery (Khan et al., 2011). However, most studies investigating the relationships of catastrophizing (as well as other psychosocial factors in chronic pain) are cross-sectional in nature. Furthermore, after controlling for variables measuring depression and anxiety, catastrophizing remained significantly associated with various outcomes of pain and its management (such as return to work or opioid misuse) (Edwards et al., 2016).

**Social aspects of chronic pain**

**Early life**

The psychological and social factors that play a role in chronic pain are similar in childhood and adulthood. Psychosocial rather than mechanical factors predispose children to LBP. Long-term prospective studies demonstrate that the increased risk of chronic widespread pain in adulthood is related to emotionally traumatic events in childhood (such as being raised in foster care, death of a parent), as well as physically traumatic events in childhood such as premature birth, very low birth weight (Jones et al., 2009; Littlejohn et al., 2012), and hospitalization for a motor vehicle accident at a young age (Wynne-Jones et al., 2006). In a meta-analytic review, traumatic events were associated with chronic pain syndromes as well as with chronic fatigue syndrome and IBS (Afari et al., 2014). The type of psychological trauma was not significant in the review. The existing evidence is prospective in nature, and the effects reported are considerable. It has also been concluded that post-traumatic stress disorder (PTSD) symptoms play a role in the relationship of chronic pain and traumatic events.
(Edwards et al., 2016). A review of chronic pain and PTSD by Brennstuhl et al. suggested that, because of similar symptoms, chronic pain associated with PTSD might also be reactive in nature (Brennstuhl et al., 2015).

**Social relations**

Having more social support is associated with better pain-related functioning, and better outcomes in conditions such as spinal cord injury, multiple sclerosis and amputation (Jensen et al., 2011). Maternal chronic pain is associated with chronic non-specific pain and chronic multisite pain among adolescents and young adults, an association which is even stronger if both parents report chronic pain (Hoftun et al., 2013). Family structures maybe important in this association and in paediatric chronic pain in general (Hoftun et al., 2013; Palermo and Holley, 2013), underlining the social aspects of adolescent chronic pain in particular. Parental catastrophizing is predictive of the development of chronic pain and related disability among children (Hechler et al., 2011; Noel et al., 2015).

In an extensive review of psychological and social factors in chronic pain, Edwards et al. reviewed studies assessing the role of significant others in patients' chronic pain conditions. For example, avoidant or anxious attachment styles were linked to increased pain intensity and poorer general well-being (Edwards et al., 2016).

Work-related factors can also influence the course of chronic pain. In acute LBP patients, social support at work reduced the probability of developing chronic back pain (Melloh et al., 2013a, 2013b). Workplace support is also associated with reduced depressive symptoms and disability in arthritis patients during follow-up (Li et al., 2006). Interestingly, in a multinational study of 2825 patients, Anema et al. concluded that return to work after chronic LBP was mainly explained by differences in job characteristics and social disability systems rather than medical interventions or patient health (Anema et al., 2009).

**Sociodemographic factors**

Chronic pain is strongly associated with sociodemographic factors. Housing tenure and employment status, for example, are associated with its prevalence (Elliott et al., 1999). Chronic pain is more common among manual workers and the unemployed than among professional workers (Raftery et al., 2011). Low socioeconomic status in childhood or adolescence created a risk of developing musculoskeletal pain in a long-term follow-up (Huguet et al., 2016). Chronic pain is more common in less educated patients (Eriksen et al., 2003; Saastamoinen et al., 2005).
Epidemiology of chronic pain

Prevalence

Approximately 50% of us have experienced an episode of pain lasting at least one day within the past month (Macfarlane et al., 2015). Approximately 19% of the European population feel that their current pain has lasted for over six months, ranging from 12% (in Spain) to 30% (in Norway) among countries (Breivik et al., 2006). Other studies have reported similar results, estimating the prevalence of severe chronic pain to be around 10–20% in the general population (Elliott et al., 1999; Eriksen et al., 2003; Fayaz et al., 2016; Gureje et al., 1998; Mäntyselkä et al., 2003). However, these prevalence estimates vary according to the population studied (Gureje et al., 1998), methodology used and the definition of chronic pain (Verhaak et al., 1990). With less strict definitions, higher prevalence estimates have been reported (Elliott et al., 1999; Fayaz et al., 2016; Mäntyselkä et al., 2003; Raftery et al., 2011).

Females appear to suffer from severe chronic pain more than males. In a European population, the percentage of females in a study sample was 52%, but the ratio of females to those suffering from severe chronic pain was 65% (Breivik et al., 2006). In a Danish population, 16% of men and 21% of women reported pain that had lasted over six months (Eriksen et al., 2003). When the prevalence estimate was higher (35–50%), no gender differences were reported (Elliott et al., 1999; Raftery et al., 2011). However, in a meta-analysis of British patients, the prevalence of chronic pain was consistently higher among females (Fayaz et al., 2016). Data from both developed and developing countries showed chronic pain to be more common among women than in men (Tsang et al., 2008).

Studies suggest that the prevalence of chronic pain increases consistently with age (Fayaz et al., 2016; Mäntyselkä et al., 2003; Raftery et al., 2011; Saastamoinen et al., 2005). However, some studies have shown that the prevalence of LBP decreases at older ages (Dionne et al., 2006), and it has been suggested that the differing prevalences in relation to age might be explained by the type and location of pain (Macfarlane, 2016).

Prevalence of chronic pain by sites and conditions

Chronic pain may be present in every location of the body. It can be a problem of a specific area, such as an amputated limb or an area innervated by a certain nerve, or it can be widespread, felt all over the body.

Of body locations, the lower back is the most common pain location. The mean prevalence of LBP is around 12%, and one-month prevalence 23% (Hoy et al., 2012). In the Dutch general population, three most common sites for musculoskeletal pain with their respective point prevalences were lower back (26.9 %), shoulder (20.9 %) and neck (20.6 %) (Picavet and Schouten, 2003). In the Finnish healthy population, the prevalence for low back pain during last 30 days was 41.4% for females and 34.6%
The prevalence of chronic widespread pain is estimated to be around 12% (Mansfield et al., 2016). FM is a chronic, non-inflammatory pain syndrome that is characterized by widespread musculoskeletal pain and associated symptoms such as fatigue, sleep difficulties and depressive symptoms. Its prevalence is estimated to be 1–5%, depending on the diagnostic criteria used (Jones et al., 2015; Vincent et al., 2013). It is more common among females than males, and other risk factors include physical trauma, stress, infection, and genetic factors (Fitzcharles et al., 2013).

**Chronic pain, health and other diseases and symptoms**

Chronic pain is usually a symptom of an underlying disease such as diabetes, rheumatoid arthritis or osteoarthritis. Certain other syndromes are also characterized primarily by pain complaints, such as FM.

**Psychiatric comorbidity**

Chronic pain and psychological symptoms often occur together and can significantly overlap. Depressive symptoms are perhaps the most common. In a literature review, the authors stated that 65% of patients with depression experience pain complaints. The prevalence of depression among people with chronic pain conditions can vary widely, ranging from 5% to 85% (depending on the study setting). Depression is most prevalent in pain, psychiatric, and other specialty clinics, and less prevalent in population-based or primary care studies (Bair et al., 2003). The authors further concluded that the presence of pain negatively affects the recognition and treatment of depression (Bair et al., 2003). In a large sample of patients treated in a specialized pain centre, the prevalence of depression was 60.8% (Rayner et al., 2016). In a study using the Structured Clinical Interview and Statistical Manual of Mental Disorders, 75%
of the patients treated at a tertiary pain clinic fulfilled the criteria of at least one psychiatric condition (Knaster et al., 2012). The prevalence numbers of anxiety and depression were six times higher than those of a corresponding sample of the general population.

Data from both developed and developing countries show that anxiety-depression spectrum disorders and their symptoms are associated with chronic pain (Tsang et al., 2008).

Chronic pain states (arthritis, migraine and back pain) are associated with an increased likelihood of depression, panic attacks, and generalized anxiety disorder, also after adjusting for confounding variables. Many studies show that anxiety disorders, particularly PTSD, panic disorder, generalized anxiety disorder (GAD) and social anxiety disorder are more frequent among chronic pain patients than in a healthy population. For example, the prevalence of any anxiety disorder is approximately twice as high as in the general population, whereas panic disorder and PTSD can be three times as prevalent among those with chronic pain (McWilliams et al., 2004). In the study, the association between pain states and anxiety was greater than that between pain states and depression (McWilliams et al., 2004).

PTSD patients in particular commonly have complaints of pain or other physical symptoms (Asmundson and Katz, 2009). Asmundson and Katz noted in their review that more research efforts should be made to clarify the temporal relation between pain and anxiety. In a study of tertiary pain clinic patients, the majority of anxiety disorders had already been present before the onset of pain (Knaster et al., 2012). The temporal relation of depression was different, as in 60% of patients, the onset of pain preceded depression (Knaster et al., 2012).

It should be noted that psychological constructs and processes are distinct to psychiatric illness. Here we covered the co-prevalence of pain and psychiatric conditions. Psychological constructs and symptoms that are not classified as psychiatric conditions are also important in chronic pain, and are addressed in the previous chapters.

**Sleep**

Chronic pain and sleep appear to have a reciprocal, bidirectional relation (Finan et al., 2013a). It is easy to imagine that both acute and chronic pain disrupt sleep (Chouchou et al., 2014; Finan and Smith, 2013; Shaver, 2008). Conversely, sleep deprivation lowers the pain threshold, lowers the ability to cope with pain, and increases pain intensity ratings (Okifuji and Hare, 2011a, 2011b; Onen et al., 2005). Longitudinal population-based studies and experimental studies reviewed by Finan et al. also suggest that sleep disturbances predict the development and exacerbation of chronic pain (Finan et al., 2013b). The authors emphasize that psychological factors also mediate the association between sleep and chronic pain, and conclude that chronic pain, sleep problems and depression are mutually interacting conditions, each increasing the risk of the other (Finan et al., 2013b). Furthermore, patients with
chronic pain who have sleep problems are more likely to have anxious and depressive symptoms than those without sleep problems (Turk et al., 2016).

**Other conditions, general health and mortality**

In a population-based study, chronic widespread pain was associated with symptom-based conditions such as chronic fatigue, IBS and psychiatric disorders, and the researchers concluded that this association was mediated by unmeasured genetic and family environmental factors (Kato et al., 2006).

Chronic pain has also shown to be related to poor self-rated health (Mäntyselkä et al., 2003), which is an independent predictor of morbidity and mortality. Patients in severe chronic pain also seem to have increased mortality (Torrance et al., 2010). In a large cohort study, the association of chronic widespread pain and mortality was clear, and adverse lifestyle factors mostly explained the excess mortality (Macfarlane et al., 2017). Other studies have shown that patients in chronic pain have higher mortality than patients with cancers or cardiovascular diseases (Macfarlane et al., 2001; Smith et al., 2014)

**The consequences of chronic pain**

*Functioning and well-being*

To suffer from chronic pain is detrimental to one’s functioning, both physical and cognitive. Conversely, the ability to function in daily life or to pursue goals is a key aspect of good health. Extensive evidence shows that chronic pain is related to disability, health problems and impaired functioning (Breivik et al., 2006; Gureje et al., 1998; Raftery et al., 2011), and that it impairs various aspects of life (Azvedo et al., 2012; Meyer-Rosberg et al., 2001; Raftery et al., 2011). Patients with chronic pain have a low level of life satisfaction (Boonstra et al., 2013). In a population-based survey, the majority of those suffering from chronic pain reported impaired ability to sleep, exercise or do physical work. Social activities were diminished or prevented because of pain in 27–49% (Breivik et al., 2006).

In a survey of people with neuropathic pain, participants reported a mean pain interference of 5 on a scale of 0 to 10, the most affected areas being general activity, work, sleep, mood, and enjoyment of life (McDermott et al., 2006). When neuropathic pain patients are compared with non-neuropathic pain patients, they appear to have greater impairment in psychological, social and occupational factors (Langley et al., 2013; Meyer-Rosberg et al., 2001).

The Global Burden of Disease Project measures the global impact of a comprehensive set of health conditions. Its central aim is to also measure health outcomes outside mortality. As measurement units it uses, for example, Disability-Adjusted Life Years (DALY), Years Lived with Disability (YLD), and Years of Life Lost due to premature mortality (YLL). The idea of DALYs is similar to that of Quality-Adjusted Life Years,
presented later in this section. YLDs measure life years lived with a disability: five years lived with a disease burden of 0.2 constitutes 1 YLD. These units are calculated using prespecified preference weights. Chronic pain conditions are among the leading causes of years lived with disability (YLD) (Vos et al., 2012): LBP is the leading cause, neck pain the fourth, musculoskeletal disorders the sixth, and migraine the eighth. LBP was globally the greatest cause of YLDs, and a sixth of DALYs, which also take into account YLLs (i.e., life expectancy).

**Health-related quality of life**

Because chronic pain impairs functioning in everyday life, it reduces quality of life. HRQoL is a measure of overall health and functioning that will be presented later in more detail. Chronic pain is consistently detrimental to HRQoL, measured in various populations and using many different measures (Boonstra et al., 2013; Eriksen et al., 2003; Keeley et al., 2008; Lillegraven et al., 2010; Meyer-Rosberg et al., 2001; Torrance et al., 2014). For example, the patients admitted to a multidisciplinary pain centre in Norway reported similar or even poorer quality of life than end-stage cancer patients (Fredheim et al., 2008). The mean EQ-5D index of patients suffering from neuropathic pain was 0.44 (McDermott et al., 2006), whereas in a Finnish sample of end-stage cancer patients in palliative care, the EQ-5D index was 0.59. As pain-related psychosocial factors are independently and strongly associated with pain-related disability, psychosocial factors are also associated with the impaired HRQoL (Nicholl et al., 2009).

**Societal costs**

Because chronic pain causes considerable disability, it is a burden to society. Chronic pain is associated with considerably elevated societal costs, both direct and indirect. Breivik et al. reviewed studies estimating the total societal costs of chronic pain (Breivik et al., 2013). The review estimated that the total cost per patient per year was approximately 5000–6000€, total societal costs being €5.34 billion in Ireland, €32 billion in Sweden, €2.8 billion in Denmark, and $560-635 billion in the United States. Because of methodological differences in obtaining these estimations, the numbers differ significantly and are not comparable.

**Health care use**

Pain is the reason for 40% of all visits to a primary care physician in Finland; chronic pain is estimated to be the reason for 10% of these visits. (Mäntyselkä et al., 2001). Azevedo et al. identified depressed mood, pain-related disability and socioeconomic determinants as the main drivers of increased medical consultations. (Azevedo et al., 2013).

In a Danish population sample, twice as many patients with chronic pain reported having used various health-care services in comparison to the controls, except for emergency room visits and on-call doctor consultations, in which case the difference was smaller. Those with chronic pain made approximately 25% more visits to health
care than controls (Eriksen et al., 2003). In another population sample, higher reported pain interference in daily activities was associated with a greater number of general practitioner and emergency room visits and more frequent hospitalizations (Blyth et al., 2004). Hospitalization is the single greatest contributor to direct health care costs of patients in chronic pain (Raftery et al., 2012).

Among tertiary pain clinic patients, depression was associated with increased health care use, the estimated costs being £731 for those fulfilling the criteria for depression and £448 for those without depression. The depressed patients also reported higher rates of work absences or inability to work (Rayner et al., 2016).

Indirect costs

It is estimated that indirect (i.e. lost productivity, sick leave, disability pension) costs account for approximately half of the total costs (Breivik et al., 2013), although in Denmark, the estimated division into direct and indirect costs was 70% and 30%, respectively. In a study of a Swedish population in 2001, 13% of all early retirement pensions were granted for back problems (Ekman et al., 2005). In Finland, spinal disorders account for €347 million of disability pension costs. In addition, lost productivity is estimated to be six times greater than disability pension costs (Asklöf et al., 2016).

In a study of the HRQoL and disease burden of neuropathic pain patients, half of the patients reported reduced employment status due to their pain (Meyer-Rosberg et al., 2001).

Interestingly, in a telephone-based survey in 15 European countries and Israel, the mean number of days lost from work due to pain during one year was 19.8 in Finland, clearly above the European mean of 7.8 days (Breivik et al., 2006). In this study, other measures of pain, such as pain intensity, were similar in Finland and other European countries. The possibility of confounding factors, such as differences in language and translation, must be taken into account concerning this result.

Treatment of chronic pain

Modern medicine has introduced various effective techniques for managing acute pain. Non-steroidal anti-inflammatory drugs, opioids, local anaesthetics and various elegant techniques used by anaesthesiologists enable fairly adequate management of acute pain. Unfortunately, the treatment of chronic pain is difficult, and to a large extent different to the management of acute pain.

Chronic pain patients are often dissatisfied with their treatment. In a population-based study, 40% of those classified as having chronic pain were not satisfied with the treatment offered to them, and 33% were not satisfied with the examinations conducted with regard to the pain condition (Eriksen et al., 2003). A meta-analysis of randomized, placebo-controlled trials for non-specific back pain found only small reductions in pain intensity (Machado et al., 2009).
**Multidisciplinary pain management**

The most effective form of treating chronic pain according to current knowledge is an approach known as **multidisciplinary pain management (MPM)**. Its foundations lay in the biopsychosocial model of chronic pain – if pain is a multidimensional problem with problems in various interacting domains of well-being, its treatment should encompass all these aspects in a co-ordinated manner.

The first multidisciplinary pain clinic was founded by the renowned pain physician and anaesthesiologist, John Bonica, at the University of Washington, where he involved many different professionals in the management of patients’ pain. Since then, the concept and treatment modalities have been refined, and evidence consistently names MPM as the most efficacious treatment of chronic pain (Kamper et al., 2015; Scascighini et al., 2008).

**Definition and organization of MPM**

IASP provides guidelines on the organization of MPM (IASP, 2009). In a multidisciplinary pain centre, clinicians from various disciplines, including physicians, nurses, mental health professionals (e.g., clinical psychologist, psychiatrist), and physical therapists work together in managing the patients’ pain. All the clinicians must have expertise in pain management. An important feature is that these clinicians work together in the same space and communicate with each other regularly and systematically. The care should be goal oriented and patient centred, and the different people participating in a patient’s management should share the same goal. Multidisciplinary pain centres should be able to treat any kind of pain, be it, for example, cancer- or non-cancer-related. For this reason, the staff should encompass people with broad experience, i.e. various medical specialties should be represented.

The guidelines define a multidisciplinary pain centre and a multidisciplinary pain clinic. They are equivalent in terms of pain management services, but in a multidisciplinary pain centre, research and academic teaching activities should be practiced.

In practice, there are many options for providing MPM. In the literature, the composition and duration of multidisciplinary programmes may vary substantially. The authors of a systematic review on MPM for chronic pain (Scascighini et al., 2008) required at least three of six categories of therapy (psychotherapy, physiotherapy, relaxation techniques, medical treatment, patient education, vocational therapy) to be included in a programme to be ranked as multidisciplinary. A Cochrane review on multidisciplinary rehabilitation for chronic LBP included studies in which the intervention involved a physical component and one or both of a psychological component or a social/work-targeted component (Kamper et al., 2015), and the different modalities were delivered by those with different professional backgrounds.
MPM can be inpatient or outpatient. In a systematic review on MPM for the management of chronic pain, Scascighini et al. reported that five of the included 27 studies took place in an inpatient setting, and four of them compared inpatient and outpatient settings (Scascighini et al., 2008). Earlier reviews on the multidisciplinary management of chronic LBP have reported that the intensity of treatment programmes (i.e., the number of hours spent in treatment per week) may be associated with the outcomes, but more recent systematic reviews on both LBP and unspecified pain patients have concluded that treatment intensity is not related to its outcomes (Kamper et al., 2015; Scascighini et al., 2008).

**Treatment modalities and roles of professionals**

In a multidisciplinary pain clinic, various professionals provide different treatment modalities. Because a multidisciplinary pain clinic can be organized in diverse ways, the following is only one option for the professionals' roles. It is a description based on the book ‘Essentials of Pain Management’ (Fikremariam and Serafini, 2011).

The physician’s role is to diagnose the pain condition, and to optimize the patient's medication. The physician is also responsible for planning and co-ordinating the multidisciplinary treatment programme. Usually, several different specialties are represented at the pain centre, including anaesthesiology, neurology, psychiatry, physiatry, rehabilitation medicine, and dentistry.

Psychologists are an important part of pain management. They assess, for example, the patient's cognitive and emotional status in relation to pain, and they may guide patients to better adopt pain-coping mechanisms. Psychologists also often assess the presence of possible psychopathologies, and whether a patient would benefit from other psychology-based interventions, such as group-based rehabilitation or mindfulness-based approaches. Cognitive-behavioural therapy, and interventions that include training and suggestions for comfort (such as relaxation techniques) have been proposed as effective approaches (Molton et al., 2007).

Physiotherapists may provide exercise counselling and assessments of the patient's physical functioning. They can also provide various physical treatments, such as Transcutaneous Electrical Nerve Stimulation (TENS) and guidance in using these machines, and acupuncture.

The role of nurses can vary substantially depending on their education and interaction with other professionals. Nurses can, for example, teach pain coping skills, and help in practising other learned skills. They can also be the contact person for patients outside the scheduled visits. The patient is perhaps in contact most often with a nurse during MPM. Therefore, nurses also represent the continuity of the treatment programme.

Social workers can guide patients if they have problems with the social support system because of their pain. They may help the patients to, for example, apply for the right benefit and to find the best rehabilitation method in view of the social system.
The authors of a systematic review on MPM for chronic pain listed the different components of MPMs used in MPM programs (Scascighini et al., 2008). Of the psychological modalities, cognitive behavioural therapy (CBT) was the most common intervention, followed by operant-behavioural approaches (OBT) and psychotherapy, which was often administered in groups. Of physical modalities, exercise therapy, aerobic exercise, muscle stretching, hydrotherapy (or swimming), and progressive muscle relaxation were the most common. It is noteworthy that a medical doctor was part of the team in only eight of the 27 studies. Patient education was carried out in 16 of the 27 studies.

Outcome measures of pain management

How can we measure if a pain management method is effective? The experience of pain is entirely subjective, and although certain physical correlates of pain exist, a person's report of pain is the gold standard for its measurement. Pain intensity is often measured on a numeric rating scale (NRS), in which a person is asked to rate their pain on a scale of 0 (no pain) to 10 (worst imaginable pain). A similar method is the visual analogue scale (VAS), in which one end of the line indicates no pain and the other the worst possible pain. The patient then marks the line in relation to the end points. In the Verbal Rating Scale (VRS), the patient is asked to indicate pain intensity as, for example, none, mild, moderate, or severe.

Most studies use reduction in pain intensity as the indicator of successful treatment outcome. In addition to the absolute reduction in pain intensity, it is common to report the relative reduction of pain intensity in percentages. For example, reduction from 6 to 3 is an absolute reduction of 3 and a relative reduction of 50%. When using an 11-point (0–10) NRS in a large, heterogeneous sample of chronic pain patients, Farrar et al. concluded that the minimum clinically important reduction in pain intensity was an absolute reduction of two points or a relative reduction of 30% (Farrar et al., 2001). Several studies have also reported the proportion of patients achieving 50% reduction in pain intensity (Dworkin et al., 2005).

The primary aim of all types of pain management is to reduce pain-related disability. As chronic pain cannot always be completely abolished, MPM aims to restore a patient's functioning rather than primarily remove pain. Due to this, evidence and decisions on chronic pain management should not only be based on reductions of pain intensity. Moreover, many clinical trials have failed to show meaningful pain reduction when studying supposedly effective analgesic medications. This has raised concerns as to whether pain intensity is the best outcome for assessment in chronic pain trials, and as to whether the validity of pain intensity assessment could be improved (Dworkin et al., 2015).

The comprehensive assessment of chronic pain should include all the different, clinically relevant domains of chronic pain in individuals. Reliable, valid assessment is also important for the accurate classification of chronic pain conditions. Fillingim et al. recommend assessing four key components in all patients: pain intensity, other
perceptual qualities of pain, bodily distribution of pain, and the temporal features of pain. Assessment should also be combined with evaluation of other important domains, including physical and psychosocial functioning. Whenever possible, pain assessment should also help to identify the pathophysiological mechanisms responsible for chronic pain conditions. These assessments may include techniques such as quantitative sensory testing (QST) for assessing abnormalities in the somatosensory pathway. Emerging assessments are outlined in a review by Fillingim et al. (Fillingim et al., 2016).

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has published recommendations on the outcomes to be assessed in every clinical trial of chronic pain treatment (Turk et al., 2003). The core outcome domains are (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, and (6) participant disposition. The IMMPACT group has also published a recommendation on which measures to use in assessing these domains (Dworkin et al., 2005).

Concerning physical functioning, the IMMPACT group authors recommend using a generic measure of the HRQoL. (Dworkin et al., 2005) This is to obtain comparable data across all disorders, and to permit cost-utility analyses. The authors recommend using the SF-36 as a generic measure of HRQoL and physical functioning (Dworkin et al., 2005). The reason for this recommendation is the amount of pre-existing data available on SF-36 that should permit comparison among different disorders and treatments. However, the authors note that as data from other HRQoL measures accumulate, other measures may offer improvements on the SF-36, and may replace it.

**Evidence of multidisciplinary pain management**

MPM is the best known approach to managing chronic pain, as suggested by recent systematic reviews (Kamper et al., 2015; Karjalainen et al., 1999; Scascighini et al., 2008). However, these reviews have all noted the relative lack of studies with good-quality design. MPM programmes have also been concluded as being cost-effective in comparison to other forms of treatment (Turk, 2002). However, certain acknowledged problems have prevented many conclusions on the effectiveness of pain management.

The outcomes of MPM vary greatly – some patients benefit substantially but others not at all, or their condition may even deteriorate despite treatment. A similar pattern has been observed in observational studies (Boonstra et al., 2015; Heiskanen et al., 2012) as well as in RCTs of pain medication (Moore et al., 2014).

All the systematic reviews on MPM have noted the heterogeneity of the outcomes used. In addition, the relative lack of studies with good-quality design prevents the comparison of different treatment modalities in the reviews. Scascighini et al. recommend stronger observance of methodological guidelines and the use of internationally established outcome measures in order to combat this problem (Flor et
Deckert et al. conducted a systematic review of the different outcomes reported in multimodal (multidisciplinary) pain therapy studies. As in the other systematic reviews, they report that studies of MPM have used extensively many different outcome measures. This limits comparability with interventions from other trials. The authors also noted the lack of recommendations for outcome domains that should be included in the clinical trials of MPM. As patients with chronic pain, as well as the available treatment modalities, are very diverse, the authors raised the question of whether the IMMPACT recommendations might not be relevant or specific enough for the chronic pain population in the MPM setting. (Deckert et al., 2016). Kaiser et al. have recently published a consensus statement on a core outcome set to be measured in MPM trials. They rigorously reviewed the MPM outcomes, recruited an expert panel, and defined the domains that should be assessed in MPM trials (Kaiser et al., 2018). The core outcome domains recommended are: pain intensity, pain frequency, physical activity, emotional well-being, satisfaction with social roles and activities, productivity (paid and unpaid, at home and at work, inclusive presenteeism and absenteeism), HRQoL, and the patient’s perception of treatment goal achievement.

Health-related Quality of Life

Ideally, treatment outcome or disease severity are things that can be measured and quantified. In clinical practice, a valuable indicator for decision-making is how the patient is feeling, but in research, we should be able to produce objective, reproducible indicators of treatment success or failure. Widely used outcomes are, for example, mortality in a given follow-up time, the size of a tumour, or the amount of cholesterol in the blood. These objective measures are important, but have certain limitations: they are often rather specific to certain diseases, some markers known as surrogate outcomes can only vaguely be related to the more important outcome (for example, improvement in progression-free survival does not always mean an improvement in overall survival or quality of life), and biological measurements do not encompass the patient’s own perception of their health. As a further example, mortality is not a sufficient outcome indicator in many diseases that are not directly fatal, and it tells us nothing of what happens before death.

Definition and aims of the measurement

HRQoL measurement aims to capture the overall, comprehensive health of a patient (Stanquet et al., 1998). Many definitions exist, but they all agree that HRQoL describes the comprehensive effect of a disease or its consequent treatment on a patient (Cella, 1995; Guyatt et al., 1993) (ISOQOL, n.d.).

The World Health Organization (WHO) defines health as the absence of physical, mental and social problems. HRQoL aims to capture and quantify all these aspects.
However, a HRQoL instrument used to study health care outcomes should be restricted to describing health – hence the name health-related quality of life. Quality of life itself is a broader concept that encompasses, for example, social roles and economic aspects, but as health care interventions cannot directly influence these, they are excluded from HRQoL measurement.

Patients are the best judges of their own health. Health is subjective, and no outsider can estimate the different aspects of a person's health, or the value one gives to different aspects of health. HRQoL is also subjective, and should be reported by the patients. Sometimes patients are unable to give their assessment due to, for example, being unconscious, and in such cases, we must settle for peers' assessments. In practice, HRQoL is measured using questionnaires, of which there are many. These questionnaires are referred to as HRQoL instruments.

HRQoL instruments may be disease specific or generic. As the name suggests, a disease-specific instrument is intended to be used with patients suffering from the disease for which the instrument was developed. Generic instruments can be used with all patient groups, and the results are intended to be comparable across all populations. As HRQoL aims to encompass the full health state of patients, generic instruments are preferred. In addition, only generic instruments can be used in cost-utility analyses.

Depending on the HRQoL instrument used, HRQoL can be represented as a profile of the different dimensions of health, as a single index score, or as both. Instruments that produce the health utility index are referred to as single index instruments.

HRQoL is often reported as a health utility index, on a scale in which 1 represents full health and 0 represents death. This index represents the value of remaining life in that health state. In other words, one year in health of 0.9 is better than one year in health of 0.4. The index is intended to also reflect the exchange rate of quality and length of life – two years in health of 0.5 are equal to one year in full health of 1. This utility index, often referred to as the HRQoL score, is used in the calculation of quality-adjusted life years (QALY), which are described later.

**Theory of measuring HRQoL**

Most often, HRQoL is measured using a structured questionnaire. The simplest way is numeric ratings or visual analogue scales (VAS); asking patients to rate their overall health. This kind of VAS is included in the EQ-5D instrument as a reference (EuroQoL Group, 1990). However, due to several limitations, VAS or NRS alone do not produce a valid estimate of HRQoL (Torrance et al., 2001). They are mainly used as a reference or in the valuation process of the health states described by HRQoL instruments (described later).

A questionnaire tool used to measure HRQoL is often referred to as an instrument. Most HRQoL measures include a **descriptive system** and a **valuation system**.
The descriptive system aims to encompass all the relevant aspects of health. It consists of several dimensions of health, and each dimension contains levels of severity. The dimensions and their content should be restricted to those whom the treatment can affect, as HRQoL is used to measure the effect of healthcare interventions. In practice, the descriptive system is a questionnaire that patients fill in. No consensus exists on which or how many dimensions should be included in an HRQoL instrument, and different instruments have significantly differing descriptive systems (Brooks, 1996; Hawthorne et al., 2001; Moock and Kohlmann, 2008; Sintonen, 1994; Ware and Sherbourne, 1992).

The **valuation system** of an instrument is a scoring algorithm, or often a set of many, used to calculate scores for the health states (the responses to the descriptive system) that represent population preferences. The score thus reflects how good or bad a health state is, according to population preferences, in relation to death and full health. HRQoL instruments typically use an indirect valuation method of health states; the patients who fill in an HRQoL questionnaire do not value their health states themselves. Instead, the instrument contains pre-defined valuation for the health states that were elicited from healthy subjects when the instrument was developed. The patients' scores are then calculated using these pre-defined values, i.e. preference weights. The following chapter describes different valuation methods.

**Valuation of health utilities**

Different methods exist for calculating preference weights. The valuation is often done on healthy subjects. It can be approached with either a direct or an indirect method. In the direct method, the health states are described, the participants imagine themselves in the health state, and then value the health state with techniques described to them shortly. In the indirect method, the preference weights are already calculated for the health states, and the patient's responses are scored on the basis of these preference weights. Direct valuation methods have shown to usually produce higher health ratings than indirect methods (Arnold et al., 2009)

Commonly used direct methods for health utility calculation are Time Trade-Off (TTO), Standard Gamble (SG), VAS, Person Trade-Off (PTO), Magnitude Estimation (MG) and Willingness-to Pay (WTP) (Green et al., 2000; Krabbe et al., 1997). SG, TTO and VAS are probably the most often used.

In TTO, the subjects imagine themselves in the described health state with two possibilities: n (defined number, e.g. 10) years in the said health state followed by death, or x (<10) years in full health followed by death. X is then varied until the two options are equally appealing. Utilities can then be calculated as x/n, for example 7/10 = 0.7.

In SG, the respondent imagines living in a carefully described, compromised health state for a defined number of years. The respondent then faces a treatment option with a probability \( p \) of full recovery, or probability \( 1-p \) of death. The \( p \) is varied until both
options are equally appealing. The $p$ is then interpreted as the utility index for the described health state. The concept of probability is both a strength and a limitation of this method, as it mimics a real-world situation involving uncertainty, and respondents may have a varying idea of the concept of probability (Guinness, 2011).

VAS is perhaps the simplest method for health state valuation - patients value their health state on a visual analogue scale, on which one end indicates death and the other full health. Despite its simplicity, it has certain limitations, and generally produces lower utility values than the other methods (Stiggelbout et al., 1996; Torrance et al., 2001).

The choice of valuation method affects HRQoL results. In several hypothetical health states, utility scores for equivalent states can vary substantially, depending on the measure used (Kopec and Willison, 2003).

Some valuation methods, most notably the commonly used method for EQ-5D, allow health utility scores below zero, in which case the health state is interpreted as worse than death.

In practice, when calculating the preference weights for instruments, not all possible health states defined by the instrument are valued. It is common to value only some of the health states, and then extrapolate the preference weights to other health states using statistical methods, for example, the linear regression model (Dolan, 1997).

**Minimum clinically important change**

The minimum clinically important change (MIC), or minimum important difference (MID) describes the magnitude of change in the HRQoL score that the patient can perceive as a change for better (or worse). It is often given as a cut-off value above (or below) which the change is noticeable. For example, the MID for improvement might be $+0.015$, which means that the HRQoL is not considered to have changed if the hypothetical HRQoL score change is between 0 and 0.0149, and changes above 0.015 are considered improvements.

Two types of methods are described to obtain MID estimates: one anchor based and the other distribution based. Distribution-based measures are effect size (ES), standardized response mean (SRM) and standard error of mean (SEM).

The terminology used in the literature is somewhat heterogenous (see for example (Alanne et al., 2015; de Vet and Terwee, 2010)). For example, in their response letter, de Vet and Terwee suggest that an anchor-based MID is a different concept to the distribution-based minimal detectable difference (de Vet and Terwee, 2010). They argue that a minimal detectable difference only shows the statistical significance of the difference between two groups of measurement, and that minimum clinically important differences should be assessed using anchor-based methods. Revicki et al. also consider the anchor-based method to be more appropriate than the distribution-based method for estimating the MID (Revicki et al., 2008).
**Quality-adjusted Life Years**

Generic HRQoL measurement is the requirement for calculating quality-adjusted life years. When the length of life is multiplied by the HRQoL utility index, where 0 represents death and 1 full health, the product is called quality-adjusted life years (QALYs). The unit is 1 QALY, which represents one year lived in full health. We can then compare, for example, two intervention groups, and calculate the differences between the QALYs of the treatments. A common measure used in cost-utility analyses is cost per QALY gained, in which the price difference between two interventions are compared to the differences between QALYs.

**Different HRQoL Measures**

HRQoL instruments can be **generic** or **disease-specific**. Generic instruments are those that can be used in all patient populations, and disease-specific are only applicable to those with a certain diagnosis. Disease-specific instruments are more sensitive to small but possibly clinically important aspects of the disease in question, and may discriminate patients better, whereas generic HRQoL instruments are not as sensitive, and may lack discriminatory power in small but important differences in certain conditions. Disease-specific instruments are well suited to, for example, assist in clinical decision-making or compare different treatments of the same condition. (Drummond, 2015)

However, disease-specific instruments cannot be used in cost-utility analyses, or in the comparison of different patient populations because they do not produce comparable data, as they are only valid in the condition for which they are designed. In addition, most do not actually produce any health utility measurements, i.e., they do not value the health states in relation to death. Examples of the disease-specific measurements of general health used in chronic pain states are the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used for osteoarthritis (McConnell et al., 2001), and the Roland and Morris Back Pain Disability Scale used for back pain (Roland and Morris, 1983). The Brief Pain Inventory (BPI) is a compact questionnaire measuring pain intensity and disability caused by pain. It was originally developed for cancer-related pain, but has also been validated for non-cancer-related pain (Tan et al., 2004).

**Generic instruments**

**EQ-5D**

Developed by the EuroQoL group, the EuroQoL 5 Dimensions Questionnaire is probably the most internationally used HRQoL instrument (Räsänen et al., 2006). Its properties have been well studied in various patient populations (Payakachat et al., 2015). Originally, the EQ-5D was intended to be a very simple HRQoL instrument:
interestingly it was not intended as a standalone HRQoL measure, but more of a reference to complement existing HRQoL instruments (Brooks, 1996).

Its descriptive system comprises five dimensions of health: motility, self-care, usual activities, pain or discomfort, and anxiety or depression. In the classic EQ-5D-3L, the dimensions are divided into three levels of severity: no problems, some problems, and severe problems. It can describe \(3^5 = 243\) health states (Rabin et al., 2014). The questionnaire also includes a VAS with endpoints of ‘the worst health you can imagine’ and ‘the best health you can imagine’. The respondent rates their health on the scale in relation to the endpoints.

In 2009, the EuroQoL group published a five-level version of the descriptive system of the EQ-5D to improve the instrument’s sensitivity and to reduce the ceiling effect. The dimensions remained the same, but they now include five levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems (Feng et al., 2017; van Hout et al., 2012).

Several valuation algorithms exist for the EQ-5D-3L. The most commonly used is based on the TTO method, created with a sample of the general population of the United Kingdom (Brooks, 1996; MVH Group, 1995). This produces health utility scores ranging from -0.594 to 1, i.e., it allows health states worse than death (2007). In the valuation process, 43 of the 243 health states were valued using the TTO method, and these utilities were used in a regression model to calculate utility scores for the other health states. The regression model includes a constant for any non-perfect health state, -0.081, which is added if problems occur in any of the dimensions. The model also includes another term called \(N3 = -0.269\), which is added if any dimension is at level three, i.e. if severe problems occur in any of the dimensions. This means that the absolute score differences between health states can be substantial. No scores between 0.888 and 0.999 can be obtained.

No consensus exists on the MID of the EQ-5D score. Some estimations have been based on longitudinal studies - a review of these MDs estimate the mean MID to be 0.074, with a range of 0.011 to 0.140 when using the anchor-based method (Walters and Brazier, 2005).

**Different value sets**

The EQ-5D-3L has several other valuation methods, such as a VAS-based valuation system. In comparison to the TTO-based method, the VAS-based method produces lower values in relatively better health states, and higher values in worse health states (Brazier et al., 1999). For economic studies and for QALY calculation, the TTO-based valuation system of the EQ-5D (Rabin and de Charro, 2001) is recommended. Many countries have their own value sets for the EQ-5D-3L, which are based on either TTO, VAS or both methods combined (2007). For economic studies, the EuroQoL group recommends choosing a TTO-based value set either from the country in which the research is being conducted, or a value set from a country that most closely approximates this (the EuroQoL Group, 2017).
A value set for the EQ-5D-5L has been published (Devlin et al., 2017), but the National Institute for Health and Care Excellence (NICE) of the United Kingdom still recommends the value set for the EQ-5D-3L, until further research is conducted on the differences and on the impact of adopting the new value set. If data are collected using the EQ-5D-5L, NICE recommends converting the results to EQ-5D-3L by using the mapping algorithm developed by van Hout et al. in 2012 (van Hout et al., 2012). These recommendations were provided in a NICE policy statement given in August 2017 (National Institute for Health and Care Excellence, 2017). This statement is to be reviewed in August 2018.

15D

The 15-Dimensional HRQoL instrument was developed in Finland by Harri Sintonen and Markku Pekurinen. Their aim was to create an instrument that can be used as both a profile and a single utility index measure (Sintonen, 2001). In other words, it produces weighed utility indices for both individual dimensions and the whole health state.

Descriptive system

The descriptive system of the 15D consists of 15 dimensions: motility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. The conceptual basis for these dimensions is the WHO's definition of health as a state of complete physical, mental and social well-being (World Health Organization, 1948). Each dimension contains five levels of severity: no, slight, considerable, severe, or unbearable problems in the dimension. The patient chooses the level of severity that best describes their current health state. In theory, the instrument defines \(5^{15}\) health states, i.e. possible combinations from the questionnaire.

One property of the descriptive system is its ability to predict a small number of missing answers. If a patient has left three or less of the 15 dimensions unanswered, the missing dimensions can be reliably predicted using linear regression methods, and the patient’s age, gender, and other dimensions as predictors (Sintonen, 1994).

Valuation system

The valuation system was created by applying the multiattribute utility theory (Sintonen, 1995). The multiattribute utility functions are used in decision making in situations, where there are many attributes (e.g., the dimensions of health) and uncertainty (e.g., the probability of death) affecting the decision. The valuation here was carried out in several representative samples of the Finnish general population in a three-stage procedure. Stages one and two aimed at establishing the relative importance of the dimensions for health, by using the magnitude estimation method.
The ratio scale nature of the valuation was emphasized using arrows and wording; For example, the arrow pointing to 90 on a scale of 0 to 100 scale reads: "9/10 as important as the most important attribute (90% of the importance of the most important attribute)". The participants rated the relative importance of the "best" levels of the dimensions for health, as well as the relative importance of the "worst", or bottom levels of the dimensions. The importance weights were rescaled so that they sum up to 1. The importance weights were estimated for the intermediate levels of the dimensions based on distances between the level values within the dimensions. These within-dimension level values were elicited as the third stage by using a similar 0-100 ratio scale and placing the most desirable level at 100, then dividing the average by 100. These within-dimension desirability level values were further rescaled to a scale of 0-1 so that the best level obtains a value of 1 and being dead = 0. The 15D score, representing overall HRQoL, is calculated by multiplying the within-dimension level values by the importance weights of the levels of the dimensions. This results in a 0-1 scale, were 1=no problems on any dimension (“full health”) and 0=being dead.

The MIC for the 15D score has been established as 0.015 (Alanne et al., 2015). This was estimated among 4903 hospital patients with 16 different disease entities (including chronic pain patients) using the anchor-based method, and a five-point Likert scale with overall health change as the anchor.

**SF-6D and SF-36**

The 36-Item Short Form Health Survey, the SF-36, was developed by the RAND Corporation. It was originally published as the result of the Medical Outcomes Study, a large-scale study on treatment outcomes and their measurement in different organizations of the United States health care (see https://www.rand.org/health/surveys_tools/mos/bibliography.html for the bibliography of publications). The objective was to create a comprehensive, psychometrically robust general health survey that would be short enough to be practical in various study situations.

The SF-36 consists of 36 items that cover eight dimensions of health (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions). The questionnaire also contains a five-point Likert-type question on general health. For each dimension, the scores of the responses are transformed on a scale from 0 to 100, which reflect the well-being in the said dimension. The SF-36 does not produce single index utility scores, and the dimension summary scores do not reflect population preferences (McHorney et al., 1993; Ware and Sherbourne, 1992). The SF-12 is a shortened version of the SF-36. It produces the physical and mental component summary scales of the SF-36 (Ware et al., 1996).

To calculate a health utility score, i.e., the HRQoL index score, Brazier et al. developed an algorithm to be used with the SF-36 (Brazier et al., 1998). This takes 12 of the 36 items to form six subscales: physical function, role limitation, social
function, bodily pain, mental health and vitality. The preference weights of the SF-6D were elicited using the standard gamble (SG) method. The algorithm produces utility scores ranging from 0.29 to 1. A similar algorithm has also been produced to be used with the SF-12 (Brazier and Roberts, 2004).

Other measures

The Assessment of Quality of Life (AQoL)-8D instrument describes eight dimensions of health: independent living, happiness, mental health, coping, relationships, self-worth, pain, and senses. Preference weights are derived using the TTO method. The Canadian Health Utility Index (HUI 3) describes seven dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. The preference weights are obtained using a combination of the VAS and TTO methods, and the utility score can range from -0.31 to 1. Further description of these and other measures are given in, for example, a comparison study of five multi-attribute utility instruments (Hawthorne et al., 2001).

Properties of HRQoL instruments

If we want to measure a patient's temperature, a device that tells us the room temperature or the patient's blood pressure is useless. 'Validity' refers to the extent to which a measurement captures what it aims to measure. The concept of validity is important in every clinical measurement, be it physical, chemical or psychological in nature.

Several aspects of validity can be differentiated. In his working paper describing the 15D, Sintonen defines the different aspects of validity and other properties of HRQoL instruments (Sintonen, 1994). In their review on generic, single-index score-producing HRQoL instruments, i.e., multi-attribute utility instruments, Richardson et al. summarize the properties that should be assessed by the different HRQoL instruments (Richardson et al., 2011).

Content validity refers to the extent to which a measure captures the important aspects of the measured condition and its treatment. In the case of HRQoL instruments, their aim is to measure overall health and functioning, so they should encompass all the relevant aspects of health. On the other hand, a measure should not contain items that are irrelevant to the measured phenomenon. In practice, content validity is often assessed by, for example, an expert panel, when developing the instrument. One example of content invalidity is the 'ceiling effect': if one instrument produces an HRQoL score of 1 (full health) but the patient group feels that the disease impairs their health, the instrument can be concluded as insensitive, because it lacks some components that are meaningful for health.

Construct validity refers to the extent to which the instrument measures what it was intended to. For example, an HRQoL instrument should measure overall health, not
only one aspect of health such as depression, or socioeconomic position. Construct validity can be further divided into the following:

- Convergent validity: correlation with other measures expected to correlate with the construct
- Discriminant validity: non-correlation with measures of different constructs, such as HRQoL and blood pressure
- Discriminative validity: ability to discriminate between different groups (patients, healthy population).

In practice, most studies assessing the validity of an instrument evaluate construct validity and convergent validity. This is done by comparing the instrument of interest with another instrument known to be valid. Bland and Altman present statistical methods for such a comparison (Bland and Altman, 1986). Most studies assessing an HRQoL instrument’s validity in a certain group of patients have assessed construct validity. It should be noted that proving only construct validity is not enough to conclude that an HRQoL instrument is valid (Richardson et al., 2011).

Criterion validity is a similar term to construct validity. It describes the extent to which an instrument behaves as expected, judged by external criteria. This criteria may be, for example, a ‘gold standard’ measure. Predictive validity means the ability to predict the measure in question using the defined criteria, or vice versa.

In addition to validity, several other properties of HRQoL instruments should be considered when estimating their performance. These are briefly outlined next.

Feasibility means how easy an instrument is to fill in. Reliability indicates the repeatability of measurements in the same population, with minimal random error. It is assessed using a test-retest method, and evaluates whether the repeated measures differ. Sensitivity means the ability to detect significant differences in health, and responsiveness to change means the ability to detect changes over time.

**Comparison of different HRQoL measures**

The various HRQoL instruments differ from each other in terms of their descriptive systems, valuation systems and combination of algorithms (additive or multiplicative) used. Most instruments also have different ranges of scores. Many studies have been carried out to compare different HRQoL instruments (Hawthorne et al., 2001; Moock and Kohlmann, 2008; Richardson et al., 2011, 2016). In summary, instruments can produce significantly differing HRQoL scores in the same patient populations.

In their review on multi-attribute utility (MAU) instruments, Richardson et al. discuss the substantial differences between the HRQoL scores produced by different instruments. Although the valuation methods (TTO, SG, VAS) are different in every instrument, the methods themselves correlate with each other to such an extent that the different valuation methods are not sufficient to explain the observed differences in the HRQoL scores. The authors conclude that the differences observed in the HRQoL scores produced by different instruments in the same patient populations are largely
due to the different descriptive systems (Richardson et al., 2011). In a later review, the authors conclude that different HRQoL instruments indeed measure different constructs, and that the results are not directly comparable (Richardson et al., 2015).

**Use of HRQoL instruments in chronic pain patients**

HRQoL is recommended as a key outcome indicator of pain management by both the IMMPACT guidelines for clinical trials on pain management, and the recent VAPAIN consensus statement on outcomes for MPM (Dworkin et al., 2005; Kaiser et al., 2018). In a review of RCTs on MPM, 37% of the included studies used HRQoL as an outcome measure (Scascighini et al., 2008). In another systematic review on outcomes used for assessing MPM, HRQoL was measured in 21% of the included studies (Deckert et al., 2016). The reviews did not report the instruments used to measure HRQoL.

Different HRQoL instruments have produced differing results in chronic pain patients. Lillegraven et al. compared 15D, EQ-5D and SF-6D among rheumatoid arthritis patients and found the scores to differ significantly. The agreement was moderate between SF-6D and 15D, but poor between EQ-5D and 15D/SF-6D. The differences were most pronounced among patients with severe disabilities (Lillegraven et al., 2010).

In a population sample with chronic pain, Torrance et al. similarly concluded that the SF-6D and EQ-5D produced notably different scores. They also noted that the patients who obtained worse-than-death scores in EQ-5D were not clustered at the lower end of SF-6D; i.e., there was no floor effect (Torrance et al., 2014). These results have incited a discussion on the use of different HRQoL instruments in patients with chronic pain. Also, as Schofield notes, the validity of HRQoL instruments has not been studied among chronic pain populations (Schofield, 2014).

**Aims of the study**

The literature review thus identified the following problems in assessing the treatment outcomes of MPM.

MPM is effective, but we do not know what makes it superior to other approaches. We also do not know which patients benefit from MPM or its components. The heterogeneity of study designs and their outcomes prevents the comparison of these different studies. This could be overcome by standardizing the outcomes used in these studies.

HRQoL is recommended as an important outcome measure in all pain interventions, including MPM. However, different instruments produce differing HRQoL results and there is no consensus on which instrument should be used to measure chronic pain. Moreover, some reviews of HRQoL instruments indicate that other HRQoL instruments, the 15D in particular, should be used instead of the EQ-5D (Richardson et al., 2016).
The aims of this thesis were the following:

1. To study the validity of two HRQoL instruments, the EQ-5D and the 15D, in patients with chronic pain.
2. To assess the impact of chronic pain on HRQoL by comparing the HRQoL of chronic pain patients with that of a general population sample.
3. To investigate which aspects of chronic pain are most significant for overall quality of life.
4. To use an HRQoL instrument to assess the prognosis of patients treated at a multidisciplinary pain clinic.
5. To identify potential patient background variables associated with the HRQoL changes after MPM.

I hypothesized that both instruments would show validity, but, based on previous comparisons and certain properties of the EQ-5D, that the 15D would appear superior to the EQ-5D. Because disability from chronic pain is linked to psychosocial burden and symptoms, I expected the HRQoL of the patients in chronic pain to be impaired, comparable to e.g. those with depression. I expected to see improvement of HRQoL after MPM, and that variables measuring the pain-related burden (such as pain intensity or pain-related distress) would be associated with the treatment outcome.

Materials and methods

Participants

The population of Study I consisted of the first 391 patients who participated in the Chronic pain and life-style factors ‘KROKIETA’ study. KROKIETA is a multicentre study of several secondary or tertiary pain management centres in Finland, which aims to analyse the connections between chronic non-cancer pain, lifestyle factors, socioeconomic and psychological properties, and metabolic and other biochemical markers. The inclusion criteria for the KROKIETA study were an age of 18–75 years, no active cancer, and the ability to answer the questions independently in Finnish. The patients for Study I were recruited between September 2013 and June 2016 from three multidisciplinary pain clinics (Turku University Hospital, Southern Karelia Central Hospital and Helsinki University Hospital, where the recruitment for KROKIETA study was carried out after recruitment for Studies II and III of this present thesis), and three tertiary facial pain centres (Kuopio University Hospital, Turku University Hospital and Tampere University Hospital). Those who participated gave their written consent.

The study population for Studies II and III were 1528 patients referred to the Multidisciplinary Pain Clinic of the Helsinki University Hospital during 2004–2012. Patients with active cancer were excluded. Some patients attended multiple treatment episodes during follow-up, and patients attending a second treatment period during 2004–2012 were excluded. All admitted patients were sent a letter of invitation, and
those agreeing to participate gave their written consent.

Admission to tertiary pain clinics is based on referral from primary health care centres or the private sector. The patients in multidisciplinary pain clinics represent the most challenging group of chronic pain patients. They have often undergone several failed treatment attempts in primary health care.

Studies II and III were approved by the surgical ethics committee of the Helsinki and Uusimaa Hospital District (decision no. 182/13/03/02/2009). The study was registered at the Helsinki and Uusimaa Hospital District Clinical Trials Registry, as number HUS2071. Study I was approved by the co-ordinating ethics committee of the Helsinki and Uusimaa Hospital District (decision no. 29/13/03/00/2012).

**Multidisciplinary pain management**

The aim of MPM is to improve patients' physical, psychological, work, and social functions, even if their pain cannot be completely eliminated.

The treatment episode at the Pain Clinic of the Helsinki University Hospital is individually tailored for each patient, and implemented as outpatient care. At the beginning of an MPM episode, patients attend a diagnostic evaluation, on the basis of which the subsequent rehabilitation episode is planned. The staff of the Pain Clinic consists of physicians, psychologists, a physiotherapist, a social worker, and nurses. Medical specialties include anaesthesiology, neurology, rehabilitation medicine, psychiatry, general medicine, and dentistry. Treatment modalities include pharmacological interventions, local analgesia, spinal cord stimulation, physiotherapeutic counselling (including exercise programmes and transcutaneous electronic nerve stimulation), psychological counselling (including pain management strategies such as relaxation and cognitive-behavioural methods), supportive psychological therapy, group-based pain management programmes, and socioeconomic counselling. In addition, each patient meets a nurse several times during their treatment episode. The treatment period is discontinued when a good treatment outcome (defined in the initial diagnostic evaluation) is achieved, or when the physician concludes that the Pain Clinic has no further treatment modalities to offer the patient that would benefit them, or if the patient lacks motivation. Most patients are referred for multidisciplinary evaluation, but a small number are referred to receive only one specific treatment modality.
Measures

Health-related Quality of Life Instruments

Studies II & III used the 15D instrument to measure HRQoL. Study I used the EQ-5D in parallel to the 15D. These instruments are described in detail in the review of the literature section. In addition to the HRQoL instruments, Study I included a five-item Likert scale question about the level of general health, which asked patients to rate their current overall health as excellent, good, average, rather poor, or very poor. This question is routinely used with the SF-36 instrument as a reference (Ware and Sherbourne, 1992). As part of the EQ-5D, patients also ranked their overall health on a 100mm visual analogue scale.

Socioeconomic background

For Studies II and III, the socioeconomic background variables were extracted from the Clinical Pain Questionnaire, which is described in the next chapter. In Study I, the questions measuring socioeconomic background were based on the questionnaire used in the FINRISKI epidemiological studies in Finland (Borodulin et al., 2015), and the questionnaire was edited to include questions concerning the history of pain symptoms. The variables extracted for Study I were age, gender, education years, working or not working, smoking status, and leisure time physical activity.

Clinical pain questionnaire

The Clinical Pain Questionnaire is used routinely in clinical practice and research in Finland. It contains questions on socioeconomic background; the history of pain symptoms; the nature of the pain, i.e., intensity; interference in daily activities, and expectations concerning treatment.

The questions in Studies II and III elicited information on the following: education and employment status; living alone or cohabiting; constant or intermittent pain; single or several types of pain; pain duration of more than or less than three years. The last question concerning the duration of pain symptoms was dichotomized from the question ‘How long have you felt the pain as it feels now?’ The cut-off point of three years was based on previous findings by Dunn et al. that LBP lasting over three years is an independent predictor of prognosis (Dunn and Croft, 2006).

The severity of pain was assessed by continuous measurements of current pain intensity, pain-related distress and the impact of pain on daily activities. Pain intensity and pain-related distress were measured using a VAS from 0 to 100 mm, where 0 refers to no pain and 100 to the worst imaginable pain intensity or distress from pain.

The impact of pain on daily activities was measured using the sum score of the question ‘How much does your pain affect the following activities?’, followed by 18 activities with the response options ‘not at all,’ ‘moderately,’ and ‘much’. The respective choices
were scored as 0, 1, or 2 points. To set the sum score to the same scale as the two VAS scores, it was represented as a percentage of the maximum score.

To eliminate the confounding effect of missing answers to single activities, the sum score was represented as a percentage of an individual patient’s theoretical maximum sum score. In other words, we used personal mean imputation to predict the missing answers to the question if the patient had answered at least five of the 18 activities. (e.g., if a patient had answered ‘moderately’ to 17 activities and left 1 activity blank, the patient would have a score of 17 out of 34, and the impact percentage would be 50%).

**Symptom-specific measures**

Study I used the following measures in parallel with the HRQoL measures in order to compare the instruments’ association with different symptoms and to assess their validity.

The **Brief Pain Inventory** (BPI) is used to quickly and easily assess the severity of pain. It can be divided into two subscales – pain intensity and pain interference in daily functioning. It consists of numeric rating scales (NRS) from 0 to 10, on which the patient rates the pain intensity and its interference in seven daily activities. Originally developed to assess cancer-related pain, it has shown to also be valid in assessing non-cancer pain (Tan et al., 2004), and is extensively used in pain research and clinical practice. A longer form of the questionnaire exists, but most studies, like the present one, have used the short form. We used the sum score of the two subscales, intensity and interference, in which a higher score indicates more intense or interfering pain.

The **Chronic Pain Acceptance Questionnaire** (CPAQ) measures how much the patient can pursue personally relevant goals and participate in personally important activities, despite a chronic pain condition (McCracken et al., 2004b; Vowles et al., 2008). It can be divided into two subscales, Activity Engagement and Pain Willingness. It consists of 20 statements which patient rates from 0 to 6, according to how much the statement reflects their views. The points are then calculated, and in certain statements the negative of the rating is used (e.g. -4 instead of 4). A higher score indicates greater acceptance.

The **Beck Depression Inventory** (BDI) is one of the most widely used measures for assessing the severity of depressive symptoms. It consists of 21 multiple choice questions that are scored according to the severity of symptoms. A higher score indicates greater depressive symptoms, and cut-off values exist for classifying the depression as minimal, mild, moderate, or severe (Beck et al., 1996).

The **Pain Anxiety Symptoms Scale** (PASS) is used to analyse pain-related anxiety, fear, avoidance behaviour, and negative beliefs. Based on the fear-avoidance theory of chronic pain, these negative emotions have been hypothesized as facilitating the development of a chronic pain condition. In the present study, we used the shortened, 20-item PASS-20 form. Four subscales (avoidance behaviour, cognitive anxiety, fear,
and physiological anxiety) can be calculated from the measure, but we used the total sum score in the present study. (McCracken, 2013)

The Basic Nordic Sleeping Questionnaire (BNSQ) was used to assess the severity of sleep problems (Partinen and Gislason, 1995). The measure is mainly used in clinical practice to aid the clinician, and does not include an established scoring system used in research. Thus, we selected the five most relevant five-point Likert scale questions concerning the severity of difficulty falling asleep, waking up during the night, tiredness in the morning, tiredness in the evening, and the use of sleep medication. The selection of the four questions was based on the ICD-10 criteria for insomnia. Based on clinical judgment, we decided to include the use of sleep medication. The individual questions were scored from 0 to 4 to indicate increasing severity, and the sum score of the five questions was used as a single index value. As a preliminary assessment of validity, we calculated Spearman’s correlation coefficient for this BNSQ index with the sleep dimension of the 15D.

**Characteristics of multidisciplinary pain management programme**

Because the MPM episode was individually tailored for each patient, we wanted to analyse the structure of the patients’ treatment. We extracted the treatment details from the electronic hospital databases, in which each visit is coded as a separate entry that contains the date, primary diagnosis and code of the treatment personnel seen. For each patient, we extracted the number of visits to each different discipline: pain specialist physician, physiotherapist, psychologist, social worker, or group-based therapy. We included only the visits that had occurred during the 15D follow-up (the 12 months following the first visit to pain clinic), during which virtually all treatment episodes would have finished.

Visits to a pain specialist nurse were not consistently recorded in the databases, as every patient meets a pain specialist nurse several times during their treatment episode, often on the same day as they visit the Pain Clinic for other treatment modalities. Thus, we did not include the visits to the pain specialist nurse in the treatment-related variables, but assumed that each patient would have received this modality of treatment.

Some patients are referred to the Pain Clinic to receive only some specific treatment modality, for example local analgesia or group-based rehabilitation. These patients include, for example, those who have attended an MPM episode before and now only need some certain modality, or those who are treated by a pain specialist working outside the Helsinki University Hospital's Pain Clinic. We assumed that these patients did not represent the MPM strategy of the Pain Clinic. We excluded those who had received only one type of treatment and had made no initial evaluation visit to a physician during the treatment episode.
Study setting

Study I

A total of 391 patients filled in the two HRQoL instruments, the socioeconomic background questionnaire and the symptom-specific questionnaire described above. The forms were administered at baseline, before the patients embarked on their MPM episode.

The HRQoL results were compared with each other and with the level of general health. We analysed the association of the HRQoL instruments with the symptom-specific questionnaires, and compared the strengths of these associations with the 15D and the EQ-5D.

Study II & III

The aim of Study II was to describe the HRQoL in severe chronic pain, and to compare it with that of a general population sample. Study II used the baseline data from 1528 patients at baseline, i.e. the data before the start of multidisciplinary treatment patients. The patients filled in the 15D questionnaire and the clinical pain questionnaire at the beginning of the MPM episode.

We also used the 15D data from the general population sample, adjusted to match the pain patients in terms of age and gender. The data for the general population came from the National Health 2011 survey, representing the Finnish general population aged 18 years and older (Koskinen et al., 2012). A sub-sample of this population was formed, whose age and gender distributions were similar to those of the chronic pain population, and we compared the respective 15D scores and profiles. Next, we compared the 15D results of the chronic pain patients to the Clinical Pain Questionnaire results.

The aim of Study III was to describe the changes in HRQoL after MPM, and to identify the variables predicting the treatment outcome. The patients filled in the clinical pain questionnaire and the 15D instrument at baseline, and the 15D follow-up was administered at six and 12 months after the start of treatment.

The 15D score change at 12 months was chosen as the primary outcome variable. We described the changes in the 15D score and profile, and analysed the association of the background and treatment-related variables with the 15D score change.

The variables used in the studies are listed in the following table.
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<th>Study I</th>
<th>Study II</th>
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<td>BPI, interference</td>
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The measures and variables used in the studies.
Statistical analyses

The statistical analyses were conducted using STATA for Study I, the IBM SPSS
Statistics version 23.0 for Study II, and R for Study III (R Core Team, 2015).

The descriptive statistics for continuous variables are presented as means and
standard deviations, and as counts and percentages for categorical variables.

Statistical comparisons between groups were performed using the chi-squared test, t-
ttest or analysis of variance (ANOVA) with post-hoc Bonferroni corrections, depending
on whether the analysed variable was continuous or categorical, or whether the
question used as a grouping variable was dichotomous or multi-class. If the theoretical
distribution of the test statistics was unknown, or in cases of violation of the
assumptions (e.g. non-normality), we employed the bootstrap method.

The 15D and EQ-5D scores in Study I were compared with each other and with the
symptom-specific measures using Spearman’s rank correlation and Kendall’s
coefficient of concordance. We studied the agreement of the two instruments using the
Bland-Altman analysis. Because of differences in both the theoretical and the observed
range of the 15D and EQ-5D scores, HRQoL scores were standardized and compared
across the levels of perceived general health status. We calculated the Pearson’s linear
correlation coefficient between the perceived general health status and the EQ-5D or
the 15D, and compared the statistical significance of the two correlation coefficients
with Fischer’s R-to-Z transformation.

In Study I, the independent association between the pain-related variables and the
scores of the HRQoL instruments was examined with multiple least squares regression.
The HRQoL score (either the 15D or the EQ-5D score) was set as the dependent
variable, and each pain- and symptom-related measure (CPAQ, BDI, PASS, BPI/intensity, BPI/interference, BNSQ) was the independent variable. To
prevent multicollinearity bias and in order to compare pain-related measures, we
analysed all the pain- and symptom-specific variables individually in separate models.
The six afore mentioned pain- and symptom-related measures were then reduced to
factors using principal component analysis (PCA), and components with Eigenvalues
of < 1 were excluded on the basis of Kaiser criteria. The principal component (PC) was
used to account for the combined variance of the pain- and symptom-specific results.
This dimension reduction was conducted to prevent multicollinearity bias.

The regression models were adjusted for the background variables of age, gender,
education years, working status, smoking, and duration of pain. Thus, each model
consisted of the HRQoL score as the dependent variable, one pain-related variable (or
PC), and all the background variables as independent variables. We then changed the
pain-related variables and compared the standardized beta coefficients (β) for the
respective pain-related variables. The β value indicates how strongly each predictor
variable influences the criterion (dependent) variable and is measured in units of
standard deviation. Cohen’s standards for β values above 0.10, 0.30 and 0.50 represent
small, moderate and large relationships, respectively.
In Studies II and III, we analysed the difference between the 15D scores using the independent or paired samples \( t \)-test, depending on whether we were testing the difference between two groups at one time point, or between two time points for one group. The differences in the 15D dimensions were tested with the non-parametric Mann-Whitney U test, as the dimensions have five levels and the distribution of dimension scores is not normal. The unadjusted association of the 15D score with other continuous variables was assessed using Pearson's linear correlation.

In Study II, we analysed the independent relation of the background and pain-related variables with the 15D score with a forward stepwise linear regression model. The results were also confirmed with a backward stepwise model.

For exploratory analyses in Study III, we compared 200 patients who reported the greatest 15D score improvement (the best HRQoL outcome) with the 200 who reported the greatest 15D score deterioration (the worst HRQoL outcome). We compared the differences between the background variables of these two groups using independent samples \( t \)-test or the chi-squared test, depending on whether the variable was continuous or categorical. We further analysed the association between the continuous variables and the 15D score change using Spearman’s correlation test.

In Study III, a binary logistic regression model was constructed to predict if a patient would achieve a clinically major improvement in quality of life (15D score change > +0.035 at 12 months). Background variables were selected for the model, based on preliminary significance and whether the inclusion was logically justified. This selection was made because the patient-reported background variables contained missing values that would cause the case to be eliminated from the model calculation. We also used a linear regression model to analyse the association between these background variables and the 15D score change.

**Imputation of missing answers**

If the patient had left three or less 15D dimensions unanswered, we predicted the missing answers using linear regression, with age, gender and other dimensions as dependent variables. In Study II, the missing dimensions of the 15D (if three or less) were predicted using multiple imputation models. A chained equation imputation model was fit to create five imputed data sets. (White et al., 2011) In the symptom-specific measures of Study II (CPAQ, PASS, BNSQ, BPI/intensity, BPI/interference, BDI), we imputed the missing values by using the personal means of the other answers if \( \leq 20\% \) of the answers were missing. Personal mean imputation has been concluded to be an appropriate method for the SF-36 instrument, comparable to the multiple imputation method (Peyre et al., 2011).
Results

Participants

*KROKIETA study sample*

The pain centres participating in the KROKIETA study were the Pain Clinic of the Helsinki University Hospital, the Pain Clinic of the Turku University Hospital, and the Pain Clinic of the South-Karelia Central Hospital. The participating facial pain centres were from the following hospitals: the Turku University Hospital, the Kuopio University Hospital and the Tampere University Hospital.

The data were collected between 2.9.2013 and 3.6.2016. Approximately 800 recruitment letters were sent – the accurate number of letters was not recorded. By the mentioned date, 391 patients had participated in the study and their data had been recorded. One hundred and thirty patients were treated at the facial pain centres, and 260 patients in the pain clinics. This data was missing in the case of one patient. A total of 342 patients answered the whole 15D questionnaire, but 31 patients had left one to three dimensions empty, and their 15D scores were imputed. Thus, 373 patients provided sufficient data for calculation of the 15D results. Of the 391 patients, 359 filled in the whole EQ-5D questionnaire. *Table 1* shows the characteristics of the study sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd)</td>
<td>373</td>
<td>46.9 (13.8)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>261</td>
<td>(70.0)</td>
</tr>
<tr>
<td>Working, n (%)</td>
<td>173</td>
<td>(46.6)</td>
</tr>
<tr>
<td>Multiple pain sites, n (%)</td>
<td>183</td>
<td>(58.5)</td>
</tr>
<tr>
<td>Never smoked regularly in their lives, n (%)</td>
<td>134</td>
<td>(35.9)</td>
</tr>
<tr>
<td>Pain duration over 2 years, n (%)</td>
<td>256</td>
<td>(69.4)</td>
</tr>
</tbody>
</table>

*Table 1* Socioeconomic and pain-related background factors of KROKIETA study sample.

*Helsinki study sample*

The data were collected between 2004 and 2012. A total of 1573 patients agreed to participate, and were given the 15D questionnaire. Twenty-one of these were duplicate
cases of patients who had attended a second treatment episode during follow-up, and were thus excluded. Twenty-four patients provided insufficient 15D data, i.e. they had left more than three of the 15 dimensions unanswered or had returned an empty form – they were thus also excluded. The number of cases included in the data of Study II was 1528.

In Study III's follow-up, 20 patients were referred for psychological consultation only and were excluded. Of the remaining 1508 patients, 1043 (69%) responded to the follow-up 15D questionnaire 12 months after the start of MPM.

In summary, the baseline data of Study II consisted of 1528 cases and the follow-up data of Study III consisted of 1043 cases.

**Table 2** shows the patient characteristics and the 15D scores respective to the socioeconomic and pain-related questions.
Table 2. Background characteristics of the Helsinki study sample, and the respective 15D scores. The p value shows the statistical significance of the difference between the question’s levels. The p value was obtained using a t-test or ANOVA with post-hoc Bonferroni corrections, depending on whether the grouping variable is dichotomous or multi-class.
*) the reference category of a multi-class question, to which other categories are compared.
HRQoL results

KROKIETA study sample

Table 3 shows the mean results of the HRQoL measurements, reference measurements and other symptoms. The mean 15D score of the patients was 0.76, with a median of 0.76 and standard deviation of 0.116, ranging from 0.39 to 1.0. The mean EQ-5D score was 0.53, with a median of 0.66 and standard deviation of 0.305. Twenty-five patients (7%) had a HRQoL score below zero, i.e. worse than death, in the EQ-5D. Eleven patients obtained a score of 1 (the best score) and 72 obtained a score of 0.8 (second-best observed score). Figure 1 shows the distribution of the two HRQoL instruments. The distribution of the EQ-5D was bimodal, as only a few patients scored close to average. The distribution of the 15D scores was close to normal.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Score</th>
<th>Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>15D score, mean (SD)</td>
<td>0.76 (0.12)</td>
<td>0–1</td>
</tr>
<tr>
<td>EQ-5D score, mean (SD)</td>
<td>0.53 (0.30)</td>
<td>(-0.594)–1</td>
</tr>
<tr>
<td>Self-rated health, n (%)</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Very good or good *</td>
<td>70 (18.9)</td>
<td>.</td>
</tr>
<tr>
<td>Average</td>
<td>102 (27.5)</td>
<td>.</td>
</tr>
<tr>
<td>Rather poor</td>
<td>154 (41.5)</td>
<td>.</td>
</tr>
<tr>
<td>Very poor</td>
<td>45 (12.1)</td>
<td>.</td>
</tr>
<tr>
<td>EQ-VAS, mean (SD)</td>
<td>0.58 (0.20)</td>
<td>0–1</td>
</tr>
<tr>
<td>BPI</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Pain intensity, mean (SD)</td>
<td>21.9 (7.1)</td>
<td>0–40</td>
</tr>
<tr>
<td>Pain interference, mean (SD)</td>
<td>33.9 (14.7)</td>
<td>0–70</td>
</tr>
<tr>
<td>BDI, mean (SD)</td>
<td>13.9 (9.8)</td>
<td>0–63</td>
</tr>
<tr>
<td>CPAQ, mean (SD)</td>
<td>57.0 (19.4)</td>
<td>0–120</td>
</tr>
<tr>
<td>PASS, mean (SD)</td>
<td>42.3 (18.9)</td>
<td>0–100</td>
</tr>
<tr>
<td>BNSQ, mean (SD)</td>
<td>15.7 (4.4)</td>
<td>0–24</td>
</tr>
</tbody>
</table>

*) In the five-item question on self-rated health, only three patients rated their health as ‘very good’: for consecutive analyses were grouped together with those rating their health as ‘good’. 
The mean 15D HRQoL score of 1528 chronic pain patients at baseline was 0.710 (95% CI = 0.705-0.716, SD = 0.114). The mean 15D score of an age- and gender-matched sample of the general population was 0.922 (SD = 0.083; p<0.001 for difference between the population and the patients). Figure 2 shows the 15D profiles, i.e., the mean scores of individual dimensions of the 15D among the patients and among the general population sample. The values of all dimensions were statistically significantly (p<0.001) lower among the chronic pain patients. The greatest differences were seen in the dimensions of ‘discomfort and symptoms’ (0.519), ‘usual activities’ (0.393), ‘sexual activity (0.357), ‘vitality’ (0.317), and ‘sleeping’ (0.292).

Figure 1. Distribution histograms of the HRQoL and health measurements.

Helsinki Study sample

The mean 15D HRQoL score of 1528 chronic pain patients at baseline was 0.710 (95% CI = 0.705-0.716, SD = 0.114). The mean 15D score of an age- and gender-matched sample of the general population was 0.922 (SD = 0.083; p<0.001 for difference between the population and the patients). Figure 2 shows the 15D profiles, i.e., the mean scores of individual dimensions of the 15D among the patients and among the general population sample. The values of all dimensions were statistically significantly (p<0.001) lower among the chronic pain patients. The greatest differences were seen in the dimensions of ‘discomfort and symptoms’ (0.519), ‘usual activities’ (0.393), ‘sexual activity (0.357), ‘vitality’ (0.317), and ‘sleeping’ (0.292).
Figure 2. 15D profiles, i.e. the mean scores of the individual dimensions of health. This shows the profiles of the KROKIETA study sample (from Study I of this thesis, n= 373), the study sample from Helsinki University Hospital’s Pain Clinic (from Studies II and III, n= 1528), and the profile of the general population sample adjusted to match the Helsinki study sample in terms of age and gender.

Agreement of HRQoL instruments

The agreement of the two HRQoL instruments in the KROKIETA study sample was analysed. Spearman's correlation coefficient between the EQ-5D and 15D was 0.66 (95% CI 0.60-0.71). The Kendall rank correlation coefficient of concordance for the two HRQoL instruments was 0.83.

The agreement of the two HRQoL instruments is plotted using the Bland-Altman analysis in Figure 3. The mean of the two measurements for each case is plotted against the difference of the two measures. If two measures agreed perfectly, their difference would be zero.
Figure 3. Bland-Altman plot of the two HRQoL instruments, the 15D and the EQ-5D. This shows the difference between the two HRQoL instruments (15D - EQ-5D) as a function of the mean of the two measurements. The dashed line indicates the mean difference between the measurements.

Figure 3 compares the mean standardized EQ-5D and 15D scores (i.e., the z-scores) across the four levels of self-reported health. Pearson’s coefficient for linear correlation between self-rated health was -0.37 for the EQ-5D, and -0.61 for the 15D, with p < 0.001 for the difference.
Figure 4. Mean standardized HRQoL scores grouped according to the levels of self-rated health. The difference between the standardized HRQoL scores is statistically significant in ‘good’ health. Pearson’s coefficient for linear correlation was -0.37 for the EQ-5D, and -0.61 for the 15D, with p< 0.001 for the difference.

HRQoL instruments and other measures of pain and symptoms

KROKIETA study sample

Table 4 compares the Spearman’s rank correlation coefficients of the HRQoL results and other pain and symptom results.
<table>
<thead>
<tr>
<th>Variable</th>
<th>15D r (95% CI)</th>
<th>EQ-5D r (95% CI)</th>
<th>p for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAQ</td>
<td>0.63 (0.56 to 0.69)</td>
<td>0.56 (0.48 to 0.63)</td>
<td>0.064</td>
</tr>
<tr>
<td>PASS</td>
<td>-0.52 (-0.59 to -0.44)</td>
<td>-0.50 (-0.57 to -0.42)</td>
<td>0.51</td>
</tr>
<tr>
<td>BDI</td>
<td>-0.69 (-0.74 to -0.63)</td>
<td>-0.58 (-0.64 to -0.50)</td>
<td>0.003</td>
</tr>
<tr>
<td>BNSQ</td>
<td>-0.59 (-0.65 to -0.52)</td>
<td>-0.47 (-0.54 to -0.38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BPI, pain intensity</td>
<td>-0.46 (-0.53 to -0.37)</td>
<td>-0.57 (-0.64 to -0.50)</td>
<td>0.004</td>
</tr>
<tr>
<td>BPI pain interference</td>
<td>-0.64 (-0.70 to -0.58)</td>
<td>-0.63 (-0.69 to -0.57)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Table 4. Spearman’s rank correlation coefficients of symptom-specific results with both HRQoL instruments. The p value indicates the statistical significance of the differences between the 15D and the EQ-5D.

To analyse and compare the independent association between pain and symptom results and the HRQoL instruments, we constructed linear regression models, each model containing either the EQ-5D or the 15D as the dependent variable and one of the pain- and symptom-specific measures (CPAQ, PASS, BDI, BNSQ, BPI/pain intensity, and BPI/pain interference) as an independent variable. We also used a principal component (PC) of the six aforementioned pain and symptom measures to describe their combined effect as a single-index value. This PC was constructed using PCA from the pain and symptom-specific measures, and it accounted for 59% of the observed variance in these measures. Each model was also adjusted for age, sex, education years, working status, and duration of pain.

In the model with the PC of the six pain-and symptom-specific measures and the background variables as the independent variables, the overall adjusted R² (i.e. the proportion of variance in the dependent variable explained by the model) was 0.65 for the 15D and 0.43 for the EQ-5D (p< 0.001 with both HRQoL instruments).

We assessed the association between the individual pain- and symptom-related measures and the HRQoL instruments by comparing the standardized beta coefficients from the regression models. All the pain-related measures displayed a strong association with both HRQoL instruments. Figure 5 shows the standardized beta coefficients and the statistical significance of the differences.
**Figure 5.** Standardized beta coefficients (b) with their 95% confidence intervals for each pain- and symptom-related measure and their combined index, the PC. In all measures but CPAQ, higher scores indicated more severe symptoms, and the association with HRQoL instruments was negative. The p value indicates the statistical significance of the difference between the two HRQoL instruments. The dashed line indicates a threshold of -0.5 for standardized beta coefficients, representing a strong association according to the Cohen standard. Each model was adjusted for age, sex, education years, working status and duration of pain. The image is reproduced with the permission of the copyright holder, the International Association for the Study of Pain (Vartiainen et al., 2017).

All the analysed pain-related measures displayed a strong association with both HRQoL instruments. The Beck Depression Inventory, CPAQ, BNSQ and the PC of the measures had statistically significantly higher standardized beta coefficients with the 15D than with the EQ-5D.

**Helsinki study sample**

**Figure 6** shows the distributions of three clinical pain assessment questions, i.e., a VAS on current pain intensity, and a VAS on pain-related distress and pain interference in daily activities. The distribution of pain-related distress was skewed, with a notable concentration of the highest values. A total of 290 patients (19%) reported pain-related distress of > 95mm/100mm, and 822 patients (61%) reported distress of over 70mm/100mm.

Pearson’s linear correlation coefficients for the 15D score and the current pain intensity VAS, pain-related distress VAS, and pain interference in daily activities were -0.342, -0.392, and -0.491, respectively.
Figure 6. Distribution histograms of the three clinical pain-related measures and the 15D score. The top-left, top-right and bottom-left histograms show pain intensity VAS, pain-related distress VAS, and pain interference, respectively, and the bottom-right histogram shows the distribution of the 15D score.

Linear regression of baseline 15D score

In a forward stepwise linear regression model with the baseline 15D score as the dependent variable, the statistically significant predictors in the model were: pain interference in daily life, pain-related distress VAS, being employed, gender, and having several pain types. Table 4 shows the regression results. Variables which were entered into the analysis but excluded from the final model were age, education level, living alone, pain duration of over three years, and current pain intensity VAS. The adjusted R² of the model, i.e., the variance in the 15D score explained by the predictors, was 0.363, with p < 0.001. The results were confirmed by the backwards stepwise model, which gave similar results.
### Table 5.
Final step of the forward stepwise linear regression model with the 15D score as the dependent variable. The table shows the variables that had a statistically significant independent association with the 15D score. In addition, the variables entered into the model but excluded as insignificant were: pain duration of over three years, age, living alone or with someone, VAS for pain intensity, and education. There was no evidence of significant multicollinearity: the highest VIF value of 1.26 was perceived in the impact of pain on daily life. The model was based of 826 patients, who had no missing variables in their data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized beta coef.</th>
<th>t value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.013</td>
<td>1.95</td>
<td>0.052</td>
</tr>
<tr>
<td>Baseline 15D score</td>
<td>-0.180</td>
<td>-6.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.000</td>
<td>-1.04</td>
<td>0.298</td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>0.0177</td>
<td>2.76</td>
<td>0.006</td>
</tr>
<tr>
<td>Pain duration over 3 years</td>
<td>-0.024</td>
<td>-3.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Employed</td>
<td>0.030</td>
<td>3.83</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Multidisciplinary pain management

The average treatment period at the Pain Clinic was 24.6 weeks. The median duration of treatment was 22 weeks (Q25-Q75 = 10–40 weeks). The mean number of visits was 3.6, median = 4 with Q25-Q75 = 2–7, ranging from 1 to 47. The duration of a treatment episode and the visits to different professionals during MPM are summarized in Table 5. In addition to the summary of the whole study sample, the 200 patients who reported the greatest HRQoL improvement were compared to the 200 who reported the greatest HRQoL deterioration. The patients also met a nurse at least once, but often several times during MPM. As the nurse consultations were not recorded in the database, they are not included in these results, despite being an important part of MPM.
<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n= 1043)</th>
<th>Worst HRQoL outcome (n= 200)</th>
<th>Best HRQoL outcome (n= 200)</th>
<th>p’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment in weeks, mean (SD)</td>
<td>25.5 (16.3)</td>
<td>28.0 (16.8)</td>
<td>23.1 (16.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total visits, mean (SD)</td>
<td>5.8 (4.7)</td>
<td>6.6 (6.1)</td>
<td>5.9 (4.7)</td>
<td>0.239</td>
</tr>
<tr>
<td>Physician visits, mean (SD)</td>
<td>3.2 (1.9)</td>
<td>3.6 (2.2)</td>
<td>3.1 (2.0)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Psychologist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultation, n (%)</td>
<td>603 (58.5)</td>
<td>122 (61.3)</td>
<td>124 (62.6)</td>
<td>0.867</td>
</tr>
<tr>
<td>Multiple visits, n (%)</td>
<td>185 (18.0)</td>
<td>42 (21.1)</td>
<td>42 (21.2)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Physiotherapist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultation, n (%)</td>
<td>382 (37.1)</td>
<td>82 (41.2)</td>
<td>73 (36.9)</td>
<td>0.434</td>
</tr>
<tr>
<td>Multiple visits, n (%)</td>
<td>127 (12.3)</td>
<td>21 (10.6)</td>
<td>35 (17.7)</td>
<td>0.058</td>
</tr>
<tr>
<td>Group-based rehabilitation methods, n (%)</td>
<td>128 (12.4)</td>
<td>24 (12.1)</td>
<td>27 (13.6)</td>
<td>0.750</td>
</tr>
<tr>
<td>Social worker, n (%)</td>
<td>20 (1.9)</td>
<td>9 (4.5)</td>
<td>2 (1.0)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Table 6: Treatment visits to the Pain Clinic. The table shows the mean number of total visits, the mean duration of treatment, and the number of patients who saw different professionals during their treatment episode. This shows the figures for the whole study sample, for the 200 patients who reported the greatest positive change in HRQoL, and for the 200 who reported the greatest negative change in HRQoL.

*) The p value shows the statistical significance of the differences between the two extreme outcome groups; either the t-test or chi-squared test was used, depending on whether the baseline variable in question was categorical or continuous.

**Change in 15D score after treatment**

The mean 15D score change at 12 months after the start of treatment was +0.017 (95% CI 9.912-0.023), from 0.711 at baseline to 0.728. The median 15D score change was 0.019 (SD 0.094). A total of 544 patients (52%) achieved a clinically important 15D score improvement (> +0.015). In 448 patients (43%), the improvement was considered major (> +0.035). However, 374 patients (36%) reported a clinically significant decrease in their 15D score, despite a low baseline score. Figure 7 shows the distribution of patients into different clinical categories of 15D score change.
Figure 7. The number and percentage of patients in the clinical categories of the 15D score changed. Of the patients, 52.8% reported a clinically significant HRQoL improvement (>0.015) at 12-month follow-up.

15D profiles and their changes

In Figure 8a, the 15D profiles, i.e. the mean scores of the individual dimensions are shown at baseline for those who reported major improvement (15D score change >+0.035) compared with the other patients. Figure 8b shows the changes of the individual 15D dimensions at 12 months after the start of treatment for three groups: those who reported major improvement, those with minor or no changes (15D score change -0.035 to +0.035), and those with major deterioration (15D score change <-0.035).
Figure 8a Baseline 15D profiles, i.e. the mean scores of the individual dimensions before treatment. The patients are divided into two groups: those who achieved a major improvement in HRQoL (15D score change > +0.035, n = 448) are compared to other patients (the 15D score change < +0.035, n = 595). After Bonferroni corrections, statistically significant (p< 0.05) differences were seen in the mental function, depression, distress, and vitality dimensions. The patients with major improvement in HRQoL had lower 15D scores at baseline (0.699) than the other patients (15D score at baseline = 0.720.)
Figure 8b. The mean changes in the individual dimensions at 12 months. The patients are divided into three groups: those who achieved a major improvement in HRQoL (15D score change $> +0.035$, $n = 448$), those with small or no changes (15D score change $-0.035$ to $+0.035$, $n = 296$) and those with major decrease (the 15D score change $<-0.035$, $n = 299$). The error bars show the 95% confidence interval for the mean.
<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 1043)</th>
<th>Worst HRQoL outcome (n = 200)</th>
<th>Best HRQoL outcome (n = 200)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd)</td>
<td>54.1 (15.4)</td>
<td>55.5 (15.9)</td>
<td>52.5 (15.6)</td>
<td>0.042</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>658 (63.1)</td>
<td>111 (55.5)</td>
<td>140 (70.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Post-secondary education, n (%)</td>
<td>323 (34.8)</td>
<td>48 (27.4)</td>
<td>83 (45.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain duration &gt; 3 years, n (%)</td>
<td>196 (23.3)</td>
<td>37 (27.6)</td>
<td>26 (15.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>Employed</td>
<td>229 (23.7)</td>
<td>26 (14.1)</td>
<td>54 (29.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Several types of pain</td>
<td>723 (80.1)</td>
<td>137 (79.2)</td>
<td>143 (81.7)</td>
<td>0.647</td>
</tr>
<tr>
<td>Current pain intensity VAS, mean (sd)</td>
<td>60.1 (24.2)</td>
<td>61.5 (22.9)</td>
<td>62.8 (23.9)</td>
<td>0.593</td>
</tr>
<tr>
<td>Pain-related distress VAS, mean (sd)</td>
<td>70.9 (25.5)</td>
<td>70.7 (25.4)</td>
<td>75.0 (24.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>Pain interference in daily life, percentage of maximum score, mean (sd)</td>
<td>60.8 (20.3)</td>
<td>63.8 (17.5)</td>
<td>64.7 (20.6)</td>
<td>0.649</td>
</tr>
<tr>
<td>Baseline 15D score, mean (sd)</td>
<td>0.71 (0.11)</td>
<td>0.71 (0.11)</td>
<td>0.67 (0.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>15D score at follow-up, mean (sd)</td>
<td>0.73 (0.14)</td>
<td>0.60 (0.12)</td>
<td>0.82 (0.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in the 15D score, mean (sd)</td>
<td>0.017 (0.043)</td>
<td>-0.117 (0.049)</td>
<td>0.148 (0.048)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Table 7. Patient characteristics at baseline. This shows the numbers for the whole study sample who responded to the 15D follow-up, for the 200 patients who reported the greatest positive change in HRQoL, and for the 200 who reported the greatest negative in HRQoL.*

*) The p value shows the statistical significance of the differences between the two extreme outcome groups; either the t-test or chi-squared test was used, depending on whether the baseline variable in question was categorical or continuous.

**Variables associated with HRQoL outcome**

*Table 7* shows the baseline characteristics of the patients in the different categories of the 15D score change. Variables with statistically significant differences in the improvement groups are: age, gender, being employed, having post-secondary
education, baseline 15D score, and pain duration over three years. Pain intensity, pain-related distress or pain interference did not appear to be associated with the 15D score change. The only treatment-related variable associated with the HRQoL change was the number of physician visits; patients with improved HRQoL seemed to have slightly less visits to a physician.

We also tested the nonparametric Spearman's correlations of the 15D score change with the continuous background variables. Significant correlations were seen in the following variables: baseline 15D score (rho = -0.12, p < 0.001), age (rho = -0.06, p = 0.05), and the number of visits to the physician (rho = -0.08, p = 0.009). No statistically significant correlations with the 15D score change were observed for the following variables: VAS for pain intensity, VAS for pain-related distress, pain interference, or total number of visits to the pain centre.

**Binary logistic regression**

We used binary logistic regression to assess the background variables' individual association with the probability of major improvement. Due to the significant amount of missing data, we limited the number of variables that we entered into the model; we only selected those that had shown a preliminary association with the 15D score change (shown in Table 7). The variables selected for the model were thus: baseline 15D score, age, gender, post-secondary education, employment, and duration of pain over three years. The independent variable was whether or not a patient had achieved a clinically major improvement (> +0.035) in the 15D score.
Figure 9. Adjusted odds ratios (OR) for major improvement in HRQoL. For continuous variables (baseline 15D score, age) the OR is shown as a change in OR per unit of change in the variable. Being employed, having post-secondary education, having pain duration of under three years, and having a lower baseline 15D score were independently associated with higher odds of major improvement.

We confirmed these results using models into which we also entered the other variables. They did not produce statistically significant odds ratios, nor did they change the odds ratios included in the model shown here.

**Linear regression**

We also made a multiple linear regression model with the 15D score change as the independent variable, and baseline 15D score, age, gender, post-secondary education, employment, and duration of pain of over three years as the predictors. Table 8 shows the results.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized beta coeff.</th>
<th>t value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.145</td>
<td>6.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.013</td>
<td>1.95</td>
<td>0.052</td>
</tr>
<tr>
<td>Baseline 15D score</td>
<td>-0.180</td>
<td>-6.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.000</td>
<td>-1.04</td>
<td>0.298</td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>0.0177</td>
<td>2.76</td>
<td>0.006</td>
</tr>
<tr>
<td>Pain duration of over 3 years</td>
<td>-0.024</td>
<td>-3.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Employed</td>
<td>0.030</td>
<td>3.83</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Table 8. Results of the linear regression model with the 15D score change as the independent variable, and baseline variables that showed preliminary association with the 15D score change as dependent variables.*

The adjusted $R^2$ of the linear model was 0.08 with $p < 0.001$, in other words the model explained 8% of the observed variance in the 15D score change.

**Duration of pain and 15D score change**

As seen in the previous analyses, pain duration of over three years appeared to be the only pain-related variable associated with the HRQoL outcome. Figure 10 more closely compares the 15D score changes among those with pain duration of < 3 years and those with pain duration of > 3 years.
Figure 10. Mean 15D score changes in respect of the duration of pain under or over three years. The x-axis shows the time of the 15D measurement, and the y-axis shows the mean 15D score and its 95% confidence interval.

Patients with missing answers

Table 2 shows the number of patients who responded incompletely to the background questions. The differences in the 15D scores between the patients who answered incompletely to the pain questionnaire and those who gave valid answers, were statistically and clinically significant in the following questions: single or several pain types (0.733 vs 0.706 for missing vs valid answers, p = 0.002), constant or intermittent pain (0.727 vs 0.705, p = 0.001), and the impact of pain on everyday life (0.737 vs 0.705, p = 0.001). In other questions, the differences were not statistically significant.

467 patients did not reply to the 15D follow-up at 12 months. Those patients were younger (49 vs 54 years, p < 0.001) and had slightly higher education (42% vs 35% completing post-secondary education, p = 0.018) than those completing the follow-up.
There were no statistically significant differences in the baseline 15D score or other background variables.

266 patients with missing answers to the background variables were not included in the regression models of the 15D score change. We compared the patients who had provided valid answers to the background questions with those not included in the models. The patients with missing answers had a smaller 15D score change at 12 months than those with complete answers (0.003 vs 0.021, p = 0.01). These groups did not have statistically significant differences regarding age, gender, or baseline 15D score.

Discussion

Principal findings

The HRQoL of chronic pain patients was very low. In Study I, both instruments used produced very low mean HRQoL scores among chronic pain patients. The EQ-5D produced lower mean scores and a greater score range than the 15D. In the EQ-5D, 23.1% obtained a score of 1 or 0.8, the two highest scores in this data. This suggests a ceiling effect, i.e. insensitivity in the highest scores. The distribution of the 15D had no ceiling or floor effects. In the EQ-5D, 8% of patients obtained HRQoL scores worse than death.

In Study II, the HRQoL of the 1528 patients was much lower (0.710) than that of the age-and gender-matched sample of the general population in Finland (0.922). All the dimension scores were statistically significantly lower among the chronic pain patients than among the healthy population, but the five most affected dimensions were discomfort and symptoms, usual activities, sexual activity, vitality, and sleep. The 15D HRQoL score correlated reasonably well with the questions used for pain assessment. The patients also reported very high pain-related distress. Median pain-related distress was 79, 822 patients (61%) reported distress of more than 70mm, and 290 patients (19.0%) reported distress of more than 95mm on a scale of 0 to 100 mm.

Although the two HRQoL instruments showed moderate agreement, they still had considerable differences. They correlated with each other moderately. In the Bland-Altman analysis, the difference between the two instruments increased as the mean of the two scores decreased (this is easy to understand, considering the greater score range of the EQ-5D). The mean difference of the measures was 0.237, with 86 patients (24%) obtaining a difference of > 0.5.

When the HRQoL scores were standardized (i.e., scaled to have a mean of 0 and SD of 1) and compared to the levels of self-rated general health, the 15D appeared to better identify patients in good health. The 15D correlated more with self-rated general health than the EQ-5D.
All the analysed measures of pain and symptoms were strongly associated with both HRQoL measures. BDI, CPAQ, BNSQ were more strongly associated with the 15D. The PC describing the symptom-specific measures was slightly more associated with the 15D than with the EQ-5D. The variance explained by the PC of the symptom-specific measures and the background variables was higher in the 15D than in the EQ-5D.

In the stepwise linear regression model of Study II, the psychosocial aspects of pain were most associated with HRQoL. Independent predictors of the 15D score were gender, number of pain types, employment, VAS for pain-related distress, and the impact of pain on daily life. Although pain intensity and the 15D score correlated well, the association was accounted for by the other variables entered into the regression model.

The mean 15D score change after MPM (0.017) at 12 months after the start of treatment was statistically significant and clinically important. Fifty-two per cent of the patients achieved a clinically important improvement in their 15D score. However, the HRQoL outcomes varied greatly, as 7% reported a minor decrease and 28% reported a major decrease in HRQoL despite an already very low baseline score. In the patients who reported major improvement of HRQoL, the most improved dimensions were those of psychological health.

Of the socioeconomic background variables, having a high education and being employed increased the odds for major HRQoL improvement. The only pain-related variable associated with the HRQoL outcome was the duration of pain over three years, which reduced the odds of major improvement. No other pain-related variables, for example pain intensity or pain-related distress, were associated with the change in quality of life.

**Comparison with other studies and significance of results**

*Health-related quality of life*

The HRQoL of chronic pain patients was extremely low. It was much lower than that of the healthy population sample. In a similar study setting of 100 patients starting their treatment at an outpatient, referral-based tertiary multidisciplinary pain clinic at the University of Alberta Hospital, the mean 15D score was 0.67, even lower than that in the present study. The authors also measured comorbidities among their patients, and concluded that these were clearly associated with a reduced 15D score (Dick et al., 2011).

A study of colorectal, breast and prostate cancer patients with an end-stage disease in palliative care measured the patients' HRQoL using the 15D and the EQ-5D. The mean HRQoL scores for the patients were 0.735 and 0.585, respectively, and the mean EQ-VAS was 55.0. Twenty-eight per cent of these patients died within three months of filling in the forms. (Färkkilä et al., 2014). In the present study, the mean 15D score of the 1528 patients from the Helsinki University Hospital was 0.710. For the KROKIETA
study patients, the mean score was 0.763, and 0.736 for non-facial pain patients of the study patients. The respective means of the EQ-5D scores were 0.650 and 0.466, and those of the EQ-VAS scores 63.6 and 54.5. The chronic pain patients thus reported similar or worse quality of life to cancer patients in palliative care. Similar results have also been reported in Norway (Fredheim et al., 2008).

A population-based study of 29 chronic conditions also measured HRQoL using the 15D and the EQ-5D. None of the disease groups, and only patients under 85 years of age, had lower 15D scores than the current study sample. Comparison of the EQ-5D produces similar results: only those with Parkinson's disease (EQ-5D score of 0.440), and only the age groups under 85 had lower EQ-5D scores (Saarni et al., 2006).

Many other studies have also shown chronic pain to be associated with markedly reduced HRQoL (e.g., Boonstra et al., 2013; Løyland et al., 2010). The chronic pain patients in the present study also reported high symptom burden in other pain-related and symptom-specific measures. Especially notable was the high pain-related distress reported by the patients: 61% reported pain-related distress of >70/100, and 19% reported distress of >95/100. These results indicate high symptom burden, low functioning, and impaired quality of life among chronic pain patients in tertiary care.

Non-participants and patients with missing answers

The information on those who refused to participate was not collected, and a large number of invited patients did not participate in the KROKIETA study. It remains to be studied whether non-participants had had, for example, more psychosocial distress, longer pain duration or more failed treatment attempts than participants, or vice versa. Those patients in the study 1 with missing answers to the background variables appeared to have similar or higher 15D scores than those with valid answers. It appears thus unlikely that those with missing answers would have more severe symptoms than those with complete answers. However, those with missing answers had lower 15D score change than those with fully completed answers.

Comparison and validity of HRQoL instruments

The two HRQoL instruments showed a moderate association, but also notable differences. The distribution of the 15D scores resembled normal, while the EQ-5D score distribution was bimodal with hints of a ceiling effect, or insensitivity in the highest scores. The EQ-5D produced lower mean scores than the 15D.

The EQ-5D and the 15D correlated moderately, as the Spearman's rho was 0.66, p< 0.001. However, as correlation is a measure of association, it is not a sufficient measure of agreement (Bland and Altman, 1986). Further, the rank correlation of 0.66 is not very good for two measures that are supposed to measure the same construct.

In the Bland-Altman plot (Figure 2), the differences between HRQoL instruments were notable. The mean difference between the two instruments was 0.238. Furthermore,
the differences had a linear-resembling trend – the lower the HRQoL scores, the greater the difference. In the low HRQoL scores, the EQ-5D produced lower scores. The relatively small number of health states and large gaps between these states in the EQ-5D are also apparent in the figure, as the EQ-5D scores appear in distinct groups and give the graph a striped appearance in higher scores.

Lillegraven et al. conducted a population-based study of patients with rheumatoid arthritis, comparing three HRQoL instruments, the EQ-5D, the SF-6D(12) and the 15D (Lillegraven et al., 2010). In their study, the agreement between the EQ-5D and the 15D/SF-6D was not good. They also showed a Bland-Altman plot between the EQ-5D and the 15D which had a similar pattern (great differences, differences increasing with lower HRQoL scores, bimodal score distribution in the EQ-5D, as well as large gaps in better health states) to that reported in the present study (Figure 2). The agreement between the 15D and the SF-6D was better. The authors also made hypothetical QALY calculations, and showed that the differences could be 2–4-fold in cost per QALY when different instruments were used (Lillegraven et al., 2010). In a study conducted in a critical care setting using the 15D and the EQ-5D, both the choice of the HRQoL instrument and the assumptions regarding the progression of disease in between measure points produced significantly differing QALY results, resulting in 2–3-fold differences in cost in QALY calculation (Vainiola et al., 2011).

In the present study, both HRQoL instruments were strongly associated with the pain- and symptom-specific measures. The 15D was more strongly associated with self-rated health than the EQ-5D. When both HRQoL scores were standardized, the 15D scores were higher in 'good' health states, whereas the standardized EQ-5D scores were approximately the same in 'average' and 'good' health states. This indicates that the 15D had better discriminatory power in good health states. In addition, Pearson's correlation coefficient was higher with the 15D than with the EQ-5D, indicating a stronger linear association of self-rated health with the standardized 15D score than with the standardized EQ-5D score. In the regression model with the pain- and symptom-specific measures as explanatory variables, both HRQoL instruments were strongly associated with the measures. The CPAQ, BDI, BNSQ, and PC of the measures were statistically significantly more associated with the 15D than with the EQ-5D.

Brazier et al. concluded that the EQ-5D would be sensitive in conditions causing primarily physical symptoms and limitations on the basis of the comparison of the absolute mean scores of the HRQoL instruments (Brazier et al., 2004). Another study assessing the instruments' validity for measuring chronic pain also made conclusions by comparing absolute score differences (Obradovic et al., 2013). In their review of six HRQoL instruments in seven disease entities, Richardson et al. compared, for example, effect sizes, and reported that the 15D had the smallest absolute differences between groups, but the largest effect sizes. The review concluded that the 15D and the AQoL appear to be more sensitive than other instruments, and that the EQ-5D was especially problematic (Richardson et al., 2016). Another review by Hawthorne et al. concluded that the 15D fared equally well or better than other HRQoL instruments (Hawthorne et al., 2001).
A notable difference in the HRQoL scores of the studied instruments is that the EQ-5D produces HRQoL scores below zero, which indicates health worse than death (WTD). In the present study, 8% obtained WTD scores in the EQ-5D. There were no hints of floor effect in the 15D scores. Torrance et al. compared the SF-6D and the EQ-5D in a population sample reporting chronic pain with or without neuropathic pain characteristics, and also reported considerable differences in the HRQoL scores. Similarly, the differences between the HRQoL scores were greater in lower absolute scores. They reported that 6% of their patients obtained WTD scores in the EQ-5D, and that no floor effect was observable in the SF-6D scores. The authors discuss that if both instruments agreed, those patients who reported health worse than death in EQ-5D should have been grouped close to the lowest score (0.29) produced by the SF-6D.

The study by Torrance et al., and the comment by Schofield discuss the comparability of the different HRQoL instruments in chronic pain (Schofield, 2014; Torrance et al., 2014). The authors raised the question as to whether HRQoL results should be interpreted in relation to the ‘floor’, i.e., the worst possible score of the instrument, rather than in relation to death. To illustrate, a score of 0.4 would indicate much poorer health in the SF-6D, in which the lowest obtainable score is 0.29, than in the EQ-5D, in which the lowest score is -0.59.

In summary, the present study confirmed the considerable differences between the EQ-5D and the 15D. Both measures appear to have good construct validity, as they are associated with pain intensity, its interference in daily life, and related psychosocial constructs shown to cause pain-related disability. The 15D appeared to be slightly more strongly associated with these measures than the EQ-5D.

15D and clinical measures of pain

Studies II and III also compared the 15D to the questions measuring pain intensity, pain-related distress and its interference in daily life. All of these were strongly associated. The 15D score was most associated with pain-related distress and interference in daily life, indicating that the psychosocial burden of chronic pain significantly impairs overall quality of life. Pain intensity did not appear to have a significant independent predictive value on quality of life. In addition, the dimensions of the 15D that were the most impaired in patients with chronic pain were mostly those associated with the psychosocial aspects of health.

Similar results regarding the significance of psychosocial aspects for the overall quality of life and functioning have been previously reported. In summary, psychosocial factors have been concluded as being more important to quality of life and functioning than pain intensity (Keeley et al., 2008; Lamé et al., 2005; Nicholl et al., 2009; Orenius et al., 2013).

Agreeing with the results of the present study, Sullivan et al. argue that psychosocial problems are the main causes of disability in chronic pain, rather than pain intensity. Therefore, pain intensity is not sufficient to describe the comprehensive problems of
the patients. They also argue that the target of chronic pain management should not be to reduce pain intensity, but to improve quality of life (Sullivan and Ballantyne, 2016).

**Effectiveness of multidisciplinary pain management**

MPM is effective in managing chronic pain. It has been shown to be more effective than ‘usual’ therapy or various unidisciplinary treatment modalities (Flor et al., 1992; Gatchel and Okifuji, 2006; Kamper et al., 2015; Karjalainen et al., 1999; Scascighini et al., 2008).

In an RCT of 93 patients with chronic recurrent LBP, patients were assigned to either receive a comprehensive pain programme (CPP, same as MPM) or a standard exercise programme. Follow-up assessments at 3.5 weeks, 4 months, 12 months, and 5 years demonstrated the greater long-term efficacy (up to 5 years) of the comprehensive pain programme group in terms of decreased disability and pain intensity scores, as well as increased work ability (Friedrich et al., 2005). Similarly, Heiskanen et al. showed in the pilot study of the present study sample that the beneficial effect of MPM on HRQoL was still observable up to the three years later (Heiskanen et al., 2012).

In a non-controlled follow-up study of 464 Swedish patients with chronic musculoskeletal pain, the patients participated in a rather intensive outpatient MPM programme. The average duration of treatment was over 20h/week, and most of the treatment contacts were carried out in groups. At 12-month follow-up, the EQ-5D score of the patients had increased from 0.33 to 0.45, which was statistically significant. The patients were also asked to rate the global improvement in retrospect: 54% reported improved pain, and 80% reported improved life situation. (Gerdle et al., 2016)

In the present study, the mean HRQoL improvement at 12 months after the start of treatment was statistically significant and clinically important. Most of the patients achieved a clinically important long-term improvement in HRQoL. However, the variations in the HRQoL outcomes were substantial, as 35% of patients also reported a decrease, and 28% a major decrease in HRQoL. This is notable because of the already very low baseline score of the patients. There was also a great deal of variation in the treatment received by the patients, as the MPM was administered individually, as indicated. In the present study, the improvement of HRQoL appeared to occur in dimensions concerning psychological health. In the patients who reported major decrease of HRQoL, the decrease was more even between the dimensions.

Moore et al. studied the decrease in pain intensity after pharmacological treatments. They found a similar pattern of change to that in the present study – most of the patients reported either a large decrease in pain intensity, or no decrease at all. A minority of patients reported slight decreases in pain intensity. This pattern was also seen in the placebo group. The authors recommend that individual-level response data should also be analysed after pain interventions (Moore et al., 2010, 2014).
When MPM programmes are compared with surgery, they produce similar or better pain relief in the management of chronic LBP. They are safer and more cost-effective than surgery, and one longitudinal study showed that the implementation of MPM reduced the number of operations due to back pain (Gatchel and Okifuji, 2006). In an uncontrolled, prospective study on paediatric patients with chronic pain, MPM was concluded to reduce hospital visits and related costs (Mahrer et al., 2018).

**Methodological considerations when assessing outcome of MPM**

MPM aims to comprehensively rehabilitate patients and improve their overall functioning, even though pain intensity might not be significantly reduced. The recommendations regarding pain management outcomes list many domains to be measured (Kaiser et al., 2018). Indeed, chronic pain is a complex problem, and it is likely that no single outcome measure would be sufficient for all heterogeneous patients with chronic pain, not even HRQoL. Thus, most pain management studies should, and hopefully will, use many outcome measures. However, many of these measures are intercorrelated, and the methods for analysing these multiple outcomes need to be developed and standardized. This involves both statistical methods as well as strategies for making conclusions based on multiple outcomes. When choosing outcome measures, it should also be noted that the goals of MPM should be set individually, depending on the nature of the pain problem.

Most studies use pain intensity reduction for assessing the outcomes of MPM, and as stated before, the other outcomes used vary between studies. Reviews have also assessed the effect of MPM on objective measures such as return to work. Kamper et al., in their systematic review on MPM for chronic LBP, found that the reduction in pain intensity and disability was superior to that achieved by usual care or single-modality treatments, but MPM did not appear to be superior when measured by return-to-work rates (Kamper et al., 2015). Conversely, Gatchel and Okifuji conducted a systematic review of comprehensive pain programmes for chronic non-malignant pain, and found that return-to-work rates were superior with MPM than among the controls (Gatchel and Okifuji, 2006). This probably reflects the heterogeneity of studies and outcome measures, but we should also bear in mind that the latter review was carried out among undifferentiated patients with chronic pain.

As a measure of overall health and functioning, HRQoL is well suited to monitoring MPM outcomes among heterogeneous patient populations. The strengths of HRQoL are that it is comparable across all patient groups, it takes into account the possible adverse effects of treatment, and it allows the assessment of cost-effectiveness. Some HRQoL instruments also allow the application of population preference weights to individual dimensions, which adds a descriptive value to the instrument. And example of this is the 15D profiles shown in the present study. HRQoL is also well suited to routine outcome measurement, as most instruments are easy to fill in. In a systematic review on the outcomes used for assessing MPM, HRQoL was measured in 15/70 studies (Deckert et al., 2016). As stated previously, no single outcome measure is likely to be
sufficient for all patients with chronic pain, but HRQoL has many advantages which make it an attractive part of an outcome set in chronic pain management trials.

HRQoL measurement is not without limitations. Generic HRQoL can be less sensitive than disease-specific outcomes, as it might not capture all the relevant aspects of the disease. Differences have also been found in the utility value of a health state, depending on whether the patient, or the general, healthy population, express their preferences (Krahn et al., 2003). In prostate cancer patients, the utility values elicited directly from the patients were higher than those elicited from a healthy population to the same health states (Krahn et al., 2003).

This raises the question of which HRQoL instrument to use. As stated previously, different HRQoL instruments have produced differing results, and the results are generally not comparable. Richardson et al. also emphasize that no HRQoL instrument is wrong or invalid; they merely differ in their sensitivity to different aspects of health. This is why extensive research efforts should be carried out to identify which instruments should be used in which contexts (Richardson et al., 2011). In another review article of the commonly used HRQoL instruments in seven different disease entities, Richardson et al. conclude that the 15D is perhaps the most sensitive to physical problems, while AQoL might be the most sensitive to psychological impairment (Richardson et al., 2016), and they recommend wider use of the two HRQoL instruments over the more popular EQ-5D. The IMMPACT recommendations advocate SF-6D because it has been used previously among chronic pain patients. However, the authors note that as more data on the properties of different instruments accumulate, this recommendation should be reassessed (Dworkin et al., 2005).

In the present study, the baseline 15D score was associated with the HRQoL change at follow-up. Better quality of life at baseline was associated with a smaller probability of major improvement in HRQoL. Moreover, the patients who reported major improvement had slightly lower scores in the dimensions of depression and distress. A cohort study of 464 patients, with multiple outcomes and rigorous statistical analyses found small associations between the background and baseline variables and the treatment outcome. To summarize, more severe symptoms at baseline predicted greater absolute improvement (Gerdle et al., 2016). A similar observation – that more severe symptoms are associated with better improvement – was also reported in a review of MPM outcomes (Boonstra et al., 2015). This might, of course, be because those with more severe symptoms simply have more room for improvement.

However, without a control group, several kinds of bias may explain the observed changes and the relation of baseline variables. As HRQoL is a measure of overall health, other diseases and their treatment probably accounts for some of the HRQoL changes. Also, the treatment of chronic pain does not necessarily stop when MPM episode is over. The treatment continues in the primary care, and for example, those in higher socioeconomic position might have better access to primary health care services. Regression to the mean, i.e., the tendency of extreme variables to move towards the mean over time, might explain why a lower 15D score was associated with greater improvement in quality of life (Glymour et al., 2005). Moreover, an effect known as response shift, an adaptation or change in an individual’s conceptions and values of
health, is known to account for some HRQoL changes (Postular and Adang, 2000). However, the effect of response shift on health utility values was studied using direct health valuation methods (VAS, TTO, SG). To my knowledge, no studies have previously assessed the role of response shift in indirect health valuation methods (i.e., the HRQoL instruments). It is justified to reason that if the patient is asked about the severity of problems in health (instead of valuing their current health in relation to death), this question would be less prone to change because of changes in their health values. The possibility of bias must nevertheless be taken into account by preferably including a control group. This may not always be possible – for example in the present study – as the Finnish law requires that treatment of patients accepted for MPM must start within three months of referral. Thus, the use of waiting list controls, for example, would be both impossible and unethical. Another possible solution would be to more accurately phenotype the patients receiving MPM, and to use statistical methods such as propensity score calculation or inverse probabilities weighing to account for differences in the groups receiving different treatments. Techniques such as group-based trajectory models might shed light on the difficult task of finding subgroups from the seemingly heterogeneous group of patients in chronic pain.

**Which patients benefit from MPM?**

Currently, we are unable to identify patients who would benefit from MPM. Many factors have been shown to associate with pain management outcomes, but the results are inconsistent. In an observational pilot study of the present study sample, Heiskanen et al. analysed 100 patients with the greatest positive changes in HRQoL, and 100 with the greatest deterioration (Heiskanen et al., 2012). Like the results presented here, employment status and education level were associated with HRQoL change. They did not find pain- or treatment-related factors that would have differed between the groups.

Socioeconomic factors have also shown to relate to the outcomes of MPM. Males have been reported to benefit more from MPM than women (Pieh et al., 2012; de Rooij et al., 2013a). In an RCT of 243 Danish patients managed at an outpatient multidisciplinary pain clinic, those applying for disability pension did not benefit as much as others (Becker et al., 1998). This study also measured HRQoL using the SF-36, but did not calculate health utility values. In the present study, being employed and having a higher education at baseline were associated with better HRQoL outcomes.

Psychological constructs associated with increased pain disability are also related to treatment outcomes. Catastrophizing has been shown to impair the effectiveness of pain management interventions (Hill et al., 2007; Karels et al., 2007). Catastrophizing has also been associated with reduced benefit from pharmacological interventions or total knee arthroplasty (Edwards et al., 2016). In an RCT assessing the effectiveness of cognitive-behavioural therapy, the authors examined a subsample of TMD patients that did not benefit from standard care or psychosocial interventions, and higher catastrophizing and its persistence after treatment were associated with poor treatment outcome (Litt and Porto, 2013). Further, patients with stronger beliefs in their ability to control pain at the beginning of MPM, and those who increased their use
of positive coping mechanisms, showed the greatest decreases in pain-related disability at six months and 18 months after treatment (de Rooij et al., 2014). Another study also found that higher levels of anxiety were associated with less improvement after MPM (de Rooij et al., 2013a). A systematic review on MPM for FM discovered moderate evidence that having more depressive symptoms predicted a poorer outcome for FM patients (de Rooij et al., 2013b).

In their review of psychosocial factors and chronic pain, Edwards et al. also presented several studies of the mediators for pain management outcomes. In RCTs in a primary care setting, antidepressant treatment of chronic pain patients with comorbid mood disorders relieved pain, which correlates with the improvement of psychosocial distress (Kroenke et al., 2009; Rej et al., 2014). Changes in cognitive factors have been deemed predictors of MPM outcome: early-treatment changes in harmful cognitive processes (catastrophizing, helplessness, anxiety) predicted pain-related outcomes in later stages of treatment (Burns et al., 2003). Further, acceptance was found to be an important mediator of pain-related disability improvement after cognitive-behavioural therapy, even when it was not targeted (Åkerblom et al., 2015). Thus, the beneficial effect of pain management appears to be at least partly because of changes in cognitive strategies and coping, and in harmful psychological constructs (Edwards et al., 2016; de Rooij et al., 2014).

However, a retrospective cohort study of 230 patients with undifferentiated chronic musculoskeletal pain did not identify any strong predictors of MPM outcome, and concluded that variables other than the baseline scores of the outcome variables were only slightly associated with treatment outcome, and that those with poor physical functioning or mental health benefitted most from pain rehabilitation (Boonstra et al., 2015). In a review of MPM outcome predictors, the authors noted the tendency for more severe symptoms at baseline to be associated with greater improvement in the respective measures (van der Hulst et al., 2005). Similarly, in the present study, poorer quality of life at baseline was associated with greater odds for improvement. This is to some degree contradictory to the results presented in the previous chapter.

A review of MPM interventions found no evidence that treatment variables such as duration or components would be meaningful for treatment outcome, but the reviewed studies were heterogeneous (Scascighini et al., 2008). Similar conclusions were made in a systematic review of MPM interventions for chronic LBP (Kamper et al., 2015). Recent systematic reviews have failed to find an association between treatment intensity and treatment outcomes (Kamper et al., 2015; Waterschoot et al., 2014). Thus, the intensity of MPM does not seem to directly influence the outcomes, and the optimal number of treatment contacts remains unknown. On the other hand, this encourages the development of less intensive outpatient MPM programmes.

Differences across studies with respect to important predictors may be due to multiple factors such as the number of potential prognostic factors analysed, cohort characteristics, statistical methods, chosen outcomes, and/or content of MPM, which have all shown to differ significantly across studies (Deckert et al., 2016; van der Hulst et al., 2005; Scascighini et al., 2008). This again underlines the need for more rigorous
consideration of the study designs and outcome measures in studies assessing MPM efficacy.

In the present study, those with incomplete answers to the background questions appeared to have slightly lower 15D score change than those with complete answers. It could be speculated that not answering to the background questions might reflect poor motivation, lack of understanding or some other underlying psychological trait that might affect the treatment outcome.

**Symptom duration and treatment outcome**

Finally, Dunn et al. have investigated the recalled duration of symptoms in determining prognosis. In their study, those with over three years of pain took significantly longer to improve (Dunn and Croft, 2006). Based on their study, we chose a cut-off value of pain duration of three years, and those with over three years of pain were not as likely to improve after MPM. Another prospective observational study also found more modest outcomes among patients with longer duration of pain (Moradi et al., 2012). A randomized, blinded experimental study showed, with n = 53 and symptom duration of < 2 years, that an early cognitive-behavioural intervention for rheumatoid arthritis patients vs. medical care alone produced significant improvements in depressive symptoms and joint involvement, and even in C-reactive protein levels (Sharpe et al., 2001). Interestingly, an fMRI study of patients who developed chronic back pain showed that the brain representation of pain shifted from nociceptive areas to emotional areas as pain became chronic (Hashmi et al., 2013). These results require further research to analyse the relation between chronic pain, its duration, related disability, and treatment outcome.

**Strengths and limitations**

The apparent strengths of the present studies are the large samples they analysed, their lack of exclusion criteria, and sufficiently long follow-up time of study III. Indeed, some observational studies have shown that improvement can be observed even after three or five years after MPM (Friedrich et al., 2005; Heiskanen et al., 2012).

The strength of the validation analyses presented here is the thorough, rigorous comparison of two HRQoL instruments, both to each other and to several pain-related measures. Similar analyses of the HRQoL instruments' validity have not previously been conducted among chronic pain patients. The results are important when comparing different HRQoL instruments' performance in chronic pain and other patient populations.

The study did not include a control group, except for the age- and gender-weighted representative sample of the general population. This limits the conclusions that can be drawn concerning the effectiveness of MPM or its components. Thus, several kinds of bias might account for the observed HRQoL changes; these are discussed in the previous section. Also, as the MPM programme was tailored individually for each
patient as indicated, we cannot compare the effectiveness of different treatment modalities. However, the primary aim of the study was not to experimentally demonstrate the efficacy of MPM components, but to describe real-world follow-up results among patients managed in a tertiary pain clinic.

The study samples of the present studies represent only a selected part of the chronic pain population. All patients included in the studies had been referred and accepted for treatment in tertiary pain clinics. The patients who end up being treated at the pain clinics represent those with the most difficult chronic pain, who have had several failed treatment attempts. Moreover, the prevalence of depressive symptoms, for example, has shown to be elevated in patients being treated in a pain clinic compared to the general population (Bair et al., 2003), and the study sample of the present studies might not accurately represent the population of all patients in chronic pain.

We did not collect information about those who did not participate to the studies. Among the population of Study I, only approximately half of those who received the letter of invitation participated in the study. It is possible that those patients refusing to participate differ from those who agreed to take part, and due to this participation bias the study sample might not accurately reflect the patient population in a secondary pain clinic.

In the longitudinal follow-up of Study III, the patients only answered the 15D questionnaire. For heterogeneous patients in chronic pain, no single outcome measure would probably be able to capture all the important aspects of the disease. It would also be important to obtain more longitudinal comparisons of various outcome measures. Different HRQoL instruments should especially be compared to each other in follow-up studies to obtain information on properties such as test-retest validity and sensitivity.

HRQoL aims to measure the comprehensive health of patients. A major limitation of the present study was that no information on diseases other than chronic pain was assessed. Comorbidities to other diseases, as well as their subsequent treatment, probably account for some of the variation in baseline scores as well as in follow-up HRQoL scores. Dick et al. have shown, using the 15D in 100 patients in chronic pain referred to a tertiary pain clinic, that comorbidities account for a significant part of the variation of HRQoL at baseline (Dick et al., 2011). Also the adverse effects of treatment might account for the HRQoL changes. Among coronary artery patients, the adverse effects of treatment have also shown to be more common among patients whose 15D HRQoL score deteriorates (Heiskanen et al., 2016).

Pain duration of over three years was associated with a smaller 15D score change at follow-up. However, the question used to elicit the duration of pain was simple. As such, it may also represent some underlying psychological trait; patients who experience that their pain has lasted a long time may have, for example, less resilience or more perceived injustice than those who have experienced shorter pain duration.
Future perspectives

The heterogeneity of the reported outcomes and study designs efficiently prevent the comparison of different studies of pain management interventions (Deckert et al., 2016). Recommendations for the core outcome domains specifically for MPM trials have been published (Kaiser et al., 2018). This kind of research on the outcomes of chronic pain management is important for determining the most significant outcomes for the patients. Future studies should consider these recommendations, in order to produce comparable data.

Future studies should also analyse the different components of multidisciplinary management and the differential effects of these components, instead of merely comparing multidisciplinary management to 'traditional' treatment. Understanding of why MPM is more effective than other forms of treatment, or what would be the most efficient way of organizing MPM is sufficient. Cost-effectiveness studies are also needed. These suggestions have also been made in a systematic review on MPM for LBP (Kamper et al., 2015).

Studies on the efficacy of MPM should also focus on identifying the patients who will benefit from the treatment. The results of the present study suggest that there is much variation in prognoses after treatment, and other studies have even found similar response patterns in placebo groups (Moore et al., 2010, 2014). This variation, combined with our insufficient knowledge on the pathologic processes of chronic pain calls for better characterization of the chronic pain patients, in order to find factors that would be associated with the treatment outcomes, and also to better understand the development of chronic pain. Studies on the efficacy of pain management should also report individual-level response data in addition to the average changes. Techniques such as group-based trajectory modelling might provide insight for the seemingly challenging task of finding subgroups from the heterogeneous group of patients in chronic pain.

Concerning the properties of different HRQoL instruments, future studies should compare these instruments in a longitudinal setting to assess, for example, their responsiveness and sensitivity. Future studies should include less often used instruments such as the 15D and the AQoL. The SF-6D and EQ-5D are currently the most used instruments, but other instruments might have even better benefits (Richardson et al., 2016). We also need more information on the natural course of HRQoL over time in the general population and in untreated patient populations.

The terminology used to describe MPM and the interventions characterized as MPM, appears to be heterogeneous. The term MPM is used in many reviews, but many smaller studies use terms such as comprehensive pain programmes, interdisciplinary treatment, multimodal rehabilitation programmes, or combinations of these. The lack of standardized terminology might distort, for example, literature searches in systematic reviews. There also appears to be great variations in programmes that are described as multidisciplinary. This evidently prevents, for example, meta-analyses of the subject.
Conclusions

The study was carried out to examine HRQoL measurement among chronic pain patients. The aims were to assess the validity of two HRQoL measures; the 15D and the EQ-5D among chronic pain patients treated in a tertiary pain centre; to describe the HRQoL of a large sample of severe chronic pain patients; to analyse the association between HRQoL, socioeconomic background and different aspects of chronic pain; to describe long-term changes in HRQoL after outpatient MPM in a tertiary pain centre; and to identify the possible predictors of good or bad HRQoL outcome from background variables. The conclusions to the specific aims of the study are as follows:

1. The EQ-5D and the 15D both appear valid for measuring HRQoL in cases of chronic pain. However, there were substantial differences among the HRQoL scores produced by the two instruments. The 15D appeared slightly more sensitive than the EQ-5D, especially in relation to the measures of psychological and social aspects of pain. The 15D was also better able to discriminate patients with higher scores, i.e., better health states.

2. The HRQoL of patients with chronic pain was very low, much lower than that of the general population sample and most patient populations. The most impaired dimensions were those of psychological health.

3. The psychosocial aspects of chronic pain were strongly associated with HRQoL; although pain intensity correlated with HRQoL, this association disappeared when we adjusted for the effect of pain-related distress and the impact of pain on daily life were adjusted. Socioeconomic factors, most notably higher education and employment status, were associated with higher baseline HRQoL as well as its greater change after treatment.

4. There was a clinically important and statistically significant mean improvement in HRQoL among 1043 patients treated in a multidisciplinary pain clinic. Most of the patients reported clinically significant improvement of HRQoL, but the changes varied greatly.

5. Pain duration of over three years was associated with worse prognosis of MPM. Higher education and being employed were associated with a higher probability of HRQoL improvement. The analysed variables explained only a small part of the variance in the HRQoL changes, indicating that many of the factors related to the HRQoL changes were not analysed. Pain duration of over three years was associated with a worse HRQoL outcome, which calls for more research on the relationship between symptom duration, related disability and treatment outcomes. This also underlines the importance of sufficiently early intervention for chronic pain.
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