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PAIN PHENOTYPES, SLEEP PROBLEMS AND OTHER COMORBIDITIES IN PATIENTS WITH PERSISTENT PAIN

Teemu Miettinen

DOCTORAL DISSERTATION

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To all who devote their time and energy to scientific research

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List of abbreviations

15D = The 15-dimensional health-related quality of life instrument

AAA = Aromatic Amino Acids

AMP = Adenosine Monophosphate

ANOVA = Analysis of Variance

AUDIT = Alcohol Use Disorders Identification Test

BCAA = Branched-Chain Amino Acids

BDI-II = Beck Depression Inventory Version II

BMI = Body Mass Index

BNSQ = Basic Nordic Sleep Questionnaire

BPI = Brief Pain Inventory

CART = Classification and Regression Trees

CBT = Cognitive Behavioral Therapy

COPD = Chronic Obstructive Pulmonary Disease

CPAQ = Chronic Pain Acceptance Questionnaire

FC = Fold Change

GABA = γ-Aminobutyric Acid

HPA = Hypothalamic-Pituitary-Adrenal

HRQoL = Health-Related Quality of Life

ICD-11 = International Classification of Diseases 11th edition

IQR = Inter-Quartile Range

KEGG = Kyoto Encyclopedia of Genes and Genomes

MPI = Multidimensional Pain Inventory

MANOVA = Multivariate Analysis of Variance

MSEA = Metabolite Set Enrichment Analysis

NAD = Nicotinamide Adenine Dinucleotide

NRS = Numerical Rating Scale

NSAID = Non-Steroidal Anti-Inflammatory Drug

OSA = Obstructive Sleep Apnea

PART = Partial Decision Trees

PASS-20 = Pain Anxiety Symptoms Scale-20

PCA = Principal Component Analysis

PTSD = Post-Traumatic Stress Disorder

RA = Rheumatoid arthritis

RF = Random Forests

REM = Rapid Eye Movement

RLS = Restless Legs Symptoms

rTMS = Repetitive Transcranial Magnetic Stimulation

SMPDB = Small Molecule Pathway Database

SVM = Support Vector Machines

SD = Standard Deviation

VAS = Visual Analog Scale

List of original publications

The thesis is based on the following original publications (Studies I-IV). The publications are referred to in the text by their Roman numerals.

I. Miettinen T, Kautiainen H, Mäntyselkä P, Linton SJ, Kalso E. Pain interference type and level guide the assessment process in chronic pain: Categorizing pain patients entering tertiary pain treatment with the Brief Pain Inventory. PLoS One 2019, 14(8):e0221437. https://doi.org/10.1371/journal.pone.0221437

II. Miettinen, T, Mäntyselkä, P, Hagelberg, N, Mustola, S, Kalso, E, Lötsch, J. Machine learning suggests sleep as a core factor in chronic pain. Pain 2021, 162(1), 109-123. https://doi.org/10.1097/j.pain.0000000000002002

III. Miettinen T, Nieminen AI, Mäntyselkä P, Kalso E, Lötsch J. Machine learning and pathway analysis-based discovery of metabolomic markers relating to chronic pain phenotypes. Int J Mol Sci 2022, 23 (9), 5085. https://doi.org/10.3390/ijms23095085

IV. Miettinen T, Sverloff J, Lappalainen OP, Linton SJ, Sipilä K, Kalso E. Sleep problems in pain patients entering tertiary pain care: the role of pain-related anxiety, medication use, self-reported diseases, and sleep disorders. Pain 2022, 163(7), e812-e820. https://doi.org/10.1097/j.pain.0000000000002497

Abstract

The validity of pain intensity as the primary measure in chronic pain treatment has been questioned. It may be important to look at other pain-related factors as well, such as how widespread the pain is or how it interferes with different life activities. These pain-related factors may combine into different pain phenotypes. Understanding how these pain phenotypes associate with, for example, lifestyle and psychological factors may help in targeting treatment better.

The aim of this dissertation was to examine pain phenotypes of patients entering tertiary pain care and the features or problems that are associated with them. More specifically, the aims were:

- to investigate pain phenotypes with respect to different levels of pain interference and factors associated with them;
- to use a data-driven approach to elucidate patient subgroups with different pain phenotypes and investigate factors associated with these, using machine learning methods from a multifactorial set of data;
- to elucidate metabolomic markers associated with more severe pain phenotypes by investigating metabolomic markers and pathways with respect to the pain phenotypes found in the previous study, and to two common comorbidities of severe pain, obesity and recurring sleep problems; and
- to examine how patients with recurring sleep problems differ from those who sleep normally in the areas of pain and pain-related anxiety, childhood adversities experienced, use of sleep and pain medications, self-reported diseases, and sleep disorders.

This was a cross-sectional study. The study data were collected at six pain clinics (three multidisciplinary and three facial pain clinics) in Finland. The whole cohort comprised 473 patients from whom broad data were collected, including sociodemographic factors, previous treatments, comorbidities, lifestyle variables, psychological factors, and others. At multidisciplinary pain clinics with 320 participants, nurses also measured patients' weight, height, waist circumference, and blood pressure; blood samples were taken for the analysis of metabolomics data.

Pain phenotypes combined with levels of pain interference showed adverse changes in different sets of factors when pain interfered highly with either the "activity" or the "affective" dimension. High activity pain interference was

associated with reduced exercising, higher body mass index, and higher avoidance of pain, than where both interference dimensions remained low. High affective pain interference was associated with more depression, greater cognitive anxiety, and lower activity engagement when pain was present. When both interference dimensions were high, the previous adverse changes accumulated, smoking was more prevalent, and pain-related anxiety was more pronounced, with fear of pain and physiological anxiety reactions higher than with other pain phenotypes.

Data-driven subgrouping of patients resulted in three groups. The groups at the extremes showed pain phenotypes with low pain intensity and pain interference at one end, and combination of high pain intensity, high pain interference and the greatest number of pain sites at the other. In the machine learning analysis, the most informative variables among pain-related factors predicting group membership were affective pain interference and number of pain sites. Of the other factors, sleep problems was the most informative, followed by fear of pain, poorer self-rated health, and lower systolic blood pressure.

When metabolomic factors were investigated in relation to pain phenotypes elucidated in the previous data-driven study (least severe pain phenotype in contrast to the two more severe phenotypes combined), obesity, and sleep problems, three metabolomic markers (NAD, AMP, and cysteine) emerged across analyses. Obesity showed association with alterations in amino acid metabolism. Sleep problems were associated with several markers relating to methionine metabolism, which results suggested was downregulated in recurring sleep problems.

Patients with recurring sleep problems showed more pain-related anxiety than those sleeping normally, and results suggested physiological anxiety reactions as significant factors for greater difficulties with sleep. Multiple health conditions (for example, asthma and depression) were more prevalent among those with recurring sleep problems. Those with sleep problems reported significantly more restless legs symptoms than those sleeping normally. Having five or more childhood adversities was associated with recurring sleep problems. Finally, the reported use of pain and sleep medications was higher in those with recurring sleep problems than in those who slept normally.

To conclude, patient subgroups with varying pain phenotypes were discovered in the studies. Previous studies have highlighted the role of psychosocial factors in those with the most severe pain phenotypes. The results of these studies suggest the importance of sleep and lifestyle-related factors as well. Research into metabolomics may give new insights to why pain becomes more severe for some. Sleep is affected by multiple factors, not only pain, in patients with chronic pain.

Tiivistelmä

Kivun voimakkuus ensisijaisena muuttujana on kyseenalaistettu pitkäaikaisen kivun hoidossa. Voi olla tärkeä huomioida myös muut kipumuuttujat, kuten kivun laaja-alaisuus tai kuinka kipu häiritsee erilaisia toimintoja. Yhdessä eri kipumuuttujat voivat muodostaa erilaisia kivun ilmiasuja, fenotyyppejä. Hoidon kohdentamista voi auttaa se, jos ymmärrämme paremmin kuinka erilaiset kivun fenotyypit yhdistyvät esimerkiksi elintapoihin ja psykologisiin tekijöihin.

Tämän väitöstutkimuksen aiheena on tutkia kivun fenotyyppejä ja niihin yhdistyviä tekijöitä potilailla, jotka tulevat pitkäaikaisen kivun hoitoon erikoissairaanhoidossa. Tutkimuksen tarkemmat tavoitteet olivat seuraavat:

- tutkia kivun häiritsevyydestä muodostettujen fenotyyppien yhteyksiä eri tekijöihin;
- selvittää aineistolähtöisesti muodostuvien potilaiden alaryhmien kivun fenotyyppejä ja niihin yhdistyviä tekijöitä laajasta muuttujajoukosta koneoppimisen avulla;
- tutkia vaikeampaan kivun fenotyyppiin yhdistyviä aineenvaihduntatuotteita (metaboliitteja) tutkimalla niitä suhteessa edellisessä tutkimuksessa esille nousseisiin kivun fenotyyppeihin, sekä kahteen vaikeampaan kipuun yhdistyvään tekijään, lihavuuteen ja uniongelmiin, sekä;
- tarkastella kuinka jatkuvista uniongelmista kärsivät ja normaalisti nukkuvat pitkäaikaisen kivun potilaat eroavat toisistaan kivun ja kipuun liittyvän ahdistuksen, lapsuudenaikaisten kuormitustekijöiden, uni- ja kipulääkkeiden käytön, muiden sairauksien sekä unihäiriöiden suhteen.

Aineisto tähän poikkileikkaustutkimukseen kerättiin kuudella suomalaisella kipuklinikalla (kolmella moniammatillisella kipuklinikalla ja kolmella kasvokipuklinikalla). Koko kohortti koostui 473 potilaasta. Heiltä kerättiin tietoa muun muassa taustatekijöistä, aiemmista hoidoista, oheissairauksista, elintavoista sekä erilaisia psykologisia muuttujia. Moniammatillisilta kipuklinikoilta tutkimukseen osallistui 320 potilasta ja heiltä klinikoiden sairaanhoitajat mittasivat lisäksi pituuden, painon, vyötärönympäryksen ja verenpaineen. Näiltä potilailta kerättiin myös verinäytteet, joista suoritettiin metabolomiikka-analyysi.

Kivun häiritsevyydestä muodostetut fenotyypit toivat esille, että kivun häiritsevyyden dimensiot (häiritsevyys aktiivisuuteen / affektiivisiin

toimintoihin) yhdistyivät eri tekijöihin. Voimakas kivun häiritsevyys aktiivisuuteen yhdistyi vähäisempään vapaa-ajan liikuntaan, korkeampaan painoindeksiin ja esillä oli enemmän kipuun liittyvää välttelykäyttäytymistä verrattuna siihen, että kivun häiritsevyys oli heikkoa kummallakin dimensiolla. Kun sen sijaan kivun häiritsevyys affektiivisiin toimintoihin oli voimakas, esillä oli enemmän depressio-oireita, ahdistunutta ajattelua kipuun liittyen sekä vähemmän kivun hyväksymisestä kertovaa itselle tärkeisiin toimintoihin suuntautumista. Kun kivun häiritsevyys oli voimakas kummallakin dimensiolla, edellä mainitut kielteiset muutokset yhdistyivät. Lisäksi tupakointi oli yleisempää ja kipuun liittyvää ahdistusta oli enemmän, sillä kivun pelkoa ja kehollisia ahdistusreaktioita oli enemmän kuin muissa kivun häiritsevyydestä muodostetuissa fenotyypeissä.

Aineistolähtöisesti erottui kolme potilasryhmää erilaisin kivun fenotyypein. Toisessa ääripäässä olevassa ryhmässä kivun voimakkuus ja kivun häiritsevyys olivat matalat, kun taas toisen ääripään ryhmässä yhdistyivät korkea kivun voimakkuus, korkea kivun häiritsevyys ja kipualueiden suuri määrä. Koneoppimisanalyysi toi esille, että kipumuuttujista parhaiten tiettyyn ryhmään kuulumista osoittivat kivun häiritsevyys affektiivisiin toimintoihin ja kipualueiden määrä. Muista tarkastelluista muuttujista paras oli uniongelmat. Uniongelmien ohella tärkeiksi muuttujiksi nousivat kivun pelko, huonoksi koettu terveydentila ja matalampi systolinen verenpaine.

Metaboliitteja tutkittiin suhteessa edellisessä aineistolähtöisessä tutkimuksessa löydettyihin kivun fenotyyppeihin (lievin kivun fenotyyppi verrattuna kahteen vaikeampaan fenotyyppiin yhdistettynä), lihavuuteen ja jatkuviin uniongelmiin. Kun näiden kolmen analyysin tuloksia tarkasteltiin yhdessä, esille nousivat metaboliitit NAD, AMP ja kysteiini. Lihavuus oli yhteydessä muutoksiin aminohappojen aineenvaihduntareiteissä. Uniongelmat olivat yhteydessä useampaan metaboliittiin metioniini-aineenvaihdunnassa, joka tuloksien perusteella näytti alentuneelta jatkuvissa uniongelmissa.

Jatkuvista uniongelmista kärsivillä potilailla oli enemmän kipuun liittyvää ahdistusta kuin normaalisti nukkuvilla. Tutkimuksen tulokset viittasivat siihen, että kehollisilla ahdistusreaktioilla oli keskeinen rooli uniongelmissa. Uniongelmista kärsivillä potilailla oli tavallista useammin oheissairauksia (esimerkiksi astma tai depressio). Levottomien jalkojen oireet olivat uniongelmista kärsivillä selkeästi tavallisempia kuin normaalisti nukkuvilla. Uniongelmista kärsivillä oli tavallisemmin taustassaan viisi tai sitä useampi lapsuudenaikainen kuormitustekijä. Uniongelmista kärsivät käyttivät enemmän uni- ja kipulääkkeitä kuin normaalisti nukkuvat.

Yhteenvetona voidaan todeta, että tutkimuksissa löytyi kivun fenotyyppien suhteen erilaisia potilaiden alaryhmiä. Aiemmissa tutkimuksissa on noussut etenkin psykososiaaliset tekijät suhteessa vaikeampiin kivun fenotyyppeihin. Näiden tutkimusten tulokset viittaavat siihen, että uni ja elintapoihin liittyvät tekijät ovat myös tärkeitä. Metabolomiikan tutkimus voi antaa viitteitä aineenvaihdunnallisten prosessien osuudesta kivun vaikeutumisessa. Pitkäaikaisessa kivussa uniongelmiin ei vaikuta pelkkä kipu, vaan myös monet muut tekijät.

Introduction

Chronic pain may cause great distress in the individuals who suffer from it and in those who share their life with the affected person. Having pain as part of one's life for months, and often years, is for many cognitively and emotionally taxing, and commonly reduces capabilities to function in significant roles in the family, work-life, and society. Besides consequences to individuals, there are major societal costs as well. Chronic pain causes direct health care costs, lost workdays, and disability compensation. Conditions associated with chronic pain are estimated to cost 3-10% of gross domestic product in Europe (Breivik et al., 2013).

Pain treatment has mostly concentrated on decreasing pain intensity, which is still a valid approach when treating acute pain. However, when patients have persistent pain, the treatment effect is usually only modest for pain intensity. Widening the scope of treatment to address other pain-related factors, such as how widespread the pain is or how it interferes with life activities, may be a more fruitful approach for understanding and treating chronic pain (Kaiser et al., 2018). To target treatment better, we should perhaps try to look at these factors together to see whether they reveal subgroups of patients (Turk, 2005). Such subgroups with varying pain phenotypes may require different treatment approaches.

Historically, chronic pain was seen merely as an extension of acute pain, meaning that it was understood in terms of tissue damage and nociception. Over the past fifty years, this concept has completely changed (Gatchel et al., 2007). As research revealed mechanisms for pain signal modulation in the central nervous system, how signaling and modulation might be disturbed in chronic pain, and how pain was an experience shaped by a variety of factors beyond simple nociception, the biopsychosocial approach became the dominant framework in the context of chronic pain. Psychological factors, such as fear of pain and depressive symptoms, are now regarded as integral for understanding chronic pain. However, the list of factors that may influence pain is far from complete, and new information may be uncovered in the fields of genetics and "omics", lifestyle factors, resilience research, and others (Edwards et al., 2016; Freidin et al., 2016).

Multidisciplinary pain treatment is considered the best approach when treating chronic pain. However, patients vary in how much they benefit from treatment and, for some, results are clearly insufficient (Vartiainen et al., 2019). We designed the present study to investigate pain phenotypes, and a wide set of factors with known or plausible associations with these, in patients entering tertiary pain care. This information may help to better identify factors that may need addressing in treatment, facilitating more individualized care.

Review of the literature

Definition of pain

Pain is fundamental to our survival in that it signals damage, or potential damage, to tissues of our body. Pain encourages us to protect injured body parts to promote healing, and pain sets for quick learning in situations where it is present, so that it could be avoided in the future. With this, pain helps us from the earliest stages of our lives. The ability to experience pain has been an evolutionary advantage. Pain and neuroplastic adaptations, such as injured body area becoming sensitized to pain, have been conserved across species through hundreds of millions of years (Price & Dussor, 2014).

Pain in humans is more complicated than the simple process of neurons transmitting nociceptive signals from the periphery to the central nervous system. This is emphasized in the definition of pain by the International Association for the Study of Pain: "A*n unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Raja et al., 2020). The sensory and emotional components of pain are affected by cognitive processes, such as attention and the meaning ascribed to the pain sensation. Contextual factors, for example where, when and with whom the pain is experienced, always play their part in how the individual pain experience forms. An example from the world of small children illustrates this well. A toddler stumbles against a piece of furniture, falls, and starts crying as the pain from the hurt elbow emerges. Crying encourages the parent to comfort, give explanation for the pain, and, if this appears to be a harmless bump, to explain that it will soon be all right. Over the course of life, many kinds of meanings, emotional tones, and ways that other people react may become associated with pain, constructing the background for future pain experiences.

Because of the multifaceted nature of pain, disciplines ranging from genetics to physiology, from psychology to anthropology, are involved in pain research.

Biopsychosocial framework

The idea that cognitive or emotional factors might affect how we experience pain has arisen as a result of a paradigm shift in the research of pain (Gatchel et al., 2007). Early conceptualizations of pain were built on a Cartesian view and postulated that the experience of pain was related simply to how extensive tissue damage was. *Specificity theory* concentrated on the identification of receptors unique to pain sensation and how this information would be transduced from the

periphery to the spinal cord and, further, to the brain. *Pattern response theory* was based on the proposal that the experience of pain was not a simple result of some specific receptor and pathway being activated, but it was connected to the activation of other pathways at the same time, and how this pattern of activation was processed. These biomedical models have guided much research and their conceptualization of pain often still prevails in common thinking.

The introduction of *Gate control theory* in 1965 (Melzack, 1999) provided a framework to incorporate the effects of psychological concepts into the construction of pain experiences. The theory encompassed concepts from the specificity and pattern response theories but complemented them with the idea that the central nervous system was able to modulate the transduction of nociceptive signals. More specifically, this modulation would take place in the dorsal horn of the spinal cord, where neurons from the periphery synapse with those of the central nervous system. In the dorsal horn of the spinal cord, the signals could be either inhibited or amplified and this modulation would be affected by varying states of the brain via descending pathways from brain to dorsal horn. This opened a new door in pain research. The dorsal horn is not merely a passive transmission station. Seeing the brain as capable of actively selecting and filtering the incoming input would lead to the understanding that factors such as attention, cognitive interpretation, and emotion could have an effect on how pain is experienced.

The *neuromatrix theory of pain* (Melzack, 2005) has theorized further on the active role of the brain in the construction of the pain experience. The core of the theory is the proposition that pain is a result of the activity of a widely distributed neural network in the brain, where cognitive, sensory, and motivational-affective components all play a part in shaping the experience. The theory, with its emphasis on the role of the brain, was partly stimulated by research in patients with spinal cord injuries and phantom limb pain. These patients report sensations, including pain, from areas of the body where peripheral mechanisms clearly do not provide sufficient explanation for them, and, therefore, processes within brain must play a part. Also, the theory proposes that the development and maintenance of chronic pain are influenced by factors, such as prolonged stress, that have negative effects on the neural networks.

With this theoretical evolution, pain research has moved into conceptualizing pain in a biopsychosocial framework (Gatchel et al., 2007; Meints & Edwards, 2018). The biopsychosocial model of pain recognizes a distinction between an objectively observable biological event (nociception) and the associated experience (pain), which may be modulated by many factors: genetic composition, events over the life-course, psychological state, and so on. There is

variation in how the affected person responds to pain, for example, in the use of coping mechanisms, and in what kind of responses the pain elicits in those around. All these affect the shaping of the pain experience. The biopsychosocial framework has been especially relevant to chronic pain, although applying to acute pain as well.

Physiology of pain sensation

Starting from the work of Sherrington in 1906, research has discovered much about the neuronal basis of pain sensation: the classes of nerve fibers participating in pain signaling; how the signals may be processed in the dorsal horn; and, with the advent of modern magnetic resonance imaging techniques, the different areas of brain that seem to be involved in the construction of pain experiences (Brooks & Tracey, 2005). Major classes of pain-signaling neurons include the thinly myelinated Aδ-fibers and unmyelinated C-fibers, of which the former are fast-acting (sharper, more specific pain sensations) and the latter slower (producing dull, diffuse pain sensations) (Dubin & Patapoutian, 2010). Different neurons may respond to distinct stimuli (temperature, mechanical, or chemical) or to multiple stimuli (polymodal), and all may differ in thresholds for activation.

Pain signaling neurons synapse with second order neurons in the dorsal horn, where the nociceptive signals enter the central nervous system (**Figure 1**) (Brooks & Tracey, 2005; Dubin & Patapoutian, 2010). From the dorsal horn, the signals ascend in the contralateral spinothalamic tract, and in the spinoreticular (to medulla and brain stem), spinomesencephalic, and spinohypothalamic (to hypothalamus) tracts. There has been much research interest in the dorsal horn because of mechanisms relating to amplification or modulation of pain signals (Woolf & Salter, 2000). One such process gives rise to increased sensitivity around the area of injury or inflammation - so-called secondary hyperalgesia – due to processes in the dorsal horn that lead neurons to become sensitized. Another is modulation of pain signaling by supraspinal structures, including higher brain areas, through descending projections into the dorsal horn. These can be either inhibitory or excitatory.

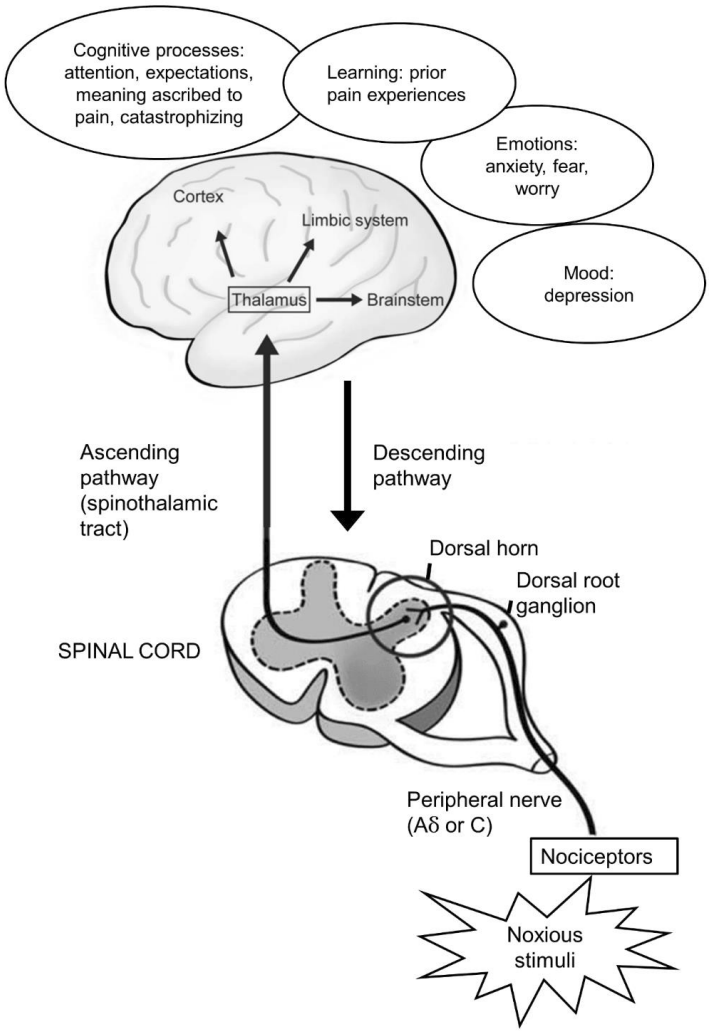

Figure 1. Noxious stimuli activate nociceptors, causing peripheral neurons to fire, sending nociceptive signals (Dubin & Patapoutian, 2010). These travel to the spinal cord, where peripheral neurons synapse with second order ones in the dorsal horn, which in turn synapse with ascending pathways to the brain, including the higher areas. Nociceptive signaling may be inhibited or excited in the dorsal horn via descending pathways from the brain (Woolf & Salter, 2000). Cognitive processes, learning, and emotions have all been associated with modulation of pain signals. Illustration adapted from the Essential Pain Management educational package (Gouke et al., 2022), distributed under Creative Commons CC BY-NC-SA -license.

Brain areas showing activation by nociceptive stimulation are often referred as the “pain matrix” and include, among others, anterior cingulate cortex, insula, frontal cortices, primary and secondary somatosensory cortices, and amygdala (Peyron et al., 2000). Some areas are known to be more involved in particular aspects of pain processing, such as somatosensory cortices in the location and intensity of painful stimuli. However, overall, the processing of pain is widely distributed in the brain, and not yet completely understood. The brain responses that have been found to be associated with nociceptive stimulation are not just nociceptive-specific brain activities but are also involved in processing salient sensory input (Iannetti & Mouraux, 2010). New research suggests that brain regions related to, for example, motivational, learning, and executive functions appear more directly related to the generation of pain experiences than has been previously thought (Geuter et al., 2020; Morton et al., 2016). As for acute versus chronic pain, there is evidence of differential activation patterns in the brain, which may suggest the importance of cognitive and emotional processes in chronic pain (Baliki et al., 2006; Vachon-Presseau et al., 2016).

Several chemical substances are involved in the activation of pain signaling neurons. In tissue damage, substances such as bradykinin, prostaglandins, potassium, histamine, and serotonin are released, and these substances may either activate or sensitize the nociceptors in the tissue (Besson, 1999; Gatchel et al., 2016). Glutamate and substance P are recognized as two key neurotransmitters in relation to nociception, but many others have been studied as well: peptides (somatostatin, calcitonin gene related peptide, neuropeptide Y, and galanin), excitatory amino acids (aspartate), inhibitory amino acids (γ-aminobutyric acid (GABA) and glycine), nitric oxide, adenosine, and monoamines (serotonin and noradrenaline). It should be noted that neurotransmitters associated with pain are extensively distributed throughout the nervous system and they are involved in many other processes as well.

Besides neuronal activity, other events occur in the body in conjunction with pain. In the hypothalamus, pain activates the secretion of three hormones (corticotropin-releasing, gonadotropin-releasing, and thyrotropin-releasing) (Tennant, 2013). This results in other hormones, such as cortisol, pregnenolone, and dehydroepiandrosterone, being released into the blood. These hormones have immune and anti-inflammatory actions, participate in glucose control, cellular protection, and many other functions that are relevant to pain and the possible tissue injury. As pain is inherently something that calls for quick action and escape –“fight or flight” – the sympathetic autonomic nervous system is activated, preparing for the response by releasing adrenalin, and increasing heart and respiratory rates (Burton et al., 2016).

Psychological factors

Pain captures attention. As its natural function is to warn of potential harm, it disrupts attentional engagement and prioritizes escape, avoidance, and the seeking of social support (Moore et al., 2012). How well it captures attention relies on several factors. Pain sensations that are more intense, novel, or unpredictable draw more attention. However, highly competitive sensory information, intense emotional states, or very engaging activities may temporarily override the interruptive effects of pain. For example, if there is an intensive need to escape from a threatening situation, pain sensations may be altogether abolished, to emerge only after safety is reached. There is a wealth of experimental animal and human studies on the effects of stress-induced analgesia, which has been found to be mediated by activation of descending inhibitory pain pathways (Butler & Finn, 2009). Understandable in the context of survival, at the same time this phenomenon illustrates well how pain experiences are affected by both pain signaling and modulation by brain states.

Expectations that we have of noxious stimuli or pain relief will influence our pain experience (Atlas & Wager, 2012). When a visual cue was associated with high or low levels of heat pain stimuli, subjects reported greater pain when the cue associated with high pain stimuli was present, irrespective of the true level of stimuli received (Keltner et al., 2006). Undeniably, these basic associative learning mechanisms work in multitude of situations for the benefit or detriment of the pain patient. For example, many types of movements may have become cues for pain, which may attune patient to expect more pain when engaging in physical activities (Alaiti et al., 2020). When expectation of pain relief causes reduction in pain, it is called placebo analgesia (Tracey, 2010). The effect has been shown with pharmacologically inert substances many times. Conversely, nocebo hyperalgesia refers to the phenomenon whereby negative treatment expectations induce increases in pain. Underlying mechanisms for placebo analgesia involve the endogenous opioid system and descending pain modulation, while nocebo hyperalgesia seems to involve cholecystokinin, also associated with anxiety responses (Benedetti et al., 2006; Eippert et al., 2009). Expectations that lead to placebo or nocebo effects may be learned through, for example, observing others or verbal suggestions (Colloca & Benedetti, 2009). Thus what we may have seen or been told of pain treatments may have significant effects on whether or how we benefit from them.

The meaning ascribed to pain influences the resultant pain experience. When pain is interpreted as signaling serious illness or greater tissue damage, it is felt as more intense (Arntz & Claassens, 2004). When the meaning of pain has a threatening component, pain sensation may draw more attention to this or induce

more anxiety. There is a long tradition in pain research of examining catastrophizing and pain-related anxiety, which refer to fearful, anxious, and helpless cognitions about pain with an accompanying tendency to avoid pain, and bodily anxiety reactions (McCracken & Dhingra, 2002; Sullivan et al., 1995). Catastrophizing has been robustly associated with experiencing more pain, using more medical services, being more disabled, and having poorer pain outcomes after surgery (Petrini & Arendt-Nielsen, 2020). These effects have been observed in both chronic pain patients and in experimental studies of healthy subjects. Conversely, interpretations of pain that decrease its threatening value and reflect a sense of control, are associated with positive outcomes. Being able to predict the occurrence of pain stimuli and to control pain relief are associated with lower pain ratings (Becker et al., 2021) and reduced stress response (Muller, 2011). Pain acceptance, i.e. interpreting pain as something that may be lived with and not needing constant control, has been associated with lower pain intensity, lower emotional burden, and better function in patients with chronic pain (Jensen et al., 2016).

Pain is unpleasant and naturally gives rise to emotions such as worry, frustration, and anxiety. In the short term, these emotions motivate behaviors that serve to resolve pain: focusing on what is causing the pain, retreating from it, and seeking help from other people. However, these and other emotions that carry negative valence, such as anger, depressive feelings, and helplessness, also seem to increase pain perception (Wiech & Tracey, 2009). For example, those with more anxiety perceive a forthcoming pain stimulus as more intense (Ploghaus et al., 2001). Pain-related fear has been under research for years, especially for the role it may have for disability (Leeuw et al., 2007). It has been observed that fear may be generalized from movements and bodily sensations originally associated with pain to others with no direct relation to pain (Meulders, 2020). If this fear is combined with avoidance, many activities will be abandoned, leading to reduced function.

Inducing positive affect in experimental studies has been associated with lower pain ratings, with neuroimaging studies suggesting that positive emotion affects pain processing in the central nervous system (Finan & Garland, 2015). It should be noted that negative and positive affect do not exclude one another: promoting positive affect is associated with positive outcomes, even in the presence of negative affect.

Behavioral reactions

Typical behavioral reactions to pain include guarding (abnormally stiff or interrupted movement), bracing (stationary position with fully extended limb), rubbing or holding the painful body area, facial expression associated with pain, and sighing (Keefe & Smith, 2002). When there is tissue damage, reactions such as guarding promote healing. Behavioral reactions also serve a communicative function, as observers will be alerted that someone else is in pain and may need help. When pain cannot be verbally expressed, as in individuals with intellectual disabilities or dementia, these behaviors serve as proxies for the level of pain experienced.

Patients with chronic pain may develop behavioral patterns that are not helpful in the long term. These behaviors may have been understandable coping strategies when pain was acute, but in chronic pain they no longer serve that purpose and with them come further problems. One such behavioral pattern is avoidance (Vlaeyen & Linton, 2000). Retreating from activities which are associated with increased pain is meaningful in acute pain. However, avoidance may easily become general so that, if originally a small number of activities was avoided, over time many other activities will become included in avoidance. Avoidance easily persists, because it prevents the person obtaining updated information about what is painful, with some previously painful activities no longer being so. Avoidance may have negative consequences, such as physical deconditioning (Basler et al., 2008).

Unhelpful behavioral patterns in chronic pain may include reliance on pain medications as the primary method for responding to pain fluctuations, seeking help from others in a way that unnecessarily compromises autonomy, or using food, nicotine, or alcohol as pain relievers and/or to soothe oneself when in pain (Amy Janke & Kozak, 2012; Ditre et al., 2011; Egli et al., 2012).

What counts as unhelpful behavior is related to the amount of negative consequences that follow. For example, finding comfort in eating may serve as a coping mechanism against the unpleasantness of pain or the anxiety that comes with it but, when relied upon too much, may lead to weight gain and to the problems that come with this.

Cultural context

Culture carries beliefs, values, and attitudes that inevitably influence the way pain is experienced by the individuals who have been surrounded by that culture. The

culture in which we have been raised will be reflected in the way we make meaning of, and act in relation to, pain.

Some aspects of pain behavior are universal across cultures, such as weeping, turned-down mouth, and other facial actions, but many specific gestures, types of vocalizations and speech, and behavior patterns, are culturally modulated (Cohen, 1995). Expression of pain is more acceptable in Western societies for children than adults, and among women than men. Historically, there has been an association between being "more highly developed" and ability to master and tolerate pain in Western societies, reflected in portraits of religious martyrdom or expectations for those in upper social classes.

Acknowledging cultural aspects becomes ever more important as people with different cultural heritages move in greater numbers to other countries. At some points in their lives, many seek help for pain. Several themes have emerged in cross-cultural pain research: whether pain is expressed or stoically endured, what kind of patient is "a good patient", how traditional or complementary medicines are used, and what meanings are attributed to pain (Pillay et al., 2014). In London, white patients of British origin and black patients of Caribbean origin, both with advanced cancer, were compared for the meaning that they ascribed to pain symptoms (Koffman et al., 2008). In both groups, views of pain as an unfairly attacking enemy emerged. However, among some of Caribbean origin, pain was seen as a test of religious faith or punishment. A cross-cultural study of patients attending pain clinics found differences in the conceptualization of chronic pain (biomedical vs holistic views) and how the impact of pain was conceived (individual vs familial) (Bates et al., 1997).

Chronic pain

Acute pain is considered a normal, predictable, and evolutionary meaningful reaction. Pain dissolves as tissues heal. Pain is considered chronic when it lasts for longer than 3 months or past the usual time needed for tissues to recover (Treede et al., 2015). In chronic pain, the alarming function of pain no longer exists in the same way as in acute pain: pain experiences have less connection to noxious stimuli or, in many cases, this connection is not really found at all. It is unclear who will develop chronic pain, but some risk factors have been recognized, and they are discussed in the following.

Various categorizations for chronic pain have been employed over the years, such as by location of pain (for example, headache), etiology (cancer pain), or the anatomical system affected (neuropathic pain). The most recent categorization is included in the 11th edition of International Classification for Diseases (ICD-11) (**Table 1**) (Treede et al., 2015).

A recent National Health Interview Survey in the United States, collected in 2019, found 20.5% of those surveyed responding that they experienced pain on most days or every day (Yong et al., 2022). Within these responders, the most common pain locations were hip, knee, or foot (44.1%), and back (40.9%). The functional limitations associated with chronic pain varied: 78.5% reported no difficulty in doing errands alone and 74.6% reported no difficulty in participating in social activities; however, a lot of difficulty or complete inability for participating was reported by 10.3% and 10.8%, respectively. Chronic pain is clearly associated with reduced capacity for work. Work limitations due to health problems were reported by 15.0% of those without chronic pain but, among those with chronic pain, this was 48.8%. In an earlier European-wide survey, 19% of responders were classified as suffering from chronic pain (Breivik et al., 2006). Approximately 60% of them reported decreased ability or inability to work outside the home.

Category	
Chronic primary pain	Pain in one or more anatomical regions that persists or recurs for more than three months, is associated with significant emotional distress or functional impairment, and cannot be better explained by another chronic pain condition.
Chronic cancer pain	Pain relating to cancer may be caused by the cancer itself and/or treatment for cancer (surgery, chemotherapy, radiotherapy, and others).
Chronic postsurgical and posttraumatic pain	Chronic pain that develops after a surgical procedure or a tissue injury due to trauma.
Chronic neuropathic pain	This relates to lesion or disease of the somatosensory nervous system. Causes of neuropathic pain include stroke, nerve trauma, and diabetic neuropathy. An increased response to a painful stimulus by the nervous system is referred as *hyperalgesia*, while pain in response to normally harmless stimuli is *allodynia*.
Chronic headache and orofacial pain	Chronic headache is defined as headache occurring on at least half of the days during at least three months. Temporomandibular disorders are the most common chronic orofacial pains.
Chronic visceral pain	Chronic visceral pain originates from internal organs of the pelvic, abdominal, and thoracic cavities, and head and neck region. The underlying mechanisms comprise, for example, persistent inflammation, vascular mechanisms, and obstruction and distension.
Chronic musculoskeletal pain	This refers to nociceptive pain due to disease processes affecting bones, muscles, or related soft tissues. Etiologies include, for example, rheumatoid arthritis. Conditions with incompletely understood mechanisms, such as nonspecific back pain and chronic widespread pain, are excluded from this category.

Table 1. Categorization of chronic pain in the ICD-11 (Treede et al., 2015).

Factors relating to chronic pain development or maintenance

Chronic pain is thought to develop and be maintained through multiple processes. For example, many patients with chronic pain suffer from symptoms of anxiety and depression. It is now understood that psychological distress may play several parts in relation to pain: in predisposing to developing chronic pain; in increasing pain; and as key factors in treating pain patients to help them regain the strength to participate in rehabilitation. Therefore, much may be achieved in relation to pain even if it is not directly targeted.

Genetic factors

Chronic pain has demonstrated at least moderate heritability when investigated through familial aggregation and twin studies (Mogil, 2012). Genetic factors may be involved in predisposing to the development of chronic syndromes or influencing pain severity, or both. Animal studies have revealed that there is genetic variation in the expression of different pain symptoms (e.g. whether induced thermally, mechanically, or chemically) and in response to analgesics (LaCroix-Fralish & Mogil, 2009; Mogil, 1999). Also, animal studies have made robust observations of interactions between pain sensitivity, animal genotypes and factors such as: sex, diet, social housing, experimenter characteristics, and circadian rhythmicity (Chesler et al., 2002; Puglisiallegra et al., 1982; Raber & Devor, 2002; Shir & Seltzer, 2001).

Some rare disorders of pain are influenced by single gene mutations. These include congenital insensitivity to pain (Nagasako et al., 2003), familial hemiplegic migraine disorders (Barrett et al., 2008), and neuronal channelopathies presenting as paroxysmal pain disorders (Kullmann & Waxman, 2010).

Studies investigating pain disorders and gene variants associated with them have concentrated on a rather narrow selection, around ten, of genes and gene complexes (Mogil, 2012). Studies exploring genome-wide associations to pain disorders have mostly been conducted in relation to migraine (Chasman et al., 2011). It is still not clear whether disease-specific genes (for example relating to back pain) are to be found or if there are genes that affect multiple pain syndromes. The question also remains that, if some gene appears to be associated with chronic pain disorders in general, is this because it participates in pain physiology or because it contributes to the possible modulators of pain? Genetics

may also influence factors such as pain catastrophizing (Finan et al., 2011) or negative affect (Bruehl et al., 2008).

Temperament, our natural disposition or style of reacting to various kinds of stimuli, is formed by genetic factors (Cloninger et al., 2019). Temperament and environmental factors shape personality traits. Research into links between pain and personality traits has found neuroticism to be associated with both greater sensitivity to pain and having chronic pain (Merlijn et al., 2003; Payne et al., 2013). Neuroticism is a trait-like tendency to experience negative affect, such as anxiety and distress, and it has been suggested that it predisposes for more pain through, for example, increased anxiety sensitivity or pain catastrophizing (Burri et al., 2018; Goubert et al., 2004).

Central sensitization

Central sensitization refers to an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity (Woolf, 2011). In several pain conditions, the pain experienced appears disproportionate to the intensity of noxious stimuli, inflammatory state, or lesion of the nervous system, presumed to be the root cause of the pain. Also, some chronic pain conditions, such as fibromyalgia or irritable bowel syndrome, have no such clear precipitating factor. Hence, it has been thought that changes in the central nervous system may alter, distort, or amplify pain, increasing its degree, duration, and spatial extent. Therefore, the experienced pain no longer reflects the specific qualities of noxious stimuli in the periphery, but rather the conditions in the central nervous system.

Central sensitization is thought to arise through several processes (Latremoliere & Woolf, 2009). Synaptic efficacy in somatosensory pathways may be increased, inhibitory mechanisms that modulate nociceptive signaling may be reduced, and normally ineffective synapses may be strengthened so that subliminal inputs may activate pain circuits. Recently, it has been additionally discovered that changes in microglia, astrocytes, gap junctions, membrane excitability, and gene transcription may also play their part in maintaining central sensitization (Chacur et al., 2009; Chiang et al., 2010; Rivera-Arconada & Lopez-Garcia, 2010). Sleep deprivation has been associated with increases in sensitivity for pain (Staffe et al., 2019) and poor sleep has been associated with processes in glial activation that may contribute to central sensitization (Nijs et al., 2017).

Central sensitization is now thought to contribute to the persistence or severity of pain for many patients who suffer chronic pain. Studies have observed signs of central sensitization in patients with rheumatoid arthritis (Hogeweg et al., 1995),

osteoarthritis (Bajaj et al., 2001), temporomandibular disorder (Fernandez-de-las-Penas et al., 2009), fibromyalgia (Desmeules et al., 2003), musculoskeletal disorders (Freeman et al., 2009; O'Neill et al., 2007), and neuropathic pain (Koltzenburg et al., 1994), among others.

Sociodemographic factors

Sex

Increasing evidence shows sex-related differences in pain sensitivity, analgesic response, and risk for developing chronic pain (Bartley & Fillingim, 2013). Women report more pain in epidemiological studies than men (Jimenez-Trujillo et al., 2019); women may also show greater sensitivity to pain than men in laboratory experiments (Bulls et al., 2015), but the findings have not been consistent for all pain modalities (Racine et al., 2012). Sex-related differences may rely on multiple mechanisms, with differences in hormones likely to play a part. Estrogens can modulate functioning of the nervous, immune, skeletal, and cardiovascular systems, and are suggested to modulate at least some types of pain disorders, such as menstrual-related migraine, temporomandibular disorder, and arthritis (Craft, 2007). Testosterone, however, may protect from pain via anti-inflammatory effects. Sex-related hormones may also modulate the endogenous opioid system. Differences have been found in the activation of μ-opioid receptors in the brain in the presence of sex-related hormones (Zubieta et al., 2002). Sex-related differences in pain may be affected by psychosocial mechanisms, as well: in experimental studies, women have shown more catastrophic thinking than men (Forsythe et al., 2011) and displayed lower self-efficacy (Jackson et al., 2002).

Age

Greater age is associated with a higher risk of chronic pain (Fayaz et al., 2016). With advancing age, there is more chance of having experienced noxious stimuli or injuries that may trigger the development of chronic pain. Also, with age, diseases and conditions with pain symptoms, such as arthritis, diabetic neuropathy and post-herpetic neuralgia, become more prevalent (Reid et al., 2015).

With age, there may be degenerative changes in dorsal horn sensory neurons and altered spinal neurochemistry, reducing capability for endogenous pain inhibition, and increased neuroinflammation that may contribute to the

development of chronic pain (Tinnirello et al., 2021). In the aging brain, there are reductions in neurotransmitters and receptors, such as serotonin and glutamate, involved in pain processing and modulation, thus possibly affecting experiences of pain.

Education level

Individuals with a lower socioeconomic status are at more risk for developing chronic diseases and having fewer years of life in good health (Head et al., 2019). Lower education level has associated with longer duration of pain problem and greater recurrence of pain with back pain patients (Dionne et al., 2001). It is also associated with environmental and behavioral factors that may impose health risks, such as more physically straining work, obesity, and more substance misuse. Furthermore, access to health services and more effective use of those services may be more difficult for those with a lower level of education.

Early life events

Patients with chronic pain report more adverse historical life experiences than those without (Kopec & Sayre, 2005; Varinen et al., 2017; Von Korff et al., 2009). The risk of chronic pain is not only increased by traumatic maltreatment, for example violence or sexual abuse, but also by other adversities, such as hospitalization due to traffic accident, maternal death, or financial problems in the family (Jones et al., 2009). Children of parents with chronic pain may be at more risk of developing chronic pain and experiencing poorer outcomes with it than other children (Higgins et al., 2015).

Adverse events may increase the risk for chronic pain through several mechanisms. Events may impose long-lasting emotional burdens and psychological distress that in turn may predispose for developing chronic pain when the person encounters injury or disease with pain (Benjamin et al., 2000; Pirkola et al., 2005). Being exposed to adverse events may predispose for higher stress reactivity (Heim et al., 2008). Patients having experienced childhood abuse are at more risk of developing post-traumatic stress disorder (PTSD) (Powers et al., 2014), which may have, for example, negative effects on emotion regulation, then contributing to more pain. Adversities are associated with many negative health behaviors, such as physical inactivity and substance abuse (Hughes et al., 2017), which may predispose for the development of chronic pain. Disadvantaged children may be at higher risk of experiencing distressing events later in life,

causing accumulating adversity throughout the life course (Schoon et al., 2003). Children of parents with chronic pain may adopt maladaptive pain beliefs and responses to pain through modeling or parental reinforcement (Stone & Wilson, 2016).

Psychological processes

Fear, catastrophizing and pain-related anxiety

One of the most influential concepts in research on psychological factors in chronic pain has been the fear-avoidance model (Vlaeyen & Linton, 2000). This was conceived to develop an understanding of why some individuals with acute musculoskeletal pain end up having persistent and disabling pain. The model proposes that, for some patients, significant fear becomes associated with movements or activities linked with pain, and this fear is counteracted by avoiding those movements or activities. Common fears are that something harmful may happen in the body, for example, that spine might be damaged while doing some activity. Cues that arouse fear may also be altering sensations in the body or features of the surroundings, such as visual or auditory cues (Meulders, 2020). The fearing and avoiding create a self-perpetuating cycle. Due to avoidance, fear persists because it is not confronted and thus found to be ungrounded. Additionally, the so-called deconditioning syndrome may develop, where reduced muscular activity leads to progressive worsening of physical fitness, which may then predispose for muscle soreness and pain more easily when resuming activities (Verbunt et al., 2003). Fear of pain has been associated with a greater risk of developing chronic pain and with worse outcomes (Linton et al., 1999; Turk & Wilson, 2010) (Boersma & Linton, 2005).

Pain catastrophizing comprises rumination about pain, magnification of the negative consequences of pain, and helplessness in relation to pain (Sullivan et al., 1995). Catastrophizing has been much studied in relation to chronic pain. It has been found as a significant predictor of pain chronicity (Burton et al., 1995; Edwards et al, 2006) and its decrease accounts for a significant portion of the reduction in pain severity and in depression with treatment (Craner et al., 2016).

Pain-related anxiety may be considered an umbrella term for fear- and anxiety-laden processes associated with pain. Besides emotional and cognitive elements, anxiety includes physiological reactions as well (McCracken & Dhingra, 2002), such as increased heart rate and respiration, elevated blood pressure, increased blood flow to skeletal muscles, and increased muscle tension, among others (Steimer, 2002). Cognitive and behavioral anxiety reactions to pain have been

studied more than physiological reactions, but physiological aspects may be important in chronic pain (Norton & Asmundson, 2003). Persistent physiological reactions may, for example, contribute to lower heart rate reactivity in patients with chronic pain (Koenig et al., 2016), and induce muscular tension that exacerbates musculoskeletal pain (Lundberg et al., 1999). Also, it may be that physiological reactions will become associated with fear, possibly leading to situations, where body sensations, such as muscle tension, trigger avoidance behavior.

Self-efficacy

Self-efficacy represents individuals' beliefs in their capability to control events that affect life (Bandura, 1983). When confronted with aversive events, those lacking self-efficacy are more prone to react with fear and heightened arousal than those with more self-efficacy. In patients with chronic pain, better self-efficacy has been prognostic of less disability in prospective studies (Costa et al., 2011; Kalapurakkel et al., 2015; Miro et al., 2011). For example, among patients with chronic low back pain, self-efficacy was an even more important factor for improvement in disability than was pain-related fear (Costa et al., 2011). In the chronic pain context, self-efficacy may be strengthened by building confidence in doing specific activities even in the presence of pain.

Resilience, pain acceptance, and psychological flexibility

In pain research and treatment, vulnerability factors are often emphasized more than those that protect from negative consequences. Resilience factors help individuals in adapting to pain (Sturgeon & Zautra, 2010). Individual personality traits (such as optimism) may serve as resilience resources and adaptive coping strategies (such as seeking social support or the ability to regulate emotions) as mechanisms that enhance resilience. More resilient patients with chronic pain have been found to have more helpful coping strategies and beliefs about pain (Karoly & Ruehlman, 2006), and with less pain-related anxiety and better social support (Newton-John et al., 2014).

Pain acceptance and psychological flexibility refer to processes that may serve as resilience factors in the context of chronic pain. Pain acceptance aligns with the approach that chronic pain may seldom be eradicated completely. Therefore, a better working approach for concentrating on managing pain, is to be aware of pain but not attempt to change it, instead engaging in behaviors that fulfill

personally important goals in life (McCracken, Carson, et al., 2004). Studies have shown that greater pain acceptance is associated with better functioning (Esteve et al., 2007). Also, greater pain acceptance seems to buffer negative affect during pain exacerbations (Kratz et al., 2017). A group of pediatric pain patients who underwent an intervention to enhance pain acceptance showed lower pain intensity, pain interference, kinesiophobia, and pain-related discomfort than those who received regular multidisciplinary pain treatment (Wicksell et al., 2009).

Psychological flexibility relates to processes of avoidance and cognitive fusion, which have been seen as important factors in the ability of a person to pursue valued life goals when unpleasant experiences, such as fear or pain, are present (Hayes et al., 2006). Avoidance refers to strategies, such as staying at home, which prevent one from meeting these unpleasant experiences. Cognitive fusion refers to the ability to distinguish between thoughts and actual events, i.e. to the ability to understand that private events are different from what may actually happen. Psychological flexibility has been found to mediate improvements in pain-related disability and life satisfaction in patients with whiplash-associated pain disorder (Wicksell et al., 2010). Acceptance and commitment-based interventions, which are targeted on increasing psychological flexibility, have resulted in reductions in emotional distress and health care utilization, and increases in physical and social functioning among patients with chronic pain (Scott & McCracken, 2015).

Sleep

Problems in falling asleep and maintaining sleep throughout the night are common in pain patients. In a Norwegian population study on insomnia and health, chronic pain conditions, such as fibromyalgia and musculoskeletal disorders, were particularly associated with sleep problems (Sivertsen et al., 2009). For those with musculoskeletal disorders, the prevalence of insomnia was 25.1%, and for fibromyalgia 39.8%. Sleep problems have been shown to predict the generalization of pain symptoms from localized to widespread (Wiklund et al., 2020)

More intense and more widespread pain are associated with greater sleep problems (Finan et al., 2013; Husak & Bair, 2020). Pain may make it difficult to find a comfortable sleeping position and increases in pain during the night may interrupt sleep. However, the association between pain and sleep problems is likely to be complicated by other factors as well, such as pain-related anxiety. Worrying or ruminating thoughts about pain may hinder falling asleep (Buenaver

et al., 2012). Also, physiological anxiety reactions to pain (for example, increased heart rate and blood flow) (McCracken & Dhingra, 2002) may well contribute to the hyperarousal that impairs sleep (Bonnet, 2010).

Problems comorbid with pain may also influence sleep. Sleep problems are a hallmark feature in the symptomatology of depression and, as pain problems frequently co-occur with depression, this is one likely factor. It has been suggested that sleep problems, pain, and depression may all be influenced by shared neurobiological processes, such as altered dopaminergic functioning (Finan & Smith, 2013). Adverse life events may increase the risk of sleep problems later in life via altered stress reactivity or PTSD (Brindle et al., 2018; Chapman et al., 2011). Somatic conditions, such as cardiac diseases, hypertension and diabetes, are associated with sleep problems (LeBlanc et al., 2018; Martikainen et al., 2003). Lastly, sleep disorders, restless legs syndrome (RLS) and obstructive sleep apnea (OSA) are more prevalent among patients with chronic pain than in the general population (Mathias et al., 2018).

Recent findings have suggested the importance of sufficient sleep for patients with pain. The glymphatic system is proposed to clear metabolic waste products from the brain during sleep, using perivascular pathways (Xie et al., 2013). There is evidence that proper clearance of these substances is preventive of neurogenerative diseases, such as Alzheimer's (Reeves et al., 2020). Disruptions in sleep and neuroinflammation associating with chronic pain states have been proposed as mechanisms that may suppress the glymphatic system (Goldman et al., 2020; Manouchehrian et al., 2021). Also, REM sleep is important for learning, for example in the extinction of conditioned fear reactions, and for the capability to regulate emotions and handle stress when awake (Vandekerckhove & Wang, 2018). Experiencing pain may be associated with many emotional reactions, such as fear and anxiety, which have been suggested as risk factors for chronic pain (Leeuw et al., 2007; Meulders, 2020), and, as pain is already a stressor in itself, restoring sleep in both acute and chronic pain appears vital.

Comorbid diseases

Depression

Depression is a common psychiatric condition in the general population, affecting annually approximately one in ten in Finland (Markkula et al., 2015). In patients with chronic pain, depression and depressive symptoms are even more common. In specialized pain care settings, major depressive disorder was diagnosed in 37% of patients when assessment was by a psychiatrist (Knaster et al., 2012). There is

a great variation in incidence when depression is assessed by questionnaires, the average being 52% for those attending pain clinics, with some studies estimating that nearly all pain patients have concurrent major depressive disorder (Bair et al., 2003).

Depressive mood is associated with greater risk of developing persistent back pain (Pincus et al., 2002). With co-occurring depression, pain patients report more pain complaints, higher pain intensity, and more exacerbations of pain symptoms, and are less likely to show recovery or remission of pain symptoms than when there is no depression (Bair et al., 2003). Various factors may account for the high co-occurrence of depression and chronic pain. The association between them is considered to be bi-directional. Biological mechanisms may include, for example, alterations in monoamine neurotransmitters or inflammatory factors (Sheng et al., 2017), while linking factors may be psychological, such as negative beliefs and catastrophic thinking (Thomas & Larkin, 2020) or deficiencies in emotional regulation (Linton & Bergbom, 2011).

Somatic comorbidities

Somatic comorbidities are likewise common in patients with chronic pain. Among those who reported chronic pain in a survey study, 56.6% also reported two or more chronic physical conditions (Dominick et al., 2012). Patients with chronic back or neck pain report more headaches, cardiovascular diseases, stroke, high blood pressure, asthma, COPD, irritable bowel symptoms, ulcers, HIV/AIDS, epilepsy, and problems with vision, than those without chronic pain (Hestbaek et al., 2003; Von Korff et al., 2005). Somatic comorbidities may contribute to problems common in chronic pain, such as with sleep (Budhiraja et al., 2015; Malhotra & Loscalzo, 2009). In general, multimorbidity may be a significant issue for health, predicting higher mortality rates, reduced function, and increased health service use (France et al., 2012).

Lifestyle factors

Physical inactivity

Physical inactivity is a natural response to acute pain as a way to protect tissues from more damage. In chronic pain, tissue damage is not so much a factor but, when pain persists, inactivity may continue, producing a more sedentary lifestyle. Chronic pain is associated with lower frequency, duration, and intensity of exercise (Landmark et al., 2011), which may have a detrimental effect for overall

health. Sedentary lifestyles increase risks of obesity, heart disease, type 2 diabetes, and some cancers, and shorten life expectancy (Manson et al., 2004).

Physical inactivity may also worsen pain. For years, it has been recognized that patients with low back pain are at risk of the so-called deconditioning syndrome, i.e. muscles losing strength and becoming sore more easily in activity (Verbunt et al., 2003). Also, there is evidence that physical activity may attenuate central sensitization (Law & Sluka, 2017). Therefore, gradually regaining physical activity has been a key target in rehabilitation programs.

Obesity

Pain complaints become more prevalent with increasing weight (Stone & Broderick, 2012). Obese individuals have a greater than two-fold risk of reporting back pain than those without obesity (Okifuji & Hare, 2015). Obesity is associated with other pain conditions as well: joint pain (Lee & Kean, 2012), chronic migraine (Chai et al., 2014), upper abdominal pain (Eslick & Talley, 2016), and widespread pain/fibromyalgia (D'Onghia et al., 2021).

Obesity may lead to experiencing more pain through increased load on joints and spine, altered body mechanics, and changes in posture (Shiri et al., 2010). Release of proinflammatory substances from adipose tissue has also been proposed as a likely factor (Hashem et al., 2018). The direction of influence may not be one-way as chronic pain may predispose for developing obesity through more sedentary lifestyles (Heinonen et al., 2013), causing increased eating as a comforting coping mechanism (Amy Janke & Kozak, 2012), or sleep problems caused by pain disturbing appetite-regulating hormones (St-Onge, 2017).

Substance use

Patients with chronic pain smoke more than the general population (Hooten et al., 2011). Smoking within chronic pain patients is associated with worse pain, more functional limitations, higher psychological burden, and worse recovery (Khan et al., 2019).

The relationship between smoking and chronic pain is likely bi-directional. Smoking may predispose for chronic back pain through reduced perfusion and malnutrition of the intervertebral discs via vasoconstriction, development of degenerative lesions in the intervertebral discs due to impaired blood supply, contribution to osteoporosis, or inflammatory mechanisms (Shiri et al., 2010). However, pain may also maintain smoking: in experimental studies, nicotine has

shown a short-term pain-alleviating effect, possibly via agonism of the nicotinic acetylcholine receptors, modulation of inhibitory pain pathways, or activation of endogenous opioid system (Ditre et al., 2011). Therefore, some patients may use smoking as a coping mechanism for pain. But nicotine is also highly addictive and withdrawal symptoms include increased pain sensitivity: as a result, continued smoking may be a method of controlling these (Ditre et al., 2018). Furthermore, since smoking is often used to control anxiety (Moylan et al., 2013), and anxiety is common in patients with chronic pain, this may be an important factor.

Alcohol has an analgesic effect (Thompson et al., 2017) but the effect diminishes over repeated use. As with nicotine, withdrawal symptoms include increased pain sensitivity (Egli et al., 2012). Alcohol was reported as a coping strategy for arthritis or facial pain by one in every four individuals in a community-dwelling sample (Riley & King, 2009).

Higher pain interference has been shown to predict the development of alcohol dependence (McDermott et al., 2018). It has been suggested that there may be genetically based differences in the shaping of neurobiological reward and stress pathways, which may predispose for developing both chronic pain and alcohol dependence (Yeung et al., 2017) so that, if some individuals experience greater alleviation of pain or stress reduction from alcohol, they may be more vulnerable to develop dependency. However, continuous alcohol use is strongly associated with anxiety and mood problems, among others, making coping with pain more difficult.

Metabolic processes

Many biological markers, such as levels of neurotransmitters or inflammatory substances, are investigated for their relation with chronic pain states. Metabolomics investigates molecules that relate to cellular metabolic functioning, such as amino acids, carbohydrates, and fatty acids. There is a growing interest in "omics", referring to such fields as genomics, proteomics, and metabolomics, in investigating pathophysiological processes in diseases (Hasin et al., 2017). Because of advances in technology, it has become possible to cost-effectively analyze large numbers of markers from suitable samples. Metabolomic analyses may be conducted with samples of tissues, blood, serum, urine, or feces, among others.

In pain research, metabolomic investigations have found markers associated with various pain conditions, such as fibromyalgia (Clos-Garcia et al., 2019; Malatji et al., 2017), rheumatoid arthritis (Adams et al., 2012; Zhou et al., 2016), or complex

regional pain syndrome (Alexander et al., 2013). For example, it has been observed that patients with fibromyalgia differ from healthy controls in levels of lipids and amino acids, and energy metabolism pathways show alterations. Ornithine levels are associated with the persistence of musculoskeletal pain (Mantyselka et al., 2017) and epiandrosterone sulfate levels are associated with widespread pain (Hadrevi et al., 2015; Livshits et al., 2015). Levels of glutamate may be associated with nociception across various pain conditions (Teckchandani et al., 2021).

Research into the metabolomics of pain is still in its early stages. Its complexity is increased by problems often co-occurring with chronic pain, such as obesity or with sleep. Obesity is known to be associated with metabolomic changes, such as elevated levels of branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs), and changes in carbohydrates, acylcarnitines, and fatty acids (Rangel-Huerta et al., 2019). Sleep problems have been associated with elevated levels of BCAAs, as well as altered glucose metabolism (Humer et al., 2020). Also, the medications used to manage pain may induce metabolomic changes (Ghosh, 2021).

Different “omics” fields may provide information in the future that help find early indicators of disease development, explain disease processes, and guide more personalized treatment (Hasin et al., 2017). However, sophisticated data analysis methods are needed to process the very complex data sets acquired.

Assessing pain and outcomes

For a long time, pain intensity has been the key measurement for treatment planning and for evaluating the success of pain treatment. For acute pain, this still holds but, for chronic pain, its utility as the primary measure has been questioned (Kaiser et al., 2018). Investigating a more varied selection of pain-related factors may reveal subgroups of pain patients with differing combinations of pain-related factors and pain phenotypes. For example, patient subgroups with high pain intensity and widespread pain may differ in many respects from those with higher, but more localized, pain.

When planning treatment of a patient, a picture needs to be composed of key areas that may contribute to pain or affect the treatment (Edwards et al., 2016), including such psychosocial variables as beliefs about pain and mood, lifestyle factors, expectations for treatment, and others. Some of these may serve as treatment targets.

For assessing outcomes of chronic pain treatment, four core domains have been recognized: pain, physical functioning, emotional functioning, and overall improvement (Dworkin et al., 2008).

Pain intensity

There are various ways to assess pain intensity. A common and simple tool is the visual analog scale (VAS), where the patient is asked to indicate the perceived pain intensity along a 100 mm horizontal line. To the left is located “no pain” and to the right “worst pain” (Hjermstad et al., 2011). Different versions may have slightly different wordings, such as “maximum pain” or “worst pain imaginable”. Also commonly used is the numerical rating scale (NRS), consisting of digits 0 to 10 (0 indicating “no pain” and 10 “worst pain”), as in the VAS. The NRS has the advantage that it may be used verbally, such as by telephone.

Verbal interpretations of VAS ratings vary somewhat between patients. Among those with postoperative pain, the following categorizations have emerged: 0 to 4 mm: no pain; 5 to 44 mm: mild pain; 45 to 75 mm: moderate pain; and 75 to 100 mm: severe pain (Jensen et al., 2003). With NRS, one common classification is 1-4 mild pain, 5-6 moderate pain, and 7-10 severe pain, but some variation exists (Jones et al., 2007). When treating chronic pain, individual changes in the ratings over time may be much more important than whether the ratings reflect some predefined category.

In any pain, intensity is not constant so, patients may be asked to rate, for example, usual, least, worst, and current pain, over the preceding two weeks (Jensen et al., 1996). Pain diaries may be used to obtain more accurate pictures of average pain and of patterns of changes in pain, but practical reasons often limit their use. A European-wide survey found that 66% of the respondents with chronic pain rated their "last experienced" pain as moderate (5-7 NRS) and 34% as severe (8-10 NRS) (Breivik et al., 2006).

Number of pain areas

Persistent pain may be located in one area of the body, but is quite often experienced in more body areas. For many chronic pain patients, pain may have been confined to one body area in the beginning, but over time spreads. Risk factors for this include, for example, longer duration of pain and female gender (Gerdle et al., 2021). Obesity and sleep problems predict the maintenance of widespread pain (Mundal et al., 2014).

Mechanisms for pain's becoming more widespread are not completely clear, but abnormalities in pain processing in the central nervous system have received much attention (Woolf, 2011). In many chronic pain conditions, pathways descending from cortical structures, hypothalamus, and brainstem to the dorsal horn of the spinal cord to modulate pain signaling appear impaired. Therefore, the capacity to inhibit the upward transmission of pain signals is not at its normal level. Abnormalities in pain processing also include enhanced neuron excitability, relating to, among others, enhanced release of glutamate and Substance P at the spinal cord level (Lee et al., 2011).

When pain is more widespread, its treatment may be more difficult. In comparison to localized pain, widespread pain is experienced as more intense and frequent, there are more difficulties with daily activities, more comorbidities (such as heart disease and hypertension), and more health care seeking (Grimby-Ekman et al., 2015). Problems with sleep, such as difficulties in initiating and maintaining sleep, have been found to be predictive of the onset of widespread pain in longitudinal studies (Aili et al., 2018; Uhlig et al., 2018).

Duration of pain

Most individuals with chronic pain have suffered from pain for many years. In a European survey, the median duration was seven years (Breivik et al., 2006). Of responders in the survey, only 12% had suffered chronic pain for less than two

years. When pain has persisted longer, more co-occurring problems may develop. Longer duration of pain has been associated with, for example, more psychological distress and sleep problems (Dunn & Croft, 2006; Tang, 2008).

Finding the correct treatment for chronic pain in its early stages seems vital. If pain had lasted over three years, there was higher risk of poor treatment outcomes for patients entering tertiary pain care (Vartiainen et al., 2019).

Pain interference

Chronic pain may interfere with many basic activities in life. Patients with chronic pain often report how such activities as everyday household chores or keeping up with social relationships have become burdensome because of pain. When pain starts to disturb such different activities, it may have far-reaching consequences for both physical and psychological wellbeing. Reducing the interference of pain with different life domains is now seen as one key outcome in pain clinical trials.

Pain interference may be assessed with differing degrees of broadness, the number of domains varying between one and nine (Amtmann et al., 2010). Often, information collected from several domains is combined into a single index, but subdimensions of pain interference may also be used. One example is the division of pain interference into "activity interference" (including walking, work, general activity), and "affective interference" (including mood, relations with others, enjoyment of life, sleep) (Cleeland et al., 1996). Investigating subdimensions instead of one single index may have benefits, as subdimensions may be related to different problems which may need addressing in treatment. Also, subdimensions may be equally or unequally affected, and this information is lost if the assessed domains are reduced to a single index.

Higher pain interference is associated with less recreational exercise (Karoly & Ruehlman, 2007), weight gain in women (Eslami et al., 2017), and substance abuse (McDermott et al., 2018). Also, more interfering pain is associated with more symptoms of depression and anxiety, and more catastrophic cognitions about pain (Adams et al., 2018; Barry et al., 2013; Means-Christensen et al., 2008).

Health-related quality of life

Health-related quality of life (HRQoL) seeks to evaluate the impact of a disease on a patient (Guyatt et al., 1993). Several studies have found HRQoL to be

significantly reduced in patients with chronic pain (Keeley et al., 2008; Lillegraven & Kvien, 2007). A similar pattern of dimensions affected was found between patients participating in the KROKIETA study and pain patients in another cohort (**Figure 2**) (Vartiainen, 2018). The most affected dimensions were sleeping, engagement in usual activities, experiencing discomfort and symptoms, sexual activity, and vitality. HRQoL was significantly reduced when comparing to the general population and improving it is an important goal in pain treatment.

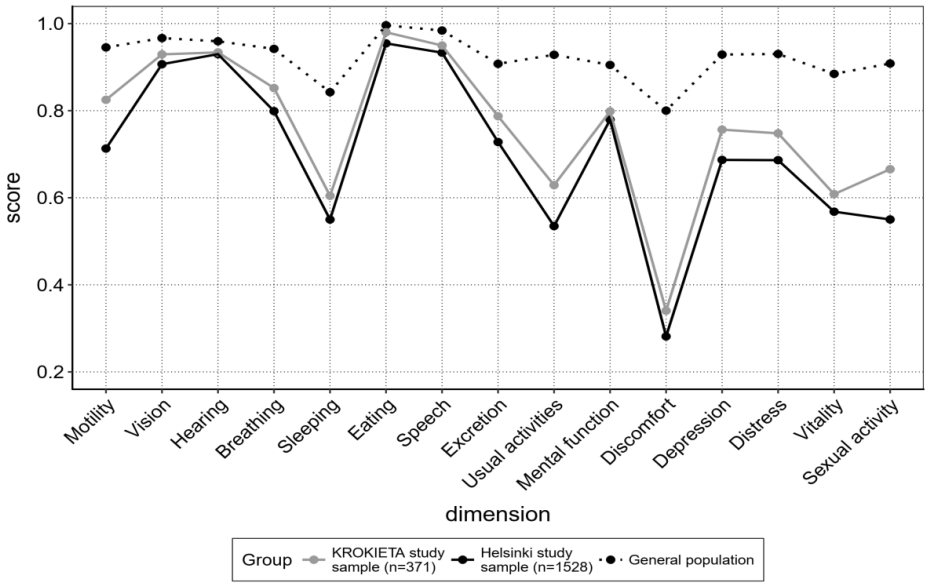

Figure 2. HRQoL dimensions in two cohorts of patients with chronic pain and in the general population (Vartiainen, 2018). Figure reprinted with kind permission of the copyright holder.

How do problems accumulate?

Many factors are now known to be risks for transition of acute to chronic pain, or for developing more severe pain. Some, such as genetics and personality traits, are pre-existing, while others may be shaped throughout the life course. The latter include worry and fear about pain, in conjunction with varying pain experiences. Other factors may come into play after pain has become chronic, such as when depressive symptoms develop alongside persistent pain. Over the developmental trajectory, factors may contribute to each other, such as when personality trait neuroticism predisposes for pain-related fear via hypervigilant behavior (Goubert et al., 2004).

Over time, understanding has grown that for enhanced treatment results we should not look only at pain diagnosis or pain variables, but also at the complexes of factors that may affect chronic pain (Edwards et al., 2016; Turk, 2005). Subgroups of patients with different trajectories for developing pain may need different approaches in treatment. Such subgroups may be based on presumed pathophysiological differences in the pain condition, such as findings about muscles and joints in temporomandibular disorder (Dworkin & LeResche, 1992) or the presence of allodynia in postherpetic neuralgia (Rowbotham et al., 1998). For acute low back pain, the STarT Back screening tool has been developed to classify patients as at low, medium, or high risk for developing chronic pain (Hill et al., 2008). Patients are classified as medium risk if there are signs of, for example, spreading of pain down the leg or reduced movement, but as high risk when four or more psychosocial items, like worrying or losing enjoyment in usual activities, are met.

Patient groups with varying profiles have been distinguished from multidimensional data sets with such data-driven approaches as cluster analysis. These studies investigate whether the data suggest similarities between certain patients, so that they may be grouped together based on these associations. This contrasts with research where patients are grouped on the basis of some pre-defined criteria, for example the level of pain-related fear (Jack et al., 2018). Data-driven approaches may uncover subgroups not previously suspected, and these groups may be more ecologically valid.

Work with the Multidimensional Pain Inventory (MPI) exemplifies a multidimensional data-driven approach to investigating subgroups of chronic pain patients. The MPI is a well-known questionnaire tool that assesses such dimensions as pain severity, social support received, and feelings of control (Kerns et al., 1985). Making use of MPI data, three subgroups of pain patients have been identified: adaptive copers (low levels of pain, limitations in

functioning, and emotional distress); interpersonally distressed (low social support, with high pain, pain interference, emotional distress, and limitations in functioning); and dysfunctional patients (high pain, pain interference, emotional distress, and limitations in functioning) (Turk & Rudy, 1988). Research on the MPI-derived subgroups and their associations to psychological measures have found the dysfunctional group to have more depression, fear-avoidance, and psychological burden than the other groups (Turk, 2005).

Among patients with spinal pain, four clusters with distinct profiles have been found (Boersma & Linton, 2005). Two showed low risk for long-term sick leave, but those with fear-avoidance tendencies showed increased risk, and those with combined fear-avoidance and depressed mood showed the greatest risk. A study examining 4,717 patients attending pain rehabilitation in Sweden also found four clusters (Backryd et al., 2018). The first showed least pain, low psychological strain, and slightly older age; the second social distress and longest pain durations; the third a combination of high pain and low social distress; and the fourth high psychosocial strain and most severe pain.

The OPPERA study investigated patients with orofacial pain using a wide range of measures, such as pressure pain thresholds, personality dimensions, and pain-related questionnaires, to study risk factors for chronic pain (Bair et al., 2016). In the study, three clusters were identified, named “adaptive”, “pain-sensitive”, and “global symptoms”. Those in the adaptive cluster were mostly free of pain hypersensitivity and scored low for psychosocial distress; pain-sensitive cluster patients showed increased muscle pain sensitivity; global symptoms cluster patients reported increased muscle pain sensitivity and greatest psychological disturbance. Reported pain severity and disability were lowest in the adaptive and highest in the global symptoms clusters. From a wide array of measures, four variables were enough to form an algorithm that assigned patients into clusters with high accuracy: muscle pain sensitivity, somatization symptoms, anxiety, and depression. The clusters have been validated in groups with mixed pain conditions as well (Gaynor et al., 2021).

When findings from studies allocating pain patients to subgroups are taken together, three or four subgroups are typically found. One group shows least pain and functional disability, one or two intermediate group(s) some particular risk factor, with the group with most severe pain showing several risks for more pain. The number of factors may be important: when more are present, they may have additive effects. For example, a subgroup of patients with both elevated pain catastrophizing and depression symptoms showed significantly more impact from pain and disability than did subgroups of patients, where only one of these was elevated (Bergbom et al., 2011; Linton et al., 2011). Also, it is important to

note that, when there is an accumulation of factors, they may influence each other as well. For example, sleep problems may increase pain, but also predispose for the development of depression, which may then contribute to experiencing more pain. These kinds of vicious cycles may be important treatment targets (**Figure 3**).

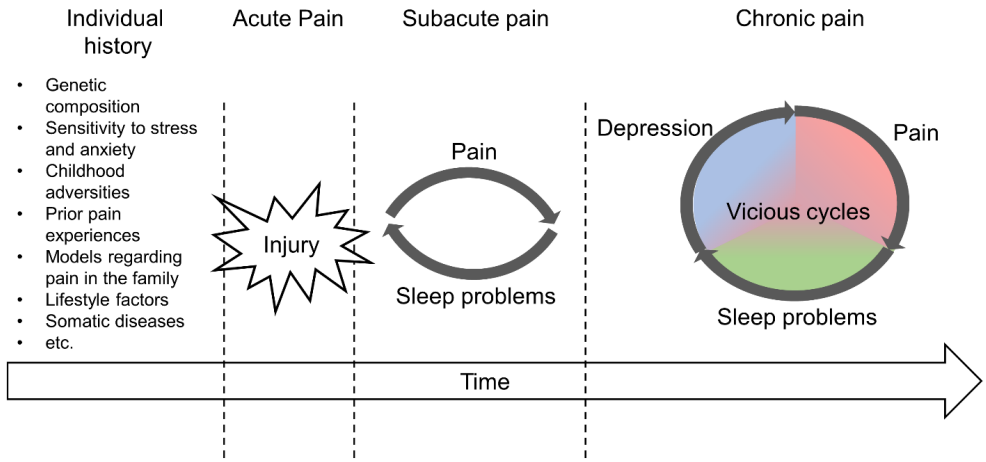

Figure 3. Individual factors may create vulnerability for developing chronic pain when confronted with a noxious event, such as injury. It must be remembered that individual factors may also serve to increase resilience and, therefore, protect from chronic pain. Many factors associated with pain are known to have bi-directional associations. A hypothesized trajectory to chronic pain might include some interacting factor having an effect in the subacute phase, as shown here with sleep problems and pain reinforcing each other. Over time, other factors may come in to play. Both pain and sleep problems may predispose for the development of depression, known to have a pain-worsening effect. Therefore, it is plausible that over time various kinds of vicious circles may form, where factors reinforce each other in a maladaptive way.

What is evident from the subgrouping studies is that, apart from pain-related factors, they have mostly concentrated on psychosocial variables. However, factors relating to lifestyle, such as obesity, exercising, and smoking, may be important as well in research on chronic pain? Also, the psychological reactions

to pain investigated have most often included pain catastrophizing, but acceptance of pain has evolved as another important area to study in chronic pain. Further, emerging areas, such as metabolomics, may suggest new mechanisms at the physiological level for patients to end up with a certain profile. As it is now evident that the development and maintenance of chronic pain is affected by factors ranging from genetics to social aspects, there is a need for research to include an ever wider spectrum of variables for understanding patient subgroups (Fillingim, 2017).

Discovering patient subgroups and examining factors associated with them may suggest mechanisms for pain development. However, an important goal is also to provide patients with more individualized treatments. Treatment matching has been suggested among patients with acute, work-related back pain (Shaw et al., 2007). The first of the two high risk groups, with severe pain and increased fear-avoidance beliefs, was suggested to benefit from interventions employing cognitive restructuring or graded activity exposure; the second, with lowered mood and stress, might be directed to CBT (cognitive behavioral therapy) interventions for depression. For the groups found with the MPI, when the adaptive group was directed to medically oriented treatment, the interpersonally distressed group to the CBT program, and the dysfunctional group to the operant group program, there were less treatment dropouts (Flor & Turk, 2011). When treatment is tailored to meet the problems of the target group, it may lead to better outcomes and adherence to treatment.

Treatment of chronic pain

Alleviating pain in chronic pain may succeed very well when the underlying disease process is capable of being targeted. Examples include the treatment of rheumatoid arthritis with biological disease-modifying antirheumatic drugs (Rein & Mueller, 2017) or joint replacement surgery (Beswick et al., 2012), which may result in significant improvements in pain. In many other chronic pain conditions, the treatment results for pain are more modest. As has been discussed, many problems may accumulate alongside pain, and these may need to be addressed in treatment as well. The goal of treatment is often more to increase function and improve quality of life than solely reducing pain intensity.

In the treatment of all health conditions, a good patient-health care provider relationship is important. However, building trust and good communication in the relationship may particularly be key factors for treatment success with complex conditions like chronic pain (Butow & Sharpe, 2013). The patient may have met several physicians and undergone different examinations without clear objective findings for the cause of the pain, potentially confusing for the patient. Therefore, empathetic contact with the patient and effective communication about the nature of chronic pain are needed and may be integral elements for patient adherence to treatment. Digitalized services have been founded to support patient education, such as Kivunhallintatalo.fi in Finland.

Multiple treatment modalities are used in the treatment of chronic pain. Pharmacological treatments vary in their efficacy (Machado et al., 2009; O'Connor & Dworkin, 2009) and often other modalities are needed as well. Psychological treatments, such as CBT, help the patient to, for example, recognize unhelpful thinking patterns, acknowledge emotional factors associated with pain, and develop better coping mechanisms. Psychological treatments have been found to have beneficial effects for disability, depression, and pain experience, although on average the effects have been small (Morley et al., 2013; Williams et al., 2020). Matching psychological treatments better to individual patients has been suggested as a way to improve results. Physiotherapy for chronic pain patients may include education on how movement and exercising promote function, and planning of graded exposure to increase movement (Semmons, 2019). In some pain conditions, physiotherapists may use techniques such as desensitization and graded motor imagery. Neurostimulation methods that may be used to treat chronic pain include both non-invasive and invasive techniques (Moisset et al., 2020). Examples of non-invasive techniques are transcutaneous electric nerve stimulation (TENS), a widely available treatment due to the affordable cost of devices and navigated repetitive transcranial magnetic stimulation (nrTMS). Spinal cord stimulation, where continuous electrical

stimulation is delivered to the dorsal column of the spinal cord via planted electrodes, is an example of an invasive technique.

Treatment of chronic pain is best accomplished in multidisciplinary pain management, where different health care professionals (for example physicians, nurses, physiotherapists, and psychologists) together participate in assessing the pain problem of the patient and providing treatment (Scascighini et al., 2008). However, most patients with chronic pain are treated in primary care, as pain clinics are not able to provide treatment for everybody. The key to good treatment of chronic pain is in the assessment of different factors relating to pain, selecting those that are most important or most amenable to change, and then tailoring treatments according to the needs of the patient.

Aims of the study

Patients who enter tertiary care are not a homogenous group, even when they have the same pain diagnosis. For some, pain is not as severe and interfering with everyday functioning than for others. We do not yet completely understand what are all the factors that contribute to this.

Chronic pain is associated with many factors relating to lifestyle, somatic health, and psychological state. This study was designed to investigate whether subgroups of patients with different pain phenotypes emerge in a cohort of patients entering tertiary pain care, and what features or problems are associated with those phenotypes. We included factors such as lifestyle, pain acceptance, somatic health, and metabolomics, which have been less researched in relation to pain phenotypes. In addition, as sleep problems appeared as significant factors in these phenotypes, they were investigated in more detail. Previous research has found factors such as pain and depression to be associated with sleep problems in pain patients, but other factors may be important as well.

More specifically the aims for the study were:

- to investigate pain phenotypes in respect to different levels of pain interference and factors associated with them,
- to use a data-driven approach to delineate patient subgroups with different pain phenotypes and investigate factors associated with them, using machine learning methods from a multifactorial data set,
- to identify metabolomic markers associated with more severe pain phenotype by investigating metabolomic markers and pathways in the pain phenotypes found in the previous study, and in two common comorbidities to severe pain, obesity and recurring sleep problems, and
- to examine how patients with recurring sleep problems differ in pain and pain-related anxiety, experienced childhood adversities, use of sleep and pain medications, self-reported diseases, and sleep disorders from those who sleep normally.

Materials and methods

Study design and participants

This is a cross-sectional study investigating pain phenotypes and associated factors among patients with chronic pain. The whole study cohort comprised 473 patients who participated in the KROKIETA study. The KROKIETA study was designed to collect data with a wide scope from patients who were beginning their treatment in tertiary pain care in Finland. Data were collected in three multidisciplinary pain clinics (in Helsinki, Turku, and Lappeenranta) and three facial pain clinics (in Oulu, Kuopio, and Tampere) between September 2013 and November 2016.

Patients in the cohort had various pain diagnoses, including low back pain, neuropathic pain, fibromyalgia, and facial pain. Patients with active cancer were excluded from the study. As patients were beginning treatment in specialized pain clinics, they would have had more than one treatment attempt in primary care, but with inadequate outcomes.

Data collected at the three multidisciplinary pain clinics were used in Studies I, II, and III, as they included measurements made by nurses at the clinic and the results of blood sample analyses (**Figure 4**). The whole KROKIETA cohort was used in Study IV.

In Study I, patients were investigated with respect to pain phenotypes that were composed of levels of "activity pain interference" and "affective pain interference". Associations between the phenotypes and variables relating to lifestyle (Body Mass Index (BMI), exercising frequency, smoking, and alcohol use risk), mood, pain-related anxiety, and pain acceptance were examined.

In Study II, data-derived pain phenotype subgroups among the patients were examined. The pain phenotypes identified were investigated using a machine learning approach for the factors that were most informative in assigning patients to the phenotypes from the broad set of variables collected in the KROKIETA study.

In Study III, metabolomic markers associated with the more severe pain phenotype were examined by machine learning methods in the pain phenotype groups found in Study II, and metabolomic analyses with respect to obesity and recurring sleep problems, two problems commonly co-occurring with more severe pain, were performed.

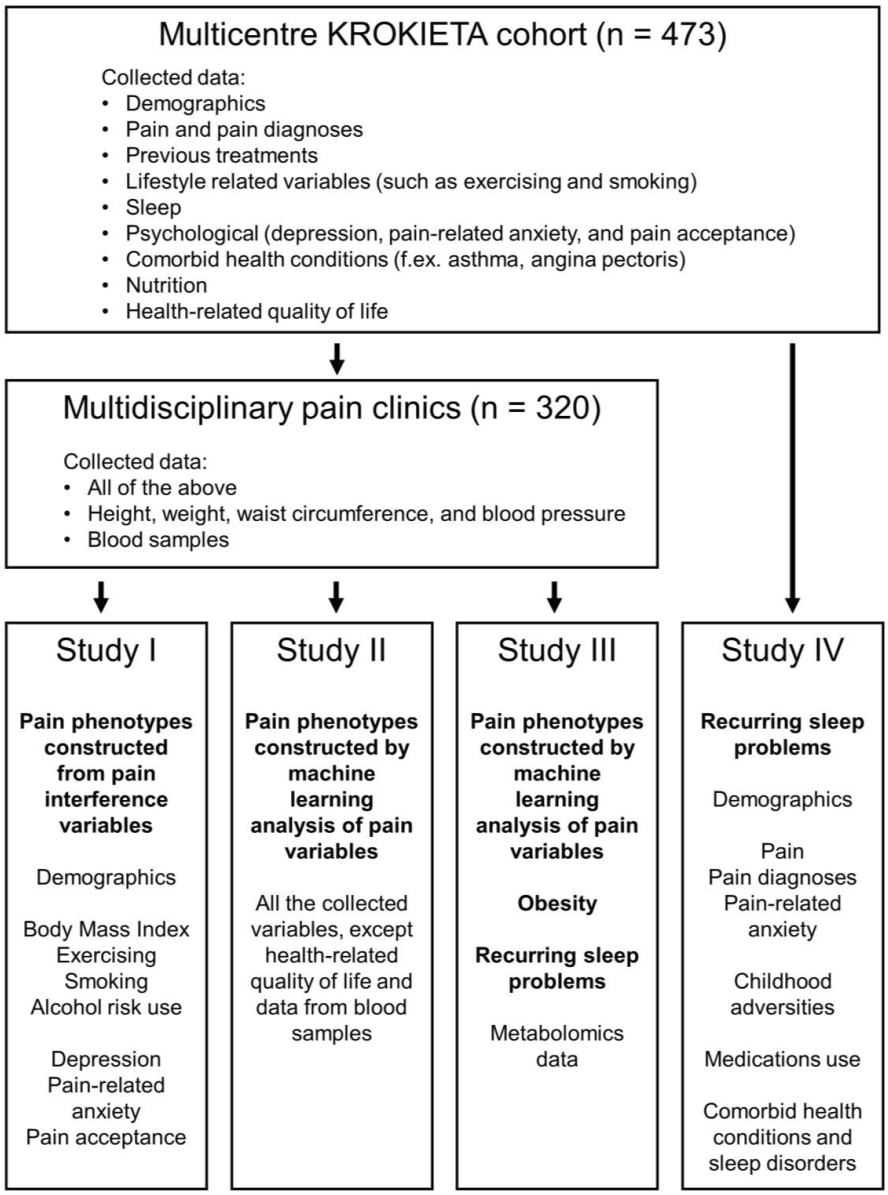

Figure 4. Main classes of variables collected in the KROKIETA study, showing which studies they were used in. [Starting points for analyses in each study shown in bold]

In Study IV, patients were divided into those with recurring sleep problems and those sleeping normally: these groups were compared for pain, pain diagnosis, pain-related anxiety, comorbidities, sleep disorders, and use of sleep and pain medications. Pain-related anxiety components were examined for importance for more disturbed sleep.

Data collection

Invitation to participate in the study was included in the mailing inviting patients to their first appointments at the pain clinic. Also included were the usual pre-appointment questionnaires on pain, health, life-style factors, and sleep, which patients completed at home. If agreeing to participate in the study, these questionnaires were included in the study data, and patients completed further study questionnaires at the clinic on psychological variables, nutrition, and substance abuse. Approximately half of invitees declined participation in the study, though the exact number of invitations sent was not recorded. During the medical examination, medications and pain diagnoses were recorded by the physician. In the three multidisciplinary pain clinics, nurses measured patients' height, weight, and blood pressure; patients were then referred to a laboratory to give blood samples.

Ethical considerations for the KROKIETA study

Patients were fully informed about the purpose of the study and what participation would involve in the mailing they received at home. It was made clear that the decision to participate or not would have no effect on their treatment at the pain clinic. Patients were not compensated for participation.

Once at the pain clinic, all patients who agreed to participate gave written informed consent. Before signing the consent form, patients had the opportunity to ask any questions about participation and were informed of their right to withdraw from the study at any time.

These measures were to ensure that all patients had enough time and information to decide on participation in the study. The study was designed so that participation involved no risk of harm to the participants, the only demand being the time to complete the study questionnaires and, for the patients at the three multidisciplinary pain clinics, to visit the laboratory to provide blood samples.

Major risks in this kind of study relate to how the collected data is handled and stored. If handled incorrectly, there is a risk that sensitive information provided by patients, including family status, medical conditions, and psychological measures, might leak out, seriously compromising the privacy of participants. All the study data were anonymized and entered into an electronic database by a study nurse, access to this being limited to researchers in the study.

Undertaking this kind of study requires resources from the participating pain clinics and, therefore, it is always necessary to assess whether the effort required is justified by the study aims. The KROKIETA study was designed to provide a wide spectrum of new information on patients with chronic pain. This information may increase understanding of how various factors are associated with chronic pain and improve treatments, justifying the use of time and resources both from participating patients and the pain clinics.

The coordinating ethics committee of the Helsinki and Uusimaa Hospital District reviewed and approved the study protocol (29/23/03/00/12).

Measures

Socioeconomic background

The pre-appointment questionnaire was used to collect socioeconomic data on age, marital status (married, cohabiting, single, divorced, or widowed), number of children, and number of people living in the participant's household. Also, participants were asked for years of education, current employment status (working full- or part-time, unemployed, on sick leave, pensioned, studying, or not working for other reasons), and household income in the previous year (pre-tax, from zero in €10,000 increments).

Pain

Pain intensity, activity pain interference, and affective pain interference were measured with the Brief Pain Inventory (BPI; (Cleeland & Ryan, 1994)). Pain intensity is measured in the BPI with four items (right now, average, least, worst); activity interference with three items (walking, work, general activity); and affective interference with four (mood, relations with other people, enjoyment of life, sleep). Mean scores of the items were used in the study. Patients were

assigned low/high status on pain interference dimensions with a cut-off of 7.00 (dimension range 0-10) (Adams et al., 2018; Von Korff et al., 1992). The psychometric properties of the scales have been found adequate in several studies (Atkinson et al., 2011; Cleeland et al., 1996; Klepstad et al., 2002).

The number of pain sites was calculated from the pre-appointment questionnaire, where the patient had indicated on a figure of a human body all the areas with pain. For the calculation, the figure was divided into eleven subareas: lower limbs, lower back, upper back, stomach, upper limbs, chest, shoulders, back of the neck, front of the neck, face, and head. The duration of pain was asked for with the following scale: less than a month, 1-3 months, 3-6 months, 6-12 months, 1-2 years, and more than two years.

Pain diagnoses and medications

Pain diagnoses were made and recorded by the physician examining the patient on their visit to the pain clinic. Categories used were: any neuropathic pain, back pain, musculoskeletal pain other than back pain, complex regional pain syndrome, headache, phantom limb pain, fibromyalgia, chronic pain syndrome, and other pain diagnosis.

Physician also recorded the pain medications in regular use, grouped for the analyses as follows: paracetamol; NSAIDs; amitriptyline/nortriptyline; venlafaxine/duloxetine; carbamazepine/oxcarbazepine/lamotrigine; gabapentin/pregabalin; codeine/tramadol; buprenorphine; oxycodone/morphine/hydromorphone/fentanyl.

Patient indicated in the Basic Nordic Sleep Questionnaire (BNSQ; (Partinen & Gislason, 1995)) the frequency of using sleep medication during the past three months on the following scale: 1 (never or less than once per month); 2 (less than once per week); 3 (on 1-2 nights per week); 4 (on 3-5 nights per week); 5 (every night or almost every night). Patients answering 4 or 5 were assigned as regularly using sleep medication. In the pre-appointment questionnaire, patients provided a list of medications that they were using: medications used for sleep were extracted from this.

Lifestyle factors

Body mass index (BMI) was calculated from the weight and height measurements recorded by nurses at the pain clinic. Obesity was defined as a BMI of 30 or over. Nurses also measured waist circumference and blood pressure. Blood pressure measurement was taken twice after a 10-minute rest, the average being used in analyses.

Patient were described as current smokers smoking regularly for at least a year and continuing. Smoking status was assessed with items from the FINRISK study (Peltonen et al., 2008).

Exercising frequency was assessed by asking the patient to estimate the number of exercise sessions per week lasting at least 20 minutes and produce at least a slight shortness of breath. Self-report measures of exercise frequency have been found consistent with electronic monitoring device measurements and results in maximal oxygen consumption tests (Kurtze et al., 2008).

Daily hours of sitting were calculated from patients' estimates of hours per day spent sitting while at work, in a motorized vehicle, and at home watching TV or at a computer.

The nutritional index was constructed from patient-reported consumption of the following food items: fruit and vegetables, fish, whole grains, dairy products, and fats. The index was the sum score of items where the consumption met the national nutritional recommendations (Fogelholm et al., 2014).

Alcohol use risk was assessed by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). AUDIT comprises ten items, which the patient answers on a scale from 0 to 4. Problematic drinking is indicated by exceeding a cut-off value of 8 (Allen et al., 1997). AUDIT has been used widely with various patient groups (Reinert & Allen, 2007). An item from AUDIT was used in the analyses for the frequency of drinking alcohol, the categories were "never", "once a month or less", "2 to 4 times a month", "2 to 3 times a week", or "4 times a week or more".

Drug abuse was inquired about with the questions "Have you ever abused drugs in your life?" and, if so, "Can you manage without the drugs for at least one week?" Based on the answers, drug abuse was assigned the labels "none", "has used", or "dependent".

Psychological measures

Pain-related anxiety was assessed by the Pain Anxiety Symptoms Scale 20 (PASS-20) (McCracken & Dhingra, 2002). The PASS-20 has four subscales to measure different anxiety components: cognitive anxiety (example item: “I worry when I am in pain”); escape/avoidance (“I avoid important activities when I hurt”); fear of pain (“When I feel pain I am afraid that something terrible will happen”); and physiological anxiety symptoms (“Pain seems to cause my heart to pound or race”). The items are answered on a 6-point scale, ranging from “never” to “always”. Studies have confirmed the factor structure of the measure (Abrams et al., 2007; Roelofs et al., 2004) and the psychometric properties of the scales have been acceptable (McCracken & Dhingra, 2002).

Pain acceptance was measured with Chronic Pain Acceptance Questionnaire (CPAQ) (McCracken, Vowles, et al., 2004). CPAQ has two subscales for assessing acceptance of chronic pain: activities engagement (orientation towards keeping up with regular life activities despite pain); and pain willingness (avoiding or controlling pain seen as ineffective strategies to handle pain). The measure comprises 20 items, which the patient answers on 7-point scales, ranging from “never true” to “always true”. Items are reverse-scored on the pain willingness scale so that on both scales increasing scores indicate increasing pain acceptance. The factor structure and psychometric properties of the scales have been confirmed (Vowles et al., 2008; Wicksell et al., 2009).

Depressive mood was assessed with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). This comprises 21 items, each yielding a score between 0 and 3. The sum scores are assigned levels of severity: mild (14-19), moderate (20-28), or severe (> 28). The BDI’s psychometric properties have also been found to be adequate among patients with chronic pain (Harris & D'Eon, 2008).

Self-rated health was scored on the scale: excellent; good; average; rather poor; very poor (Mantyselka et al., 2003; Reyes-Gibby et al., 2002).

Childhood adversities

Childhood adversities (present before the age of 16) were inquired about with a list that has been used in the Health 2000 Survey (Pirkola et al., 2005). The list included the following adversities: financial difficulties in the family, parental unemployment, parental serious illness, alcohol abuse by father, alcohol abuse by mother, father suffering from serious psychiatric condition, mother suffering

from serious psychiatric condition, serious conflicts within the family, parental divorce, own serious illness, being bullied at school.

Comorbid diseases

Patients recorded in the pre-appointment questionnaire whether there had been any physician-diagnosed comorbidities during the previous twelve months. These included: hypertension, heart failure, angina pectoris, diabetes, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, disease of joints other than rheumatoid arthritis, low back pain, depression, and other psychiatric disorder. Patients were also asked about the type of diabetes (if diagnosed by a physician), and whether they had ever had high blood pressure, had ever used antihypertensive medication, had ever had high levels of cholesterol, or were using medication for lowering cholesterol.

Sleep

Sleep problems were assessed with an index measure and a categorization criterion. The sleep problems index was the sum score of five items from the BNSQ, selected previously for research purposes based on the criteria for insomnia in the *International Classification of Diseases, Tenth Revision*, and on clinical judgement (Vartiainen et al., 2017). The items were: difficulties in falling asleep, waking during the night, frequency of using sleep medication, tiredness in the morning, and tiredness during the day. BNSQ is a standardized questionnaire to assess sleep disorders, such as problems in initiating or maintaining sleep, obstructive sleep apnea (OSA), and restless legs symptoms (RLS) (Partinen & Gislason, 1995). Symptoms over the past three months are inquired about. It measures different symptoms with the following scale: 1 (never or less than once per month); 2 (less than once per week); 3 (on 1-2 nights per week); 4 (on 3-5 nights per week); 5 (every night or almost every night).

Patients were assigned to the sleep problems categories “sleeping normally” or “recurring sleep problems” with the following procedure: subjective sleep difficulties were extracted from 15D HRQoL questionnaire (Sintonen, 2001), a standardized questionnaire validated with chronic pain patients (Vartiainen et al., 2017), and measuring 15 dimensions of health (such as mobility, mental function, and sleep). For the sleep item, patients indicate whether they are sleeping normally or experiencing mild, marked, great, or extreme sleep difficulties. Patients who responded sleeping normally were assigned as “sleeping normally”. Those patients who responded as having marked, great, or extreme

difficulties were further assessed for recurring sleep problems with core items (Tan et al., 2015; Ylikoski et al., 2015) from the BNSQ. A patient was assigned as having recurring sleep problems if there had been at least one of the following problems over the past three months: difficulty falling asleep at least three times per week; waking up at least three times per night, on at least three nights per week; extreme morning tiredness at least three times per week. In addition to these three criteria, daytime tiredness at least three times per week was needed as a mark of impact on daytime functioning.

RLS was assessed with the BNSQ item that describes RLS key symptoms (urge for moving legs when sitting or lying down; accompanying dysesthesia; movement produces relief in the symptoms; symptoms are worse during the evening or night) (Allen et al., 2003). RLS was assigned if the patient indicated these symptoms as present on three or more nights per week over the past three months. Self-reported OSA was assigned with BNSQ items according to the criteria used previously (Niiranen et al., 2016): snoring three or more nights per week, and, in addition, either loud and irregular snoring with stertorous breathing and/or occasional respiratory pauses, or respiratory pauses on one or two nights per week.

Metabolomic markers

The metabolomics analysis panel included 110 polar metabolite markers from 24 metabolite classes (Nandania et al., 2018). The metabolites were analyzed from serum. The analyses were conducted at the Finnish Institute of Molecular Medicine.

The procedure in analyzing serum samples was as follows. Ten microliters of labeled internal standard mixture were added to 100 µL of biofluid sample. Samples were allowed to equilibrate with the internal standard. Then, for protein precipitation, 400 µL of extraction solvent (1% formic acid in acetonitrile) were added. After this, samples were centrifuged (14,000 rpm, 40°C, duration 15 min). Supernatants were collected and dispensed into an OstroTM 96-well plate (Waters Corporation, Milford, USA), and then filtered on a Hamilton robot's vacuum station (vacuum at delta pressure 300–400 mbar, duration 2.5 min). Filtered sample extract (5 µL) was injected into ACQUITY UPLC system that was connected to Xevo® TQ-S triple quadrupole mass spectrometer (Waters Corporation). Chromatographic separation was conducted with 2.1 × 100 mm Acquity 1.7um BEH amide HILIC column (Waters Corporation). Temperature was kept constant at 45°C. The total run time was 14.5 min and it included 2.5 min of equilibration step at a flow rate of 600 µL/min. Initially the gradient

started with a 2.5 min isocratic step at 100% mobile phase B (ACN/ H_2O, 90/10 (v/v), 20 mM ammonium formate, pH 3), and then rising to 100% mobile phase A (ACN/H_2O, 50/50 (v/v), ammonium formate, pH 3) over the next 10 min and maintained for 2 min at 100% A and finally equilibrated to the initial conditions for 2.5 min. Sample extract (5 µL) was injected with two cycles of washes, seal wash and partial loop. The detection system, a Xevo® TQ-S MS was operated with polarity switching electrospray ionization (ESI) having capillary voltage at 0.6 kV in both polarities. The settings used throughout the analysis were: source temperature 120°C; desolvation temperature 650°C; desolvation gas high pure nitrogen (600 L/hr); collision gas argon (0.15 mL/min). In data acquisition, handling and instrument control, MassLynx 4.1 was used as software. TargetLynx software served for data processing. Labeled internal standards and external calibration curves were used in metabolite quantification.

Previous treatments

Patients were asked in the pre-appointment questionnaire about previous treatments for pain and what the result had been. The number of positive and negative treatment experiences was calculated for the analyses. Treatment was recorded as positive if the result had been mediocre to very good and as negative if the treatment had made pain worse or the result was poor. The list of treatments inquired about included: guidance on pain management, NSAID medication, muscle relaxant medication, opioid medication, neuropathic pain medication, physiotherapy, exercise regime for muscles or joints, relaxation training, increase in movement, hot or cold packs, pain management group, transcutaneous electrical nerve stimulation, acupuncture, voice massage therapy, chiropractor/naprapathy/osteopathy, traditional massage, manipulation of trigger points, laser treatment, temporomandibular joint manipulation, occlusal splint, occlusal adjustment, injections of cortisone, surgery, and treatment other than specified.

The numbers of physician visits and workdays missed due to sickness over the previous twelve months were also queried in the pre-appointment questionnaire.

Statistical analyses

Descriptive statistics are presented as counts and percentages for categorical variables, medians and inter-quartile ranges (IQR) for ordinal variables, and means and standard deviations (SD) for continuous variables.

For analyzing group differences, chi-squared tests, t-tests, Mann-Whitney U-tests, Kruskall-Wallis tests, Analysis of Variance (ANOVA), and Multivariate Analysis of Variance (MANOVA) were used, as appropriate. With multiple comparisons, statistical significance levels were adjusted by Hommel's multiple comparison procedure and Tukey's Honestly Significant Difference test (Study I), and Bonferroni's correction (Study II). When the theoretical distribution of the test statistics was unknown or when assumptions were violated (for example, of normality), the bootstrap method was used (Study I). In all analyses, values of $p < 0.05$ were considered as indicating statistical significance.

Data-derived pain phenotypes were analyzed with unsupervised and supervised machine learning methods (Studies II and III). First, pain phenotypes were searched with cluster analysis. The variables included in the clustering were pain intensity, activity pain interference, affective pain interference, number of pain sites, and duration of pain. Before clustering, the correlation structure between the variables was inspected and, if relevant correlations appeared, principal component analysis (PCA) was used to obtain uncorrelated variables. PCA used unit variance scaling including centering of the data. Principal components with eigenvalues > 1 were retained for the cluster analysis (Guttman, 1954; Kaiser, 1958). Cluster analysis used hierarchical clustering with the Ward method (Ward, 1963) and the Euclidean distance. K-means clustering (MacQueen, 1967) was used to improve the initial partition obtained from hierarchical clustering; a maximum of 10 iterations was allowed for this procedure. Repeated cluster analyses (1000 times) in random sets of bootstrap resampled original data were used to verify the number of clusters, stability of clusters, and assess cluster quality. Second, supervised methods were used to investigate variables that were most informative in assigning patients to the identified clusters. This started with the variables that were used in the clustering, continued then with all non-pain related variables (Study II), and was used again for metabolomic markers (Study III). In Study II, computed ABC analysis (Ultsch & Lotsch, 2015) was used, which allocates variables into three subsets (A, B, C). Set A contains "the important few" variables, i.e. variables that produce maximum yield with minimum effort (Juran, 1975). This was repeated 1000 times on randomly resampled data and the most common size of set A was chosen as set size. Variables in set A were then used for constructing classifiers. In building classifiers, two algorithms were used: Classification and Regression Trees (CART) and Partial Decision Trees (PART). The aim was to obtain simple and understandable rules in the classifiers. Classifier performance was evaluated by balanced accuracy, sensitivity, specificity, positive and negative predictive values, precision, and recall. Classifiers were trained with randomly permuted data to control possible overfitting; i.e. using these data, the classifiers should not perform better than guessing (balanced accuracy equal or close to 50%). In Study IV, the Boruta

approach was used for selecting the important metabolomic markers (Kursa & Rudnicki, 2010). Eight different classifier algorithms were then used to build classifiers: Random Forests (RF), Support Vector Machines (SVM), adaptive boosting, k-nearest neighbors, Conditional Interference Trees (CTREE), CART, the hierarchical tree-based C5.0 classifier, and PART.

In Study III, univariate analysis of metabolomic markers was conducted with t-test and Fold Change (FC). Quantitative metabolite set enrichment analysis (MSEA) algorithms were used for pathway enrichment analyses. These analyses were made using the web-based metabolomics data processing tool MetaboAnalyst (version 5.0, accessed on September 1, 2021) (Pang et al., 2021). In the pathway enrichment analyses, KEGG metabolite IDs and the Small Molecule Pathway Database were used. A cut-off of two entries in metabolite sets was used. Hits/expected was calculated for enrichment ratio.

In Study IV, a series of cumulative odds ordinal regression models were constructed when assessing the role of pain-related anxiety components in recurring sleep problems. In these models, the assumption of proportional odds was assessed by a full likelihood-ratio test, which compared the fitted model to a model with varying location parameters. The dependent variable comprised three groups (those with recurring sleep problems; the intermediate group with mild or infrequent sleep problems; those sleeping normally). Pain-related anxiety components were first inspected individually as predictors in the model and the resulting model fit indices (Nagelkerke pseudo R^2) were used for comparing components for their importance to more sleep disturbance. Higher model fit index indicated higher importance (Lacy, 2006). Then, the component with the highest model fit index (physiological anxiety) and the variables pain intensity, number of pain sites, and pain duration were used to construct a full model. The pain variables were included in the full model on theoretical grounds as they have previously shown association with sleep problems. The chosen pain-related anxiety component was further evaluated in the full model by individually adding the remaining three pain-related anxiety components to the model and inspecting whether the chosen component would stay as a statistically significant predictor in the model.

The statistical package used for the analyses in Study I was Stata 1.15 (StataCorp LP, College Station, TX, USA), in Studies II and III R software package version 3.6.1 for Linux, and in Study IV SPSS 25.0 software package for Windows (IBM Corp. Released 2017. Armonk, NY; USA).

Data preprocessing

Data were inspected for missing answers and variable ranges checked for abnormal values.

In Study I, missing values were imputed by mean imputation to BPI activity pain interference and affective pain interference scales if only one or two items were missing; if more missing items, the data were declared missing.

In Study II, patients were first screened for intact data on pain-related variables, key demographics, and psychological variables, and those with missing data removed from analysis. For the machine learning analyses, missing values for variables with less than 20% missing were imputed by median for ordinal or continuous variables, and by mode for nominal data; if more than 20% of values were missing, the variable was excluded from the analysis.

In Study III, missing values for metabolites where less than 20% were missing were imputed by non-parametric imputation by Random Forests (Breiman, 2001); metabolites with more than 20% missing values were excluded from the analysis. To normalize metabolomics data, log-transformation and autoscaling were used.

In Study IV, missing values were imputed by median to the BNSQ items used for classification of sleep problems if only one or two items were missing; if more, the overall classification was considered missing.

Results

Characteristics of the patients

In the whole KROKIETA cohort, approximately two out of three patients were women (**Figure 5**). The mean age in the cohort was 47.0 (SD: 13.8, range 18-81). Of the patients, 64.5% were married or cohabiting and 75.9% had at least one other person living in the household.

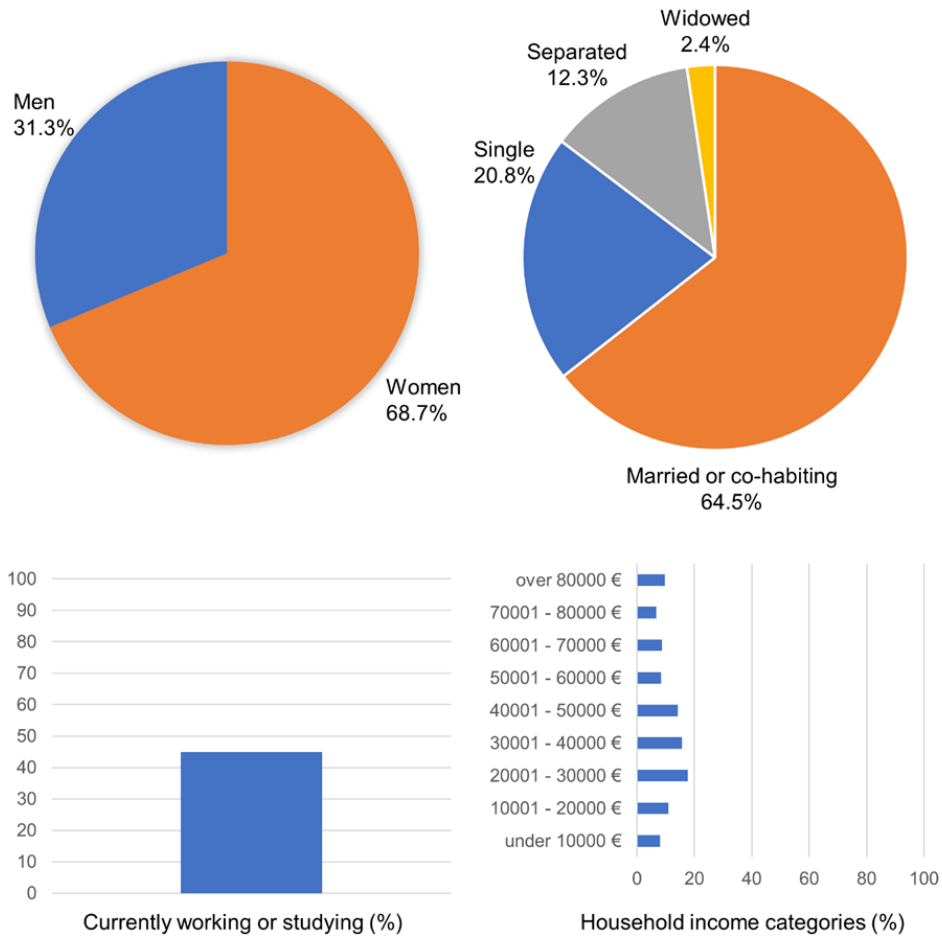

Figure 5. Demographic data from the whole KROKIETA cohort (n = 473).

The mean number of years of education was 13.4 (SD: 3.79). Currently working or studying full-time were 45.0%. The median category for previous year household income was €30,001 – 40,000. Patients in the three multidisciplinary pain clinics subcohort were similar to the whole cohort in these demographics (**Table 2**)

Women, n (%)	206 (64.4)
Age, mean (SD)	45.9 (13.4)
Education years, mean (SD)	13.3 (3.46)
Marital status, n (%)	
Married or cohabiting	195 (60.9)
Single	76 (23.8)
Separated	35 (10.9)
Widowed	7 (2.2)
Living alone, n (%)	82 (25.6)
Currently working or studying, n (%)	137 (42.8)
Household income category, median (IQR)	4.0 (4.0)

Table 2. Socioeconomic factors for patients attending three multidisciplinary pain clinics (n = 320).

Pain interference and associated factors (Study I)

Investigation of pain phenotypes derived from levels of pain interference involved 311 patients (age, mean (SD) 45.8 (13.3); women n, (%) 205 (65.9)), as data on BPI were missing for nine patients. The pain phenotypes were comprised the dimensions "activity pain interference" and "affective pain interference", using a pre-defined cut-off of 7.0. Thus, patients were divided to four pain phenotype groups: A (low on activity dimension, but high on affective dimension; n = 38, 12% of those studied), B (high on both dimensions; n = 119, 38%), C (low on both dimensions; n = 117, 38%), and D (high on activity dimension, but low on affective dimension, n = 37, 12%) (**Figure 6**).

There were no differences between the groups in age, sex, number of years of education, in the duration of pain > 2 years, or in scores for alcohol use risk (AUDIT questionnaire).

Group C (low on both interference dimensions) showed mean (SD) BMI of 27.0 (6.0) (mean BMI in overweight category), mean (SD) exercising frequency of 2.4 (1.7) times per week (11% reported inability to exercise), and current smoking was reported by 31% in the group. Mean BDI-II total score in the group was 11.7 (SD 7.5), which indicated no depression on average.

Group A (low activity interference, high affective interference) differed from Group C in that on average patients showed more depressive symptoms (BDI-II total score mean (SD) 17.7 (7.3), $p < 0.001$), pain-related cognitive anxiety symptoms 2.8 (95% CI 0.7 to 4.8) scale scores higher in the group ($p = 0.02$), and less pain acceptance in activities engagement 9.7 (95% CI: 5.5 to 13.8) scale scores lower in the group ($p < 0.001$).

Group D (high activity interference, low affective interference) differed from Group C in that on average patients were heavier (BMI mean (SD) 31.0 (7.3), $p < 0.001$), exercised less often (exercising frequency mean (SD) 1.5 (1.6), $p < 0.001$), and showed more escape/avoidance in pain-related anxiety 3.7 (95% CI: 1.7 to 5.8) scale scores higher in the group ($p = 0.001$). Group D did not differ in pain acceptance from Group C.

Group B (high on both dimensions) differed from Group C in that on average patients were heavier (BMI mean (SD) 29.9 (6.1), $p < 0.001$), exercised less often (exercising frequency mean (SD) 1.2 (1.7), $p < 0.001$; and 47% in the group reporting inability to exercise), were more often current smokers (49% of the group, $p = 0.045$), and showed more depressive symptoms (BDI-II total score mean (SD) 20.3 (10.6), $p < 0.001$). There was more pain-related anxiety in all assessed components: mean cognitive anxiety was 4.1 (95% CI: 2.7 to 5.6),

escape/avoidance 4.0 (95% CI: 2.6 to 5.3), fear of pain 4.6 (95% CI 3.1 to 6.1), and physiological anxiety 4.3 (95% CI 2.8 to 5.8) scale scores higher (all differences $p < 0.001$). Patients in the group had less pain acceptance than those in Group C: activities engagement was 12.7 (95% CI: 9.6 to 15.7) and pain willingness 6.5 (95% CI 4.4 to 8.5) scale scores lower (both differences $p < 0.001$).

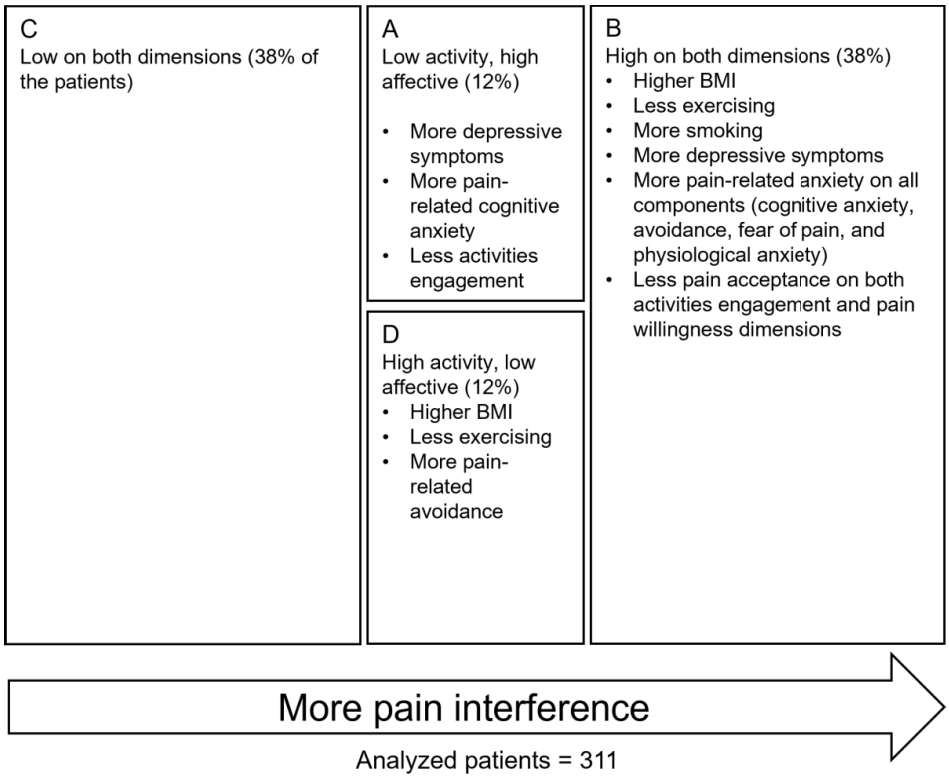

Figure 6. Different subgroups according to their pain interference phenotype. Within the group are displayed factors that differed statistically significantly with respect to the group with low pain interference on both dimensions.

As recurring sleep problems and obesity would come into focus in the following studies, a re-analysis of the data was made to investigate the proportions of patients in the pain interference phenotype groups sleeping normally or having recurring sleep problems, and who were obese (**Figure 7**).

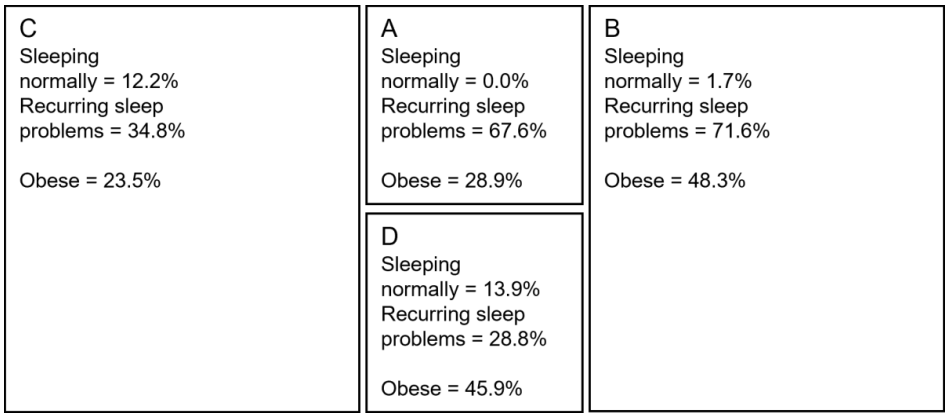

Figure 7. Percentages of those sleeping normally or with recurring sleep problems, and with obesity in different pain interference phenotype groups.

Data-driven pain phenotypes and associated factors (Study II)

The data-driven analysis of pain phenotypes included data from 277 patients (age, mean (SD) 45.7 (13.2), women n, (%) 181 (65.3)), after removing those with incomplete data in pain-related factors, key demographics, and psychological variables.

The data-driven analysis of pain phenotypes resulted in a three-cluster solution. For the analysis, the correlation structure between the variables that the analysis was based on was first investigated. Pain intensity, affective pain interference, and activity pain interference showed moderate or higher correlations (pain intensity and affective pain interference Spearman's $\rho = 0.58$; pain intensity and activity pain interference $\rho = 0.59$; and affective and activity pain interference $\rho = 0.65$). The number of pain sites was weakly correlated with duration of pain ($\rho = 0.2$), affective pain interference ($\rho = 0.11$), and pain intensity ($\rho = 0.16$). Due to significant correlations between the variables, a PCA was performed to obtain uncorrelated variables. This resulted in two principal components with eigenvalues > 1, first with main loadings from pain intensity, affective pain interference, and activity pain interference (explaining 45.9% of total variance in the analyzed variables), and second with main loadings from number of pain sites and duration of pain (explaining 22.9% of total variance). The subsequent cluster analysis was performed on these PCs using hierarchical clustering with Ward's method and the Euclidean distance, and the clusters were further consolidated by using k-means clustering to improve the initial partition. A three-cluster solution was the most common solution among 1000 retries with randomly resampled data and with the 30 statistical indices used.

There were 81 patients in cluster #1, 109 in cluster #2, and 87 in cluster #3. Clusters showed difference in all pain-related factors: pain intensity (Kruskall-Wallis test; $x^2 = 111.86$, df = 2, $p < 2.2 \cdot 10^{-16}$); activity pain interference ($x^2 = 132.52$, $p < 2.2 \cdot 10^{-16}$), affective pain interference ($x^2 = 157.11$, $p < 2.2 \cdot 10^{-16}$); number of pain sites ($x^2 = 87.314$, $p < 2.2 \cdot 10^{-16}$); and duration of pain ($x^2 = 60.258$, $p < 2.2 \cdot 10^{-16}$). Cluster #1 was with least severe pain, cluster #2 in the middle, and cluster #3 with most severe pain (**Figure 8**).

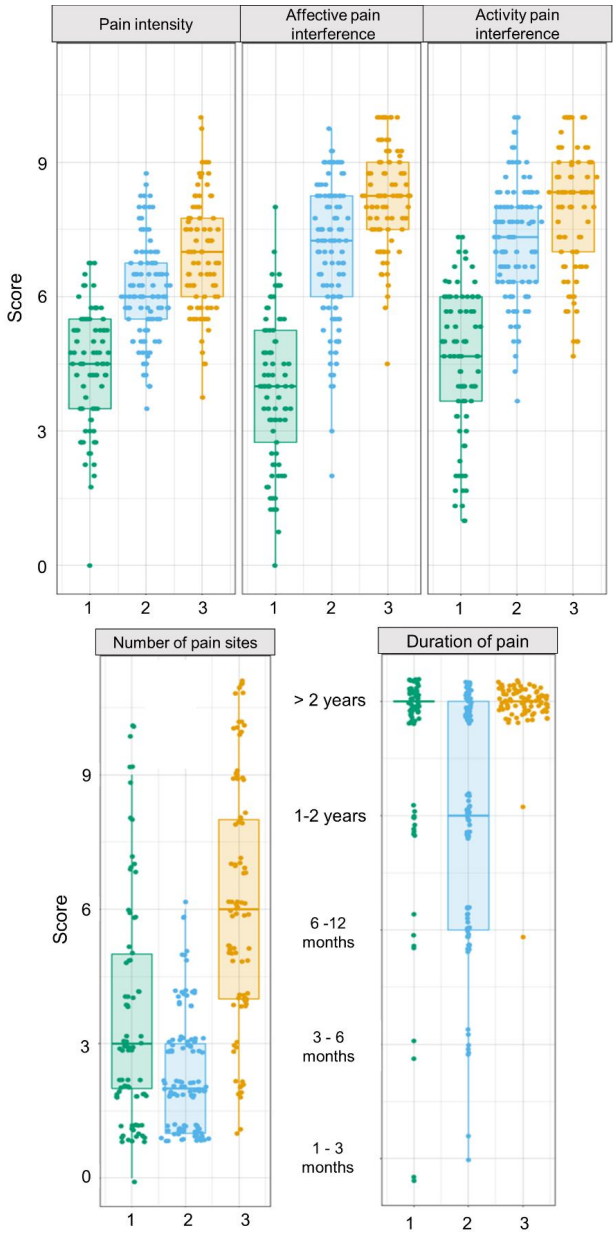

Figure 8. Pain variables in the three clusters found in Study II. Box and whisker plots show median, quartiles, and minimum and maximum values for the variables. Individual data points, shifted slightly by a random value to avoid overlaps, are laid over the boxplots.

The key factors for interpreting the clusters found were searched with feature selection methods. Among the pain-related variables used for clustering, it was found that the size of the A set ("the few most important factors") in ABC analysis using three different algorithms (CART, PART, and RF) was most often two. These factors were affective pain interference and number of pain sites. The CART algorithm was used in the subsequent analyses to build class assignment rules, because it provided simplest solutions, while also performing well with respect to the other algorithms. Using CART, affective pain interference was in set A 693 times in the 1000 repeated runs, while the number of pain sites was in set A 637 times.

When investigating the key factors among the rest of the 59 variables included in the study, the analysis concentrated on the two clusters in the extremes (#1 lowest pain intensity and pain interference; #3 high pain intensity and pain interference, and greatest number of pain sites) because, for the cluster in between, the balanced accuracy occasionally included 50% for the classifiers, which meant that the classifier was not doing better than guessing. In the analysis, the extreme clusters were contrasted against the other two clusters. In these analyses, the variables "use of blood pressure medication", "nutritional index", "drug abuse", and "alcohol consumption frequency" were excluded as they had more than 20% missing values. The size of the A set for both clusters was most often three. For cluster #1, the key factors were the sleep problems index (638 times in set A), fear of pain (406 times), and lower systolic blood pressure. For cluster #3, the key factors were the sleep problems index (439 times), fear of pain (401 times), and poorer self-rated health.

The variables selected for the classifiers are shown in **Figure 9**. The CART classifiers built from pain-related variables (affective pain interference and number of pain sites) succeeded with median balanced accuracies of 86.6% (cluster #1), 70.9% (cluster #2), and 83.7% (cluster #3). For the non-pain-related variables, the median balanced accuracies were 64.5% (cluster #1) and 64.6% (cluster #3).

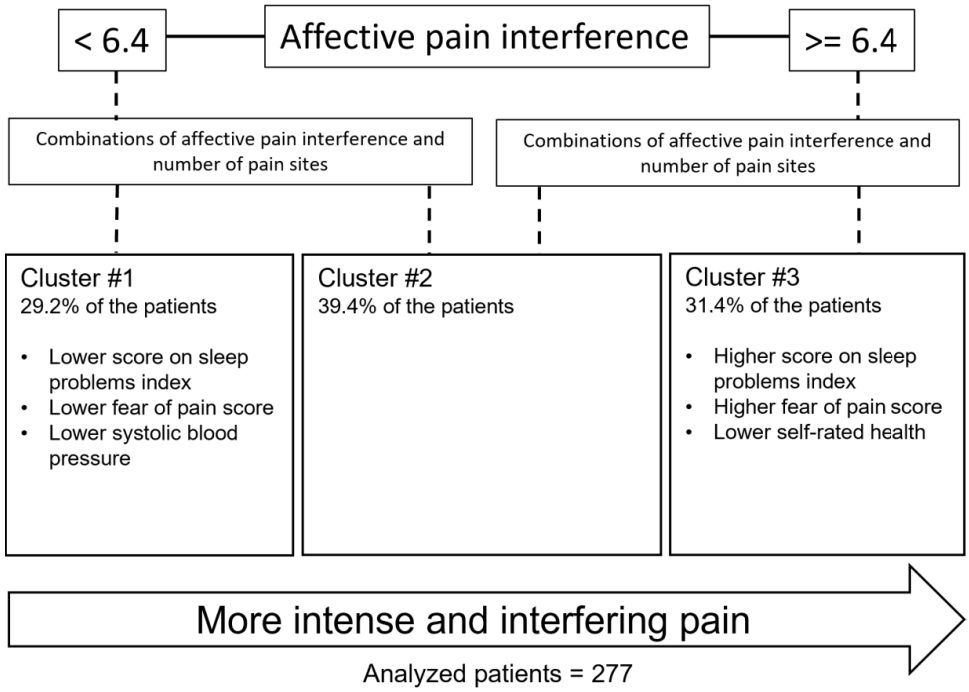

Figure 9. Variables selected as the most informative with respect to the identified clusters and used to build the classifiers. The classifier that was composed of selected pain-related variables (affective pain interference and number of pain sites) started from affective pain interference score, which already decided whether assignment was heading towards cluster #1 or cluster #3. Combinations of affective pain interference and number of pain sites decided after that whether the assignment was for the extreme pain phenotype or the one in the middle. In the boxes for clusters #1 and #3 are shown variables in the classifiers built from the non-pain-related variables.

Metabolomic markers associated with the more severe pain phenotype (Study III)

Machine learning methods were also used to examine metabolomic markers that may be important for the more severe pain phenotype by using the established clusters in Study II. In this analysis, cluster #1 was compared to the other two clusters, i.e. the rest in the cohort with more severe pain. Blood samples were available from 193 patients (women n, (%) 122 (63.2)) analyzed in the clustering. Of them, 57 belonged to cluster #1. The metabolomics panel included 110 markers but 13 had more than 20% missing values and were therefore excluded from the analysis.

A feature selection method, this time the Boruta approach, indicated five metabolomic markers as definitely important: adenosine monophosphate (AMP), asparagine, deoxycytidine, glucuronic acid, and propionylcarnitine. Tentatively important were cysteine and nicotinamide adenine dinucleotide (NAD). Subsequently, when eight different classifier-building algorithms were used, it emerged that all these seven markers were needed to build a classifier to distinguish cluster #1 from the rest in the cohort (**Figure 10**). Based on this

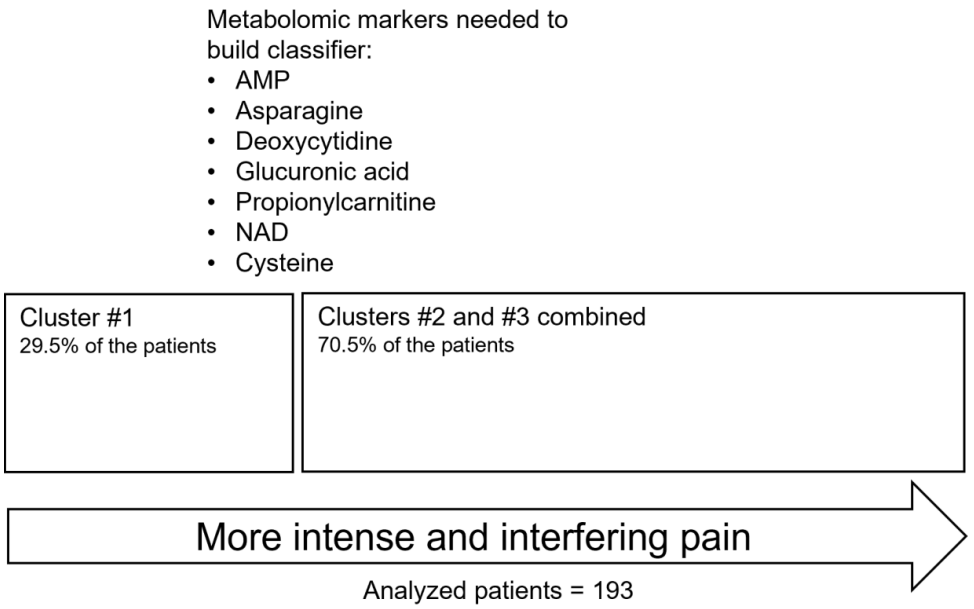

Figure 10. Metabolomic markers assigned as important in the machine learning analysis in relation to data-derived pain phenotypes.

finding, these seven markers were all considered as important. The median classification accuracy for the Random Forest classifier was 59.1%.

The seven metabolomic markers were again investigated with statistical comparisons between cluster #1 and the rest in the cohort. Two markers showed statistically significant differences, AMP ($W = 3057$, $p = 0.0208$) and glucuronic acid ($W = 3163$, $p = 0.04415$), Both markers were lower in cluster #1 than in the rest of the cohort. A tendency toward statistical significance ($p < 0.01$) was observed for two markers, asparagine and propionylcarnitine. It should be noted that these statistical comparisons did not include corrections for multiple comparisons and, if used, differences would not appear significant.

The investigation of metabolomic markers in relation to the more severe pain phenotype continued with analyses of two problems commonly co-occurring with more severe pain: obesity and recurring sleep problems. These analyses were made with the web-based metabolomics analytics tool MetaboAnalyst, which provided univariate analyses of metabolomic markers using t-tests of Fold Change, and quantitative metabolite set enrichment analysis to find associations with defined metabolite sets in the SMPDB.

For obesity, univariate analysis elucidated statistically significant differences in 23 different metabolomic markers (**Table 3**). Eleven belonged to amino acids, and the rest to acylcarnitines, alkylphenylketones, sugar acids, purine nucleosides, bile acids, (5'→5')-dinucleotides, and pyrimidine nucleosides. For recurring sleep problems, seven markers with statistical difference emerged (**Table 4**): six belonged to amino acids and seventh was choline.

Metabolomic marker	FC	$\log_2$(FC)	p	$-\log_{10}$(p)
Amino acids				
Glutamate	1.1076	0.14741	7.385e-05	4.1317
Asparagine	0.97389	-0.038168	0.00060007	3.2218
Glycine	0.96871	-0.045858	0.0013494	2.8698
Tyrosine	1.0282	0.040139	0.0018034	2.7439
Valine	1.0209	0.029846	0.0019009	2.721
Alanine	1.0211	0.030172	0.0030191	2.5201
Isoleucine	1.0301	0.042839	0.0061138	2.2137
Symmetric dimethylarginine	0.88753	-0.17213	0.0066633	2.1763
Creatinine	0.98053	-0.028359	0.012257	1.9116
Creatine	1.0483	0.068066	0.013068	1.8838
Citrulline	1.0376	0.053191	0.02039	1.6906
Acylcarnitines				
Isovalerylcarnitine	1.155	0.2079	0.0053701	2.27
Propionylcarnitine	1.1127	0.15403	0.0097422	2.0113
Hexanoylcarnitine	1.1638	0.21882	0.020064	1.6976
Alkylphenylketones				
Hydroxykynurenine	1.2256	0.29344	0.009839	2.007
Kynurenine	1.0443	0.062527	0.034	1.4685
Sugar acids				
Glucuronic acid	1.1245	0.16928	0.011138	1.9532
Purine nucleosides				
Inosine	1.2492	0.32101	0.02406	1.6187
Adenosine	1.2961	0.37413	0.032691	1.4856
Guanosine	1.4269	0.51284	0.047952	1.3192
Bile acids				
Chenodeoxycholic Acid	1.0856	0.11852	0.024663	1.6079
(5'→5')-dinucleotides				
NAD	0.73752	-0.43924	0.036641	1.436
Pyrimidine nucleosides				
Cytidine	1.0567	0.079523	0.047004	1.3279

FC = Fold change

Table 3. Results of univariate analyses of statistically significant metabolites with respect to obesity. Negative $\log_2$(FC) values indicate marker decreased in those with obesity, and positive increased.

Metabolomic marker	FC	$\log_2$(FC)	p	$-\log_{10}$(p)
Amino acids				
Serine	0.98126	-0.027298	0.017081	1.7675
Symmetric dimethylarginine	0.91811	-0.12326	0.021126	1.6752
Homocysteine	0.85203	-0.23103	0.021403	1.6695
Dimethylglycine	0.9218	-0.11747	0.028466	1.5457
GABA	0.87712	-0.18915	0.03143	1.5027
Asymmetric dimethylarginine	0.91048	-0.1353	0.031587	1.5005
Choline	0.96778	-0.047256	0.049881	1.3021

FC = Fold change

Table 4. Results of univariate analyses of statistically significant metabolites with respect to recurring sleep problems. Negative $\log_2$(FC) values indicate marker decreased in those with recurring sleep problems, and positive increased.

Pathway enrichment analyses elucidated metabolite pathways in the SMPDB that obesity and recurring sleep problems showed most relation with (**Table 5**). Obesity showed association with pathways related to amino acid metabolism and energy production, among others. Recurring sleep problems showed association with pathways related to, for example, phospholipid biosynthesis and methionine metabolism.

To investigate which metabolomic markers might be especially important for the more severe pain phenotype, the results from the machine learning and pathway enrichment analyses were examined together. In the top 25 metabolomic pathways associated with obesity appeared four markers that machine learning analyses showed to be important: NAD (in 18 pathways), AMP (11), cysteine (4), and asparagine (2). In respect of recurring sleep problems, three markers appeared: NAD (in 17 pathways), AMP (4), and cysteine (2). AMP, NAD, and cysteine therefore appeared in the results of all these analyses.

Obesity	Recurring sleep problems
Alanine metabolism	Catecholamine biosynthesis
Glutathione metabolism	Homocysteine degradation
Propanoate metabolism	Thyroid hormone synthesis
Glucose-Alanine cycle	Methionine metabolism
Ammonia recycling	Pyrimidine metabolism
Glutamate metabolism	Oxidation of branched chain fatty acids
Aspartate metabolism	Betaine metabolism
Tyrosine metabolism	Phenylalanine and tyrosine metabolism
Folate metabolism	Glutamate metabolism
Arachidonic acid metabolism	Inositol metabolism
Tryptophan metabolism	Tyrosine metabolism
Arginine and proline metabolism	Inositol phosphate metabolism
Phenylalanine and tyrosine metabolism	Phosphatidylinositol phosphate metabolism
Amino sugar metabolism	Phospholipid biosynthesis
Warburg effect	Fatty acid biosynthesis
Urea cycle	Taurine and hypotaurine metabolism
Cysteine metabolism	Mitochondrial beta-oxidation of saturated short-chain fatty acids
Histidine metabolism	Fatty acid metabolism
Valine, leucine, and isoleucine degradation	Mitochondrial beta-oxidation of saturated long-chain fatty acids
Malate-aspartate shuttle	Tryptophan metabolism
Nicotinate and nicotinamide metabolism	Biotin metabolism
Purine metabolism	Phosphatidylcholine biosynthesis
Bile acid biosynthesis	Phosphatidylethanolamine biosynthesis
Beta-Alanine metabolism	Ketone body metabolism
Porphyrin metabolism	Butyrate metabolism

Table 5. Metabolomic pathways that pathway enrichment algorithm selected as the top 25 enriched metabolite sets with respect to obesity and recurring sleep problems (further details in the published manuscript).

Sleep problems and associated factors (Study IV)

Sleep problems were investigated in the whole KROKIETA cohort. Patients with recurring sleep problems were compared to patients sleeping normally to detect factors that might be important for sleep in patients with chronic pain. For these analyses, 458 patients (age, mean (SD) 47.0 (13.8); women n, (%) 318 (69.4)) were available, after excluding those with more than two missing answers on the BNSQ items that were used for sleep problem classification. From these, 199 (43.4%) were defined as having recurring sleep problems, 61 (13.3%) were sleeping normally and 198 (43.2%) remained in between these groups with mild or infrequent sleep problems.

Comparing sociodemographic factors between those with recurring sleep problems and those sleeping normally, the groups were similar in age, sex, and years of education. However, those with sleep problems were less often working or studying (38.1% vs 59.0%, $p = 0.004$) and, among these, it was more common to be living alone (28.1% vs 14.8%, $p = 0.04$).

For pain, those with sleep problems reported higher pain intensity than those sleeping normally (mean, (SD) 6.3 (1.5) vs 4.2 (2.2), $p < 0.001$), with a greater number of pain sites (median, (IQR) 4.0 (5.0) vs 2.0 (4.0), $p < 0.001$), while pain had more often lasted over two years (78.1% vs 61.0%, $p = 0.01$). Those with sleep problems had a diagnosis of back pain more often than those sleeping normally (26.5% vs 10.3%, $p = 0.01$), but less often a diagnosis of facial pain (19.9% vs 63.8%, $p < 0.001$).

Pain-related anxiety was higher in all assessed components among those with sleep problems than those sleeping normally: cognitive anxiety (mean, (SD) 15.4 (5.1) vs 10.8 (6.9); escape/avoidance (13.4 (4.9) vs 9.7 (6.5); fear of pain 10.5 (5.7) vs 6.7 (5.4); and physiological anxiety 9.7 (5.3) vs 4.7 (5.0) (all $p < 0.001$).

When comparing the groups for experience of childhood adversities, there were no differences for any individual adversity or for the median number of adversities experienced. However, having experienced five or more adversities was more common among those with sleep problems than those sleeping normally (15.3% vs 5.1%, $p = 0.04$). Generally, adversities were common in the whole cohort, with 75.3% having experienced at least one childhood adversity, the most usual being parents' divorce (29.0%), having been bullied at school (28.8%), and own serious illness (12.7%).

Those with sleep problems reported multiple comorbid health conditions more than those sleeping normally (**Figure 11**). Differences were found in the

incidences of angina pectoris ($p = 0.04$), asthma ($p = 0.001$), non-RA joint disease ($p = 0.04$), low back problems ($p < 0.001$), and depression ($p < 0.001$).

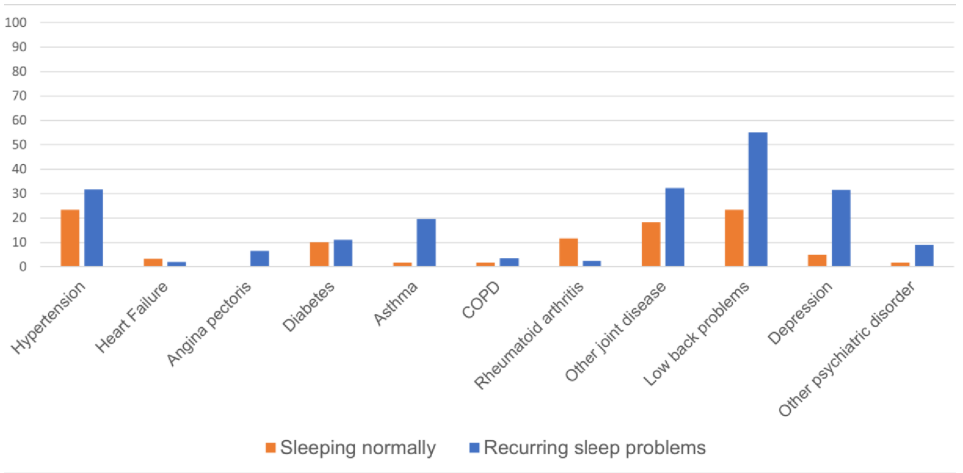

Figure 11. Percentages of self-reported diseases in those sleeping normally and those with recurring sleep problems.

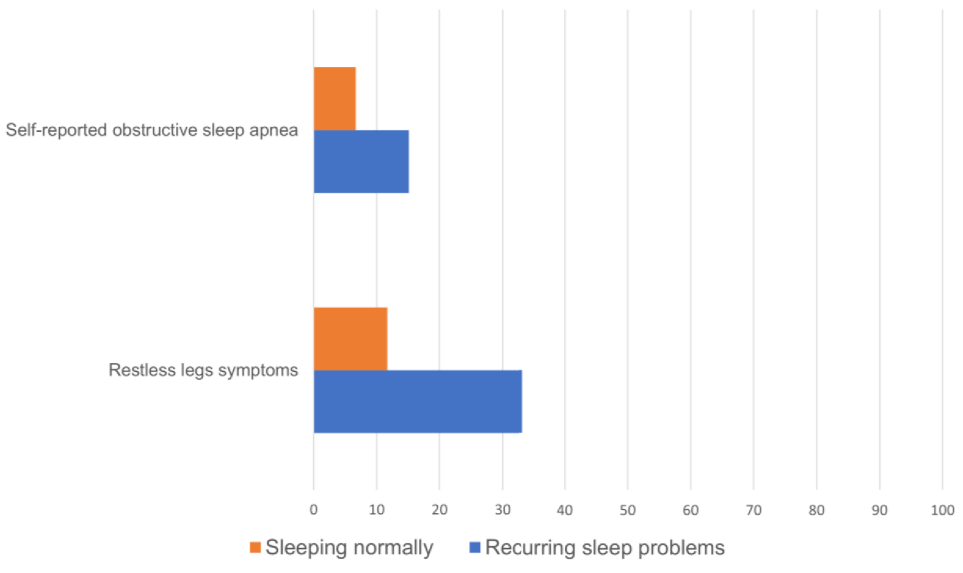

Figure 12. Percentages of sleep disorders in those sleeping normally and those with recurring sleep problems.

There were no differences in incidences of hypertension, heart failure, diabetes, chronic obstructive pulmonary disease, and psychiatric disorders other than depression. RA was more common among those sleeping normally than those with sleep problems ($p = 0.01$).

Restless legs symptoms were more common in those with sleep problems than those sleeping normally ($p = 0.001$) (**Figure 12**). OSA was reported by 15.1% of those with sleep problems and 6.7% of those sleeping normally, but the difference was not statistically significant ($p = 0.12$).

Patients with recurring sleep problems reported more regular use of sleep medications than those sleeping normally (27.8% vs 3.3%, $p < 0.001$). Of sleep-affecting medicines, patients with recurring sleep problems reported most often using zolpidem and melatonin, both used by 12.6% of these patients. Patients with sleep problems used more pain medications as well (**Figure 13**).

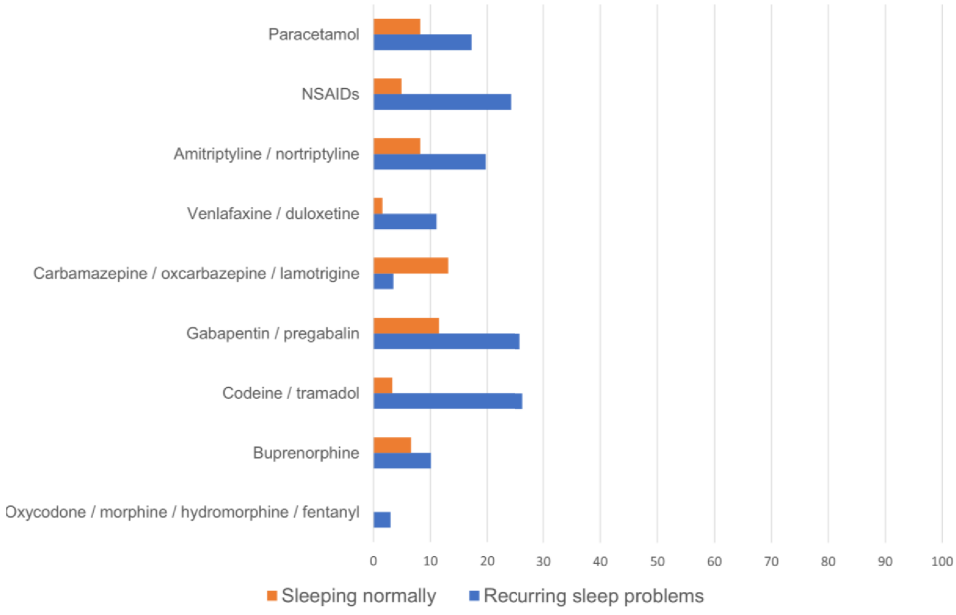

Figure 13. Percentages of pain medications in regular use in those sleeping normally and those with recurring sleep problems.

Medications more often used by them when comparing to those sleeping normally were codeine-combinations/tramadol ($p < 0.001$), gabapentin/pregabalin ($p = 0.02$), NSAIDs ($p = 0.001$), amitriptyline/nortriptyline ($p = 0.04$), and venlafaxine/duloxetine ($p = 0.02$). In the use of paracetamol, buprenorphine, and oxycodone/morphine/hydromorphine/fentanyl, there were no differences. Those sleeping normally reported more often using carbamazepine/oxcarbazepine/lamotrigine than those with sleep problems ($p = 0.01$).

We were still interested in investigating the importance of individual pain-related anxiety components (cognitive anxiety, escape/avoidance, fear of pain, and physiological anxiety) in more disturbing sleep problems. This analysis was made in the whole cohort with a series of ordinal logistic regressions. When the components of pain-related anxiety were individually inspected in relation to the level of sleep problems (dependent variable), it was physiological anxiety that showed the highest model fit value (Nagelkerke pseudo $R^2 = 0.137$). After this, a full model was constructed with pain intensity, number of pain sites, pain duration > 2 years, and physiological anxiety as independent variables. The dependent variable was statistically significantly predicted by the model over and above the intercept-only model ($x^2(4) = 111.278$, $p < 0.001$; Nagelkerke pseudo $R^2 = 0.265$). When the other components (cognitive anxiety, escape/avoidance, or fear of pain) were added one by one to the model beside physiological anxiety, none of them appeared statistically significant. Therefore, based on this and the best fit value on its own, it was concluded that physiological anxiety appeared as statistically the most important pain-related anxiety component in more disturbing sleep problems.

Discussion

Main findings

Patients with the most severe pain phenotypes in these studies show a number of problems that may have contributed for pain becoming so severe or why it is maintained that way. In Study I, those patients who had high pain interference on both activity and affective dimensions showed more weight problems, lack of exercise, smoking, depressive symptoms, pain-related anxiety, and less pain acceptance than those with low interference on these dimensions.

In Study II, the most informative factor for assigning patients to the subgroup with the most severe pain phenotype was having more sleep problems. Re-analysis of the data showed that recurring sleep problems were present in 71.6% of those with high pain interference in both dimensions in Study I. In Study II, other important factors for assigning patient to the subgroup with the most severe pain phenotype were having more pain-related fear and worse self-rated health. The finding on pain-related fear aligns with the finding on pain-related anxiety in Study I.

When the pain phenotype is less severe, there appear to be a lesser accumulation of problems. In Study I, when pain interference was high only for the activity dimension, there were weight problems, exercising was reduced, and there was more avoidance behavior, but on average the level of depressive symptoms did not indicate depression and were the same as for those with low interference on both dimensions. When pain interference was high only on the affective dimension, there were more depressive symptoms, indicating on average mild depression, but the average exercising frequency and weight were similar to those with low interference on both dimensions.

As this is a cross-sectional study, it must be remembered that based on the findings here it is not possible to make any definite conclusions that pain phenotype had become more severe because of these associated problems. The direction of influence may go either way. More intense, more interfering, and more widespread pain may contribute to the development of many difficulties.

Findings in Study III suggest that having a more severe pain phenotype and more associated problems may be shown in metabolomic processes. For identifying pain phenotypes, the machine learning analysis suggested seven metabolomic markers as relevant. In the analyses for obesity and recurring sleep problems, it was found that obesity was associated with, for example, alterations in the levels of amino acids, and sleep problems with decreased levels of several markers in

the methionine pathway. When the findings regarding pain phenotypes, obesity, and sleep problems were looked at together, three metabolomic markers appeared across the findings: NAD, AMP, and cysteine, which participate in numerous metabolic processes. It is intriguing to think that some problems associated with more severe pain also show interactions at the metabolomic level.

Study IV revealed that recurring sleep problems in patients with chronic pain are most likely influenced not just by more severe pain, but by other factors as well. Physiological anxiety reactions to pain emerged as significant factors in sleep problems. Restless legs symptoms were also highly prevalent in those with recurring sleep problems. Multiple health conditions, such as asthma, angina pectoris, low back problems, and depression were reported more often by patients with recurring sleep problems. Sleep medications were more often in regular use and there was more use of pain medication than with those sleeping normally. As pain patients with sleep problems are more likely to be burdened by many health conditions, the finding of more sleep problems associated with lower self-rated health in Study II may not be surprising.

Comparison with other studies

Obesity, exercise, smoking and alcohol risk use

Previous research has found more intense and interfering pain to be associated with increasing BMI and prevalence of obesity in a sample of chronic pain outpatients (Basem et al., 2021) and an epidemiological survey of adolescents (Deere et al., 2012). A study among patients at a university pain clinic did not find an association between BMI and pain intensity, but increasing weight related to more days with decreased activity and complete disability, and with anxiety and depression symptoms (Marcus, 2004). In our results, the more severe pain phenotype was associated with both increases in weight and reduced physical activity. When patients reported high activity pain interference, they were heavier and their frequency of recreational exercise was lower than in those with low activity pain interference.

Obesity may predispose for the development of pain. In the prospective population-based Tromsø study, obesity was found to predict the development of chronic musculoskeletal pain over a 13 year follow-up (Andorsen et al., 2017). A longitudinal study among older adults found that, in those with no pain at baseline, there was a two-fold increased risk of pain complaints after three years

for those in the highest quartile for BMI in the cohort (N. Heim et al., 2008). Mechanisms behind the obesity and pain association may include, for example, obesity causing increased load on joints and changes in posture (Okifuji & Hare, 2015), or obesity inducing a low-grade inflammatory state, which may have a negative effect on pain modulation, thereby increasing pain (Hashem et al., 2018).

Obesity may develop through a sedentary lifestyle, with imbalance in energy intake and expenditure. The finding here that increased weight is associated with less exercise may support this. It may be that patients without exercise as part of their lives have been gradually gaining weight, and this gain has predisposed them to develop chronic pain or more severe pain. However, other trajectories are possible as well. It may have been that previous exercising routines had been given up only after developing chronic pain. But, even with pain, possibilities for various kinds of exercise exist that the patient might take on. It was interesting that less exercise was associated with pain-related avoidance - perhaps it may be a driving factor here? As patients start experiencing pain and react by beginning to avoid activities, this may have led to giving up previous exercise, but also the search for alternatives. Weight gain may have followed this when activity levels decreased.

There are other possible mechanisms that relate pain and development of obesity. For example, those with the more severe pain phenotype more often had weight and sleep problems. Fragmented sleep has associated with higher BMI and risk of obesity, while sleep duration showed a U-shaped association with BMI (Cooper et al., 2018; van den Berg et al., 2008). Sleep restriction has been found to influence hormones that participate in regulating metabolism and energy expenditure. Patients with chronic pain report increases in urges to eat (Amy Janke & Kozak, 2012), which may be associated with hormonal changes. Also, poor sleep is associated with daytime fatigue, which may contribute to decreased physical activity. Therefore, sleep problems due to pain may cause changes in eating patterns and reductions in activity levels, leading to imbalance between energy intake and consumption, and to weight gain.

Patients with chronic pain report less frequent and shorter durations of exercising (Landmark et al., 2011). Having more interfering pain is associated with reductions in exercise (Karoly & Ruehlman, 2007) and the finding in our study is in line with this. Patients who had low pain interference on both dimensions reported exercising on average 2.4 times per week, similar to Finns in general (Borodulin et al., 2012), but those high on both dimensions reported only 1.5 exercise sessions per week on average. As noted with respect to findings here, pain-related avoidance may play a part in decreased exercise. Fear-avoidance

beliefs have been found to be related to lower adherence to exercise programs in patients with musculoskeletal pain (Taulaniemi et al., 2020), which highlights the need to assess such beliefs when planning exercise programs for pain patients. Also, the association between reduced exercise and increased BMI found here should be noted: increased weight may make exercising more demanding for the patient.

Exercising is now regarded as an integral part of pain rehabilitation. Exercising is important for pain patients to sustain muscle mass and aerobic capacity, and for maintenance of weight. But exercising may be beneficial for pain as well. Exercise activates inhibitory pain modulation mechanisms, leading to increases in pain thresholds (Vaegter & Jones, 2020). However, in some pain conditions, like fibromyalgia, inhibitory pain mechanisms may fail to activate during exercise, which may lead to flare-ups in pain (Lannersten & Kosek, 2010). This may be one explanatory factor for the loss of exercise with some patients and highlights the need for patient pain education and for planning exercise regimes accordingly. Cochrane reviews of exercise for low-back pain (Hayden et al., 2005) and chronic pain in general (Geneen et al., 2017) conclude that exercise programs have some effect in reducing pain severity and in improving physical function, though the quality of evidence was considered limited because of small sample sizes.

Smoking appears in longitudinal studies as a risk factor for developing chronic pain, such as low back pain (Deyo & Bass, 1989) and widespread pain (Bendayan et al., 2018). In our study, smoking incidences ranged between 31 and 45% in the pain interference phenotype groups. A more severe pain phenotype was associated with more smoking, also found previously (Goesling et al., 2015; Hooten et al., 2009). Incidences of smoking in our subgroups were all higher than national averages, which in 2017 ranged from 16% for women (regular and occasional smoking combined) to 24% for men in Finland (Koponen et al., 2018). A population sample in the United States from 2012 found smoking incidences of 25.2% for patients with fibromyalgia, 22.8% for low back pain, and 21.2% for chronic headache, while the population estimate for smoking incidence was 18.1% (Orhurhu et al., 2015). The rather large difference in smoking between patients in our study and the general population may be explained by comorbid problems; patients at pain clinics have more anxiety and depressive symptoms, which may play a part here too. However, pain patients have not always showed more smoking than people in general. In a largescale study with patients attending tertiary pain care in California, smoking incidence was similar to that in the general public, around 10% (Khan et al., 2019). But this study also found smoking to be associated with more intense and interfering pain, and also with poorer physical functioning, and problems with depression, anxiety, and sleep. An important finding in the Californian study was that smokers had worse pain

outcomes in treatment, even after controlling for depression, anxiety, and other covariates. Worse pain outcomes may relate to, for example, increased pain sensitivity caused by withdrawal effects from nicotine, smoking impairing oxygen delivery to tissues, or inflammatory mechanisms (Shiri et al., 2010). It was rather worrying that overall smoking was so prevalent in our study, both for its adverse health consequences and the possibility of poorer treatment outcomes.

We did not find signs of alcohol use risk, the average scores on the AUDIT questionnaire remaining clearly in the range of low risk for all pain interference phenotype groups. This finding is in contradiction to previous research. Alcohol may be used as a self-management strategy for pain, which may predispose for developing alcohol dependency (Thompson et al., 2017). In epidemiological data, more interfering pain has been found associated with developing alcohol dependency (McDermott et al., 2018). Many patients in our study have severe pain which had persisted for considerable periods, so problematic alcohol use would have had time to develop, if a patient was so predisposed. In tertiary care in Sweden, 9.7% of the patients were diagnosed with alcohol dependency (Hoffmann et al., 1995). However, in that study, diagnoses were made by structured interviews as part of regular evaluation procedure, and all but a handful of patients completed the assessment. In our study, patients with alcohol use risk may have declined participation, or it may be that they had never been referred to specialized care, as problematic alcohol use is something that should be excluded before referral.

Depression symptoms

Depression symptoms often tax the psychological resources of patients with chronic pain. With depression, mood and energy levels are lower than normal, negative or hopeless thinking patterns often persist, and there may be changes in eating and sleeping behaviors. It has been estimated that on average 52% of patients attending pain clinics may suffer from depression (Bair et al., 2003).

In our study, those with the more severe pain phenotype showed more symptoms of depression than those with less intense and interfering pain. Previously, it has been found that those with depression report higher pain intensities (Knaster et al., 2012), more pain in daily situations (Hermesdorf et al., 2016) and greater interference from pain (Means-Christensen et al., 2008). There may be various mechanisms for this. More severe pain and depression may link through, for example, shared neural pathways, or effects on neurotransmitters, such as serotonin and norepinephrine, which mediate descending pain modulation (Benarroch, 2008). Many studies have investigated whether reports of more pain

in those with depression might be associated with lowered pain thresholds. However, findings on the relationship between depression and pain thresholds are variable: meta-analysis has found no differences between controls and those who were depressed with high-intensity noxious stimuli, though, with low-intensity stimuli, mean pain thresholds were actually a little increased in those with depression (Thompson et al., 2016). In a study where depression was associated with lowered pressure pain threshold, the association disappeared when it was controlled for poor sleep quality and physical inactivity (Hermesdorf et al., 2016).

Psychological processes may play a part in the link between depression and greater pain. Research seems to suggest now that depression is not the precipitating factor for chronic pain development but more of a catalyzing factor (Linton & Bergbom, 2011). Depressive symptoms are associated with more catastrophizing thoughts about pain, which may reflect the cognitive processing style that depression may predispose to. Catastrophizing is associated with experiencing more severe pain and having more disability (Craner et al., 2016; Hirsh et al., 2011; Osborne et al., 2007; Sullivan et al., 2001). At the same time, catastrophizing thoughts about pain may be contributing to the negative emotions inherent in depression.

Depression and catastrophizing thoughts about pain may have additive effects for the severity of pain and disability. In a study with 632 participants from Sweden and Australia, it was found that both depression and catastrophizing alone had negative effects on the impact of pain, but together the effects were significantly increased (Linton et al., 2011). In our study, too, those with the most severe pain showed the most depressive symptoms and the most anxious and fearful reactions to pain.

Those with most depressive symptoms in our study presented with increased weight. Overweight and obesity were found as risk factors for developing depression in a meta-analysis of longitudinal studies investigating this association (Luppino et al., 2010). With overweight, the risk of developing depression was heightened, and obesity increased the risk even more. However, the relationship appeared bi-directional, individuals with depression showing 58% increased risk of developing obesity. Mechanisms for increased weight predisposing to depression may include inflammatory states (Vaccarino et al., 2007) or dysregulation of the HPA axis induced by weight gain (Pasquali & Vicennati, 2000). Depression has been suggested to predispose for weight gain through sustained activation of the HPA axis and effects on cortisol levels (Bjorntorp, 1996, 2001).

Finally, sleep problems may be an important factor for depressive symptoms too, and recurring sleep problems co-occurred often in our study in those with the most severe pain. Longitudinal population-based twin study found onset of poor sleep to predict incident depression (Paunio et al., 2015). Meta-analysis of longitudinal studies found non-depressed subjects with insomnia to show a twofold increased risk of developing depression than those sleeping normally (Baglioni et al., 2011). Sleep problems may predispose for depression, for example, through adverse effects on emotional regulation (Baglioni et al., 2010) and on the processing of emotional content during REM sleep (Walker & van der Helm, 2009). It must be noted that sleep problems and depression are now known to have a bi-directional relationship (Fang et al., 2019).

Pain-related anxiety and acceptance of pain

Persistent pain experiences may be reacted with varying levels of anxiety. Some patients regard pain as strenuous but endurable, while in others it provokes worry and fear, and attempts to avoid the pain as much as possible. Anxiety induces physiological stress responses, which may be felt as increases in heart rate and difficulties in calming the body down. Besides pain, patients with persistent pain may experience significant anxiety in relation with the condition underlying pain.

Catastrophizing cognitions have been related to heightened pain experience in patients with varying chronic pain conditions (Sullivan & Deon, 1990), such as RA (Keefe et al., 1989), fibromyalgia, (Edwards et al., 2006), multiple sclerosis (Osborne et al., 2007), and low back pain (Flor et al., 1993). Our results on pain-related anxiety are in line with these findings.

Pain-related anxiety may affect the experience of pain by altering cognitive processing. Anxiousness may induce attentional bias to pain, therefore making it more difficult to focus attention elsewhere as there is more anticipation of pain (Crombez et al., 1998; Eccleston & Crombez, 1999). In our findings, it was interesting that the cognitive anxiety component of pain-related anxiety was associated with high affective pain interference and increased depressive symptoms. Therefore, it seemed that problems disengaging from thinking and worrying about pain were associated with lowered mood. This may reflect similar inflexibilities in cognitive processing in pain-related anxiety and depression (Linton & Bergbom, 2011).

When examining components of pain-related anxiety with respect to pain interference phenotypes, we found that in those with the most severe pain phenotype fear of pain and physiological anxiety symptoms were increased in

comparison with the less severe phenotypes. It may be that truly fearing the exacerbation of pain induces more intense emotional reactions, which then show in the intensity and interference of the pain experienced, and in the physiological anxiety symptoms (Steimer, 2002). Again, the co-occurring problems need to be noted. It may be that the regulation of emotions may be more difficult because of associated sleep problems (Baglioni et al., 2010).

Acceptance of pain is seen as an important goal for patients with chronic pain. In our study, those with the least severe pain phenotype had the most pain acceptance, those with high affective pain interference showed reductions in the activities engagement dimension of pain acceptance, and those with the most severe pain phenotype endorsed the least pain acceptance. In previous research, having more pain acceptance has been associated with lower pain intensity, less pain-related anxiety, and better function (McCracken, 1998; McCracken, Carson, et al., 2004; Weiss et al., 2013). Acceptance of pain has been proposed as a protective factor for the negative emotions associating with it, so that when pain levels increase, they are more tolerable because of the lower associated emotional reactivity (Kratz et al., 2007). Having more pain acceptance has been associated with experiencing less interference from pain and with higher levels of physical activity (Kratz et al., 2017). The activities engagement dimension of pain acceptance has shown a more robust association with these than has the pain willingness dimension. In our results, lower activities engagement showed more association with affective pain interference than with interference to activities, such as work and movement, a slightly different finding. As affective pain interference captures the interference that pain has with social relationships and enjoyment of life, it may be that lower activities engagement in our results reflects withdrawal from interpersonal and personally meaningful activities.

Blood pressure and self-rated health

The machine learning analysis suggested the absence of high blood pressure as one significantly informative factor for patients belonging to the least severe pain phenotype. Acute pain is associated with increases in blood pressure, followed by reductions in pain sensitivity to restore arousal levels (Sacco et al., 2013). However, in chronic pain this relationship appears reversed. It has been found that the elevated blood pressure levels are associated with increased sensitivity to pain and higher reported pain intensities in patients with chronic pain (Maixner et al., 1997; Olsen et al., 2013). Decrements in cardiovascular regulation, such as reduced baroreflex sensitivity and heart rate variability, known to link with hypertension, have been proposed as mechanisms that associate higher blood pressure and more severe pain in patients with chronic pain (Bruehl et al., 2018;

Chung et al., 2008). Our results might then suggest that preserved regulation in the cardiovascular system would protect patients from more severe pain.

Poorer self-rated health was an important factor linked with belonging to the most severe pain phenotype. Self-rated health has been found reduced in those with chronic pain in the general population who experience pain more frequently (Mantyselka et al., 2003). Poorer self-rated health in those with chronic pain is associated also with functional impairment and presence of chronic diseases (Reyes-Gibby et al., 2002). In our study, those with the most severe pain had the most interference with life activities from pain and reported reduced exercising, corroborating the association between poor self-rated health and functional impairment. Also, poorer self-rated health has previously been found to be associated with decreased HRQoL in patients with chronic pain, with sleep and psychosocial dimensions being most compromised (Vartiainen et al., 2017). In our study, sleep problems were associated with the most severe pain phenotype. Further, sleep problems in our study were associated with more co-occurring somatic health problems, perhaps also explaining the poorer self-rated health of those with the most severe pain.

Metabolomic factors

The metabolomics analysis made use of two approaches to identify significant metabolomic markers for more severe pain. Data-driven machine learning analysis elucidated seven markers as informative in distinguishing the group with the least severe pain phenotype from those with more severe phenotypes: asparagine, AMP, deoxycytidine, glucuronic acid, propionylcarnitine, cysteine, and NAD. Three of these markers (NAD, AMP, and cysteine) appeared in the top 25 metabolomic pathways in relation to obesity and recurring sleep problems, two common problems co-occurring with more severe pain.

Previous research has found obesity to be associated with alterations in amino acid metabolism pathways. Increased levels of BCAAs valine and isoleucine, and of glutamate and alanine, have been suggested to represent a metabolomic profile reflecting an overload of BCAA catabolism (Newgard et al., 2009). This may be associated with the development of glucose intolerance or may affect neurotransmitter production. Our results showed similar metabolite profiles with obesity. The levels of amino acids may be associated with pain as well. Increased levels of BCAAs have been suggested to be associated with increased neuroinflammation, which may lead to more pain (Rockel & Kapoor, 2018; Zhenyukh et al., 2017). Glutamate is an excitatory neurotransmitter associated with pain sensation and elevated levels have been associated with more severe

pain (Teckchandani et al., 2021). Further, the metabolomic marker glucuronic acid appeared in relation to obesity and in the results of the machine learning analysis. Glucuronic acid has been shown to activate Toll-Like Receptor 4, which may lead to increased nociception due to release of inflammatory substances (Lewis et al., 2013).

Experimental sleep studies have observed sleep deprivation to reduce levels of cysteine and homocysteine (Andersen et al., 2004; Trivedi et al., 2017), and simulated night shifts are associated with lower levels of choline and two other metabolites in the methionine pathway (Kervezee et al., 2019). In our study, four metabolites in the methionine pathway were found to be decreased with sleep problems: choline, homocysteine, dimethylglycine, and serine. This may suggest downregulation of the methionine pathway with sleep problems. However, the finding for homocysteine contradicts previous research, which has suggested a link between elevated homocysteine and several diseases, such as cardiovascular diseases and dementia, where sleep problems have been proposed to play a part (Seshadri et al., 2002). The findings on elevated homocysteine levels have been found in relation to OSA and greatly reduced sleep durations (< 5h) (Lebkuchen et al., 2021), and it may be that the effects are different when sleep is, for example, fragmented. Stimulating the methionine pathway has been studied for possible pain-alleviating effects in relation to chronic pancreatitis (Ligthart-Melis et al., 2020).

Pain, obesity, and sleep problems often co-exist in patients with chronic pain. We were interested in whether the results in our study might suggest interactions at the level of metabolomic processes relevant to these problems. Our results suggested obesity to be associated with alterations in the glutathione pathway. This might be related to elevated glutamate or decreased glycine availability (Wu et al., 2004). As discussed previously, sleep problems appeared associated with a downregulated methionine pathway. Cysteine is a product of this pathway and needed for glutathione synthesis (Reed et al., 2008). It may be hypothesized that, if obesity affects the glutathione pathway, sleep problems could take these alterations further via reduced cysteine availability due to the downregulated methionine pathway?

NAD appeared in most pathways related to obesity and sleep problems, and machine learning analysis picked it as one of the informative markers for pain phenotypes. Previous research has found decreased NAD levels with obesity, which may relate to increased levels of inflammatory substances (Okabe et al., 2019). NAD has been suggested to play part in the processes associated with internal circadian clocks, which may then have an effect on sleep regulation (Xie et al., 2020).

Elevated levels of AMP have been found in obesity and diabetes (Park et al., 2015). In our study, the level of AMP was higher in those with the more severe pain phenotype. AMP is hydrolyzed to adenosine, which has been found to have antihyperalgesic and antiallodynic effects (Zylka, 2011). However, persistently elevated adenosine levels have been associated with mechanical and thermal hypersensitivity, which might then contribute to more severe pain (Hu et al., 2016).

The relationship between pain and metabolomics is complex. Besides these co-occurring problems analyzed here, there are other likely factors that may have an effect, such as used pain medications (Ghosh, 2021).

Sleep

Sleep problems were suggested as the key factor by machine learning analysis for the least and most severe pain phenotypes in our study. When incidences of recurring sleep problems were examined in respect to pain interference phenotypes, it was clear that those with the most interference from pain showed many more sleep problems than those with the least; for the former, the incidence of recurring sleep problems was 71.6% and for the latter 23.5%. Recurring sleep problems were identified for 43.4% of patients in the whole KROKIETA cohort.

In a population-based study, the incidence of insomnia was 25.1% in those with musculoskeletal disorders and 39.8% in those with fibromyalgia (Sivertsen et al., 2009). In a meta-analysis, the pooled prevalence of sleep disorders in chronic pain was 44% (Mathias et al., 2018). Different ways to measure sleep problems between studies affect how many of the patients are diagnosed with them. As patients in our study have been referred to tertiary pain care, it is expected that the incidence of sleep problems is greater than found in population-based studies; patients are more likely to have other problems, like depressive symptoms, that may induce difficulties with sleep.

Patients with chronic pain who have more intense and widespread pain report more sleep problems (Finan et al., 2013; Husak & Bair, 2020), and our findings are in line with this. Also, catastrophizing, especially rumination of distressing thoughts about pain, has been found previously to be associated with sleep problems in pain patients (Buenaver et al., 2012; Byers et al., 2016). Our results confirmed that pain-related anxiety is increased in those with sleep problems. Ruminating thoughts may make falling asleep difficult or, if woken at night by pain, may hinder falling asleep again (Riemann et al., 2010). However, an interesting finding in our study was that when components of pain-related

anxiety were investigated with respect to level of sleep disturbance, physiological anxiety reactions appeared as the most important factor in sleep problems. Previous research in pain has often used the Pain Catastrophizing Scale, which does not assess physiological reactions (Sullivan et al., 1995). Increased physiological anxiety reactions (difficulties in calming down and heart racing while in pain) would intuitively seem to make falling asleep difficult. Sleep research suggests hyperarousal as a key factor for sleep problems, and that those who are at risk of sleep problems may show dysregulation of stress responses (Bonnet & Arand, 2003; Kalmbach et al., 2018). Heightened arousal has been associated with misperceptions of sleep onset latencies and underestimations of total sleep time, and these cognitive processes may contribute to maladaptive sleep behaviors (Harvey, 2002).

Previous research has found several health problems to be associated with sleep problems: angina pectoris, asthma, arthritis, low back pain, joint diseases, depression, diabetes, obesity, and stroke (Alsaadi et al., 2011; Koyanagi et al., 2014; Luyster et al., 2016; Nicassio et al., 2012; Taylor-Gjevre et al., 2011). In our study, those with recurring sleep problems reported more often than those sleeping normally having been diagnosed with angina pectoris, asthma, back pain problems, joint disease, or depression. Our results underline the involvement that depression may have in the relationship between sleep and pain (Fang et al., 2019; Finan et al., 2013; Rayner et al., 2016). The high incidence of asthma in those with recurring sleep problems (19.6%) was significant as well. Insomnia has been shown to increase the risk of developing asthma (Brumpton et al., 2017). Also, when sleep problems are present, asthma control is poorer (Luyster et al., 2016). Contrarily, asthma may lead to more sleep problems via physiological mechanisms, such as increase in bronchial hyperresponsiveness (Kavanagh et al., 2018). The association of arthritis in our study was surprising and in contradiction to previous research: those who slept normally reported more arthritis than those with sleep problems. This may be explained by arthritis not being the main cause of pain in patients in our study, and that nowadays arthritis symptoms are typically well controlled with pharmacological treatments.

RLS were common in those with recurring sleep problems in our study (33.2% vs 11.7% in those sleeping normally). In a meta-analysis, RLS were found on average in 32% of chronic pain patients with sleep disorders (Mathias et al., 2018). In the general population, estimates for RLS vary between 5 and 10% (Didato et al., 2020). Factors that may predispose to RLS include genetics, brain iron deficiency, dopaminergic alterations, and anxiety or depressive symptoms (Bonakis et al., 2020; Stehlik et al., 2014; Winkelmann et al., 2005). Somewhat unexpectedly, OSA did not differ in our study between those who slept normally and those with sleep problems. OSA was observed on average in 32% of pain patients with sleep

problems (Mathias et al., 2018), but the rate has varied greatly between studies. In our study, 15.1% of those with recurring sleep problems were assigned with OSA.

Patients with recurring sleep problems in our study used more sleep and pain medications than those sleeping normally. Benzodiazepine derivatives and melatonin were used for sleep most often. Patients with chronic pain usually have long-term sleep problems, which opposes the management of sleep problems by solely pharmacological approaches (Bastien, 2011). Some medications, such as benzodiazepines, may affect sleep structure negatively and may cause dependence, and therefore long-term use is not recommended. As patients with sleep problems have more severe pain, the higher use of pain medications was not unexpected. Medications for pain may both help and hinder sleep, though research is still limited here (Bohra et al., 2014).

In our study, those diagnosed with back pain had more recurring sleep problems than those with facial pain, a difference previously found (O'Brien et al., 2010). We conducted additional analyses in this and found that patients with facial pain reported on average lower pain intensity and shorter pain durations, less psychological distress, asthma, and RLS. These complicating factors are likely to play a part in the difference for sleep problems, but why patients with facial pain have fewer of them remains an open question.

We expected that having experienced more childhood adversities would be associated with sleep problems, and, as childhood adversities have been linked to proneness for anxiety symptoms and more psychosocial distress in adulthood, it might be expected that those with recurring sleep problems in our study would report more of them. However, only in the cumulative number of adversities of five or more did there appear a difference between those with recurring sleep problems and those sleeping normally. In previous research, the accumulation of adversities has been linked to more sleep problems as well (Chapman et al., 2011; Felitti et al., 1998; Von Korff et al., 2009). It may be that the negative effects of childhood adversities begin to show only after the distress from them surpasses the protective effects of resilience factors. It is noteworthy that overall the incidences of childhood adversities in the study cohort were higher than in the general population (Pirkola et al., 2005). For example, maternal alcohol abuse was reported nearly five times, and paternal psychiatric problems two times, more frequently by pain patients. As childhood adversities may already themselves have created vulnerability for the development of pain problems (Kopec & Sayre, 2005; Linton, 1997; Nicol et al., 2016), it may be that the effects on sleep problems in the cohort are masked by this.

Strengths and limitations

For these studies, a broad selection of variables was collected, and this may be considered a strength. It is now clearly recognized that pain experience and the effect of pain are affected by a multitude of factors. Research on chronic pain has investigated previously the effects of psychological factors, especially pain-related anxiety and depression, but less those of lifestyle factors in the context of patients entering pain treatment. Research on sleep and pain has expanded significantly in recent years and metabolomics is an emerging area of research. It is probable that, to understand chronic pain and its treatment better, research needs to pursue this kind of multifactorial approach (Edwards et al., 2016).

Patients in the KROKIETA cohort have mixed pain etiologies, allowing better generalization of the results to all pain patients. The current thinking in pain research acknowledges that factors predisposing to the development of chronic pain or to worse outcomes in pain are more likely shared between different diagnostic groups than to be specific to some pain diagnosis (Gatchel et al., 2007).

It must be noted that patients who participated in the studies were all referred to specialized pain care. This raises the question whether the results apply to patients beyond specialized care. Patients referred to pain clinics have had one or more treatment attempts in primary care without adequate result. Treatment attempts have taken time, and as was found in the studies, most of the patients have had pain for over two years. There has been more time for different problems to develop than for those who are just beginning treatment in primary care. However, specialized pain care is available for only a portion of patients and many patients with years of chronic pain are only treated in primary care; it is conceivable that factors similar to those found here, like sleep problems, are also at play.

A limitation is that information on those who declined participation in the KROKIETA study is not available. Patients were free to decline participation and no demographic data were stored. Approximately half of those who were invited did not participate. However, we compared the sample from the three multidisciplinary pain clinics to a different study sample, which collected data on all patients entering one of these three clinics (Vartiainen et al., 2016). This comparison revealed no differences in the gender distribution or the proportion of middle-aged subjects in the samples. However, there were fewer older patients and fewer with less than nine years of education in our sample. It has been found that older patients report less anxiety in pain inventories (Gagliese & Melzack, 1997) so reported pain-related anxiety levels might have been lower had there been more older patients in our sample. Also, highly distressed patients may have

disproportionately declined participation. The study protocol included completing several questionnaires and, for those in the multidisciplinary pain clinics, visiting a laboratory: highly distressed patients might have found this too demanding. Patient non-compliance reduced the number of patients who visited the laboratory, so this was probably experienced as an inconvenience or burden. Highly distressed patients would have probably been assigned to the more severe pain phenotype. If so, our results may represent a patient group with fewer problems than average.

The data comprised self-report questionnaires, apart from measurements taken by nurses at the pain clinics (height, weight, waist circumference, and blood pressure), and blood samples. It has been observed that, for example, sleep problems may be overestimated by those who have more anxiety (Tang & Harvey, 2004). Sleep problems and pain-related anxiety were associated in our results, so it is possible that this bias has had an effect.

If we want to match the identified pain phenotype subgroups with distinct lines of treatments, there are clear difficulties to keep in mind. When investigating the different pain interference phenotype groups, it was noted that the patients' average score was, for example, in the "mild depressive symptoms" category in BDI-II in one of the groups. As this is an average, the group would also include patients with "no symptoms" and "moderate symptoms" so different aspects should probably be emphasized for these patients in their treatment. Also, while measures such as AUDIT and BDI-II have established categories for severity, although not always clear-cut (Knaster et al., 2016), for many measures there are no categories that would imply some course of action. For PASS-20, there are only preliminary categorizations (Abrams et al., 2007; Brede et al., 2011), and for CPAQ none. There were statistical differences between the phenotypes in these measures, but more research is needed for assessing the clinical importance of these.

Machine learning algorithms were used for knowledge discovery about the most informative factors for pain phenotypes. They were not built as tools that could be used to divide patients into certain groups in the clinic setting. Their function was to elucidate from the complex data those variable combinations, formed into algorithms, that best associate with certain pain phenotype groups. When the algorithms were built with pain-related variables, the performance indices were reasonably good. With non-pain variables (where sleep was found as the most important factor) and with metabolomic variables, the performance of the algorithms was only modest. However, several different algorithms were used in the analyses, and they provided similar results, with for example sleep problems appearing repeatedly as the most important variable, which supports the validity

of the results. Permuted data were used to ascertain that the built algorithms were true findings: in these analyses, the results were as expected, meaning that algorithms based on permuted data performed with an accuracy below guesswork.

Clinical implications

The first implication for the clinic from these studies is that patients with more severe pain phenotypes are more likely to have several problems that contribute to the severity. These may interact with each other, creating vicious cycles that affect not only pain, but probably treatment results as well. Thorough assessment is a necessity for all patients, but the findings here should alert the clinician to carefully examine, for example, the psychological dimensions, sleep quality, and lifestyle factors in those with severe pain. It is not uncommon to encounter in clinical practice a patient who seeks first and foremost that pain be less intense. If treatment revolves around the reduction of pain intensity with pharmacological means, the attempt is not likely to be very successful (Machado et al., 2009). However, if different components of the cycle are targeted, treatment results may be much better: for example, treating pain-related anxiety and depression may reduce the load of negative emotions associated with the pain problem, lead to better function, and at the same time lessen pain intensity.

In these studies, sleep problems emerged as a key feature in both the least and most severe pain phenotypes. Sleep complaints are common among patients with chronic pain, but their assessment and treatment may not have been as well established as other factors, such as fear-avoidance. Some patients might benefit in treatment from educational material and guidance on sleep hygiene, and others from CBT programs for sleep, the latter having been found effective in alleviating sleep problems among pain patients (Selvanathan et al., 2021). One such program was found to help with pain as well for some patients, the results for sleep and pain lasting longer than with a CBT program for pain only (McCrae et al., 2019). Working in treatment to reduce sleep problems may be more acceptable for some patients than factors deemed “psychological”, like fear of pain. Yet, working with sleep problems may also help in recognizing pain-related distress; if the patient begins to recognize worrying thoughts that appear when trying to fall asleep (“pain will flare up soon, it is almost hopeless to try to sleep”), then they may begin to identify them in other activities as well, such as work or movement.

When sleep problems are assessed in pain patients, the findings here suggest that co-occurring factors should be assessed too. Pain-related anxiety, with an emphasis on physiological anxiety reactions, would be one area to target. Relaxation training is one method that the patient may learn and then use to control physiological anxiety reactions. Sleep medications had been in recurring use for some of the patients in our study, suggesting a need for evaluation of their continued use. Depression, asthma, joint and back pain, and RLS were frequent conditions associated with recurring sleep problems and, as they may contribute to these, checking on their treatment should be remembered.

It is intriguing to speculate whether the pain phenotypes found in these studies could be used to guide treatment for more specific goals. In previous research, patients have been similarly divided to three or four subgroups (Hill et al., 2008; Larsson et al., 2017; Turk, 2005). Research on subgroups discovered using the MPI found that treatment dropouts were fewer when patients in the subgroup with least severe pain and least distress were directed to medically oriented treatment programs, those with interpersonal distress to CBT programs, and those with most severe pain, distress, and functional limitations to operant group programs (Flor & Turk, 2011). The phenotypes found by using the activity and affective pain interference dimensions would allow easy and practical assigning of patients to different subgroups. Those low on both dimensions might fare best in multidisciplinary treatment with physician consultations only, as on average they had normal mood, were exercising the most, had fewer weight problems and problems with sleep, and the most helpful psychological reactions to pain. Those high on the affective interference dimension might benefit from working with a psychologist as they showed lower mood and more anxious thought patterns about pain. Those high on the activity interference dimension presented with weight gain, reduced exercise, and avoidance behavior, which physiotherapists might help with overcoming. Those high on both interference dimensions showed on average most problems in all areas. Patients in this subgroup would probably benefit from the help of a multidisciplinary team. However, as noted previously among limitations, individuals within subgroups vary and, with respect to many measurements, there is a lack of knowledge about clinically meaningful differences between the scores. Before applying the phenotypes to guide treatment at individual level, significant validation research would be required. Nevertheless, the phenotypes do suggest in broad terms the extent and type of problems that patients in the subgroups may have.

Future perspectives

Several risk factors for chronic pain or for the development of more severe pain have been found but there are still many aspects that future studies should investigate. Research has concentrated mostly on problems, such as maladaptive cognitive patterns and negative emotions. This is understandable as many research questions may arise from clinical settings where these problems stand out. However, how individuals manage with health concerns is not only affected by the level of problems, but by positive resources too. This line of thinking is reflected in concepts such as resilience and cognitive flexibility, which pain research has started to investigate. Interesting areas for research to broaden into may include how the quality and extent of social networks, work engagement, or skills that lead to healthy lifestyles may be associated with pain trajectories. These factors may be enhanced, for example as part of health promotion in schools or in occupational health, to help prevention of chronic pain.

Research with so-called big data may also give insights into new areas to discover. One source for big data is in electronic patient records. These may show, for example, the longitudinal sequence of different health conditions. In our results, asthma appeared significantly more often in those with recurring sleep problems than those sleeping normally but, due to the cross-sectional nature of the data, no conclusions could be made about when the asthma developed. Interesting research questions would be to investigate which health conditions may have appeared before chronic pain was diagnosed, whether combinations of some health conditions are important, or how various health conditions may develop alongside chronic pain. Also, by using artificial intelligence there may be possibilities to elucidate patterns in the big data that reveal factors in relation to chronic pain that have gone unnoticed before (Obermeyer & Emanuel, 2016). However, what patient records often lack is the regular measurements of pain variables, even pain intensity. Developing records so that pain was measured and recorded in a standardized manner in health care, with enough detail, is an area for development. Also, it should be noted that, in many countries, health records in primary and specialized care are kept in different storage systems. Integration of these would be useful as often the point of interest in research is the patient's whole trajectory with pain, irrespective of where it was treated.

Metabolomics is a new research area and may in future reveal more on the processes in chronic pain development, and on relations between pain and associated factors. If the studies show that there are some metabolomic processes that are down- or upregulated, as was suggested here for methionine and recurring sleep problems, these processes may be targeted. If the processes show

overabundance or deficiencies in some molecules, perhaps it is possible to affect them by, for example, changes in nutrition (McNiven et al., 2011).

As patients with chronic pain often have several factors simultaneously that may affect pain, it may be asked whether it is more effective if treatment starts from one of these. For example, if sleep is important for both learning and regulation of emotions, would patient with both sleep problems and high fear of pain benefit more if sleep problems are alleviated first and fear targeted afterwards? Perhaps a patient with significant sleep problems, who engages in fear-eliciting movements as part of graded exposure, is limited in the ability to learn that movements are safe, or that the fear reactions too easily reach so high a level that they are not beneficial. Or maybe graded exposure should be offered before helping sleep, because fear extinction might relieve worry, leading to more exercising, which would then enhance sleep? This kind of research question may lend itself to the use of number-of-1 (N-of-1) research trials (Punja et al., 2016). N-of-1 trials may generate treatment information when randomized controlled trials (RCTs) are not available or practical. N-of-1 trials are suitable for chronic and relatively stable conditions, like chronic pain, and they may reveal individual-level responses, which are lost in conventional RCTs. They are prospective, multiple crossover investigations conducted in a single subject, where interventions may be randomized and blinded, but not if not feasible. Using N-of-1 trials might lead to elucidating the most beneficial treatment packages for patients. At the same time, they may help treatment providers to quickly recognize and respond to new treatment needs, for example when a treatment package is not proving effective for some new patient group, and, thus, actively develop clinical practice.

An important issue for the future is how components of treatment that patients with chronic pain need are to be made available. Most patients with chronic pain are treated in primary care. Important aspects of treatment, like that of sleep problems, may be advanced in primary care by educating nurses to conduct individual and group-based interventions for sleep. A four-session hybrid program for pain and sleep in primary care has been developed in the United Kingdom (Tang et al., 2020). However, resources vary in primary care, which may limit the extent of interventions that can be made available. Digitalized treatment programs, like those found already in Finland for sleep problems, and proven effective elsewhere (Selvanathan et al., 2021), may be excellent opportunities to augment treatment of pain patients in primary care. For which kind of patient with chronic pain they may work best, and whether digitized sleep programs may need modifications in the context of chronic pain, are very interesting research questions for the future.

Conclusions

In these studies, patient subgroups with varying pain phenotypes were discovered. Previous studies have highlighted the role of psychosocial factors in those with the most severe pain phenotypes. The results of these studies suggest the importance of sleep and lifestyle-related factors as well. Research into metabolomics may uncover how pain and the problems associated with it may show, and possibly interact, in metabolomic processes. Sleep problems are affected by multiple factors, not only pain, in patients with chronic pain.

The conclusions to the specific aims of the studies were as follows:

1. Pain interference phenotypes were associated with different profiles of problems. Patients low on both activity and affective pain interference had on average fewest problems: there were less weight problems, more regular exercising, better mood, and psychological reactions to pain were the most helpful in this patient population. When only affective interference was high, there was an elevation in depressive symptoms, more anxious thinking about pain, and engagement in life-fulfilling activities was reduced. With only activity interference high, exercising frequency was reduced, there was an increase in the average weight of the patients, and there was more pain avoidance behavior. In those high on both interference dimensions, the problems showed most accumulation: there were more problems with weight, exercising was reduced, smoking was more prevalent, there were more depressive symptoms, and the psychological reactions to pain were least favorable in all dimensions.

2. Three subgroups of patients with different pain phenotypes were found when a data-driven approach was employed. The first group had the lowest pain intensity and pain interference, the second was in the middle, and the third showed a combination of high pain intensity and high pain interference, and the greatest number of pain areas. Machine learning analysis revealed that sleep problems were the most important factor in assigning patient to the two extreme phenotypes. For the group with the least severe pain, having less fear of pain and lower systolic blood pressure appeared important, while for the group with the most severe pain, having more fear of pain and lower self-rated health showed as important.

3. Three metabolomic markers (NAD, AMP, and cysteine) appeared across the findings from the analyses with respect to pain phenotypes, obesity, and recurring sleep problems. Analyses in relation to obesity found, for example, alterations in levels of amino acids and, for recurring sleep problems, several decreased

markers in the methionine pathway were found. These findings may suggest metabolomic processes associated with having more severe pain.

4. Recurring sleep problems were associated with not only to having more pain, but several other factors as well, which may be of importance. Physiological anxiety symptoms were important in relation to sleep difficulties. Restless legs symptoms were highly prevalent in those with recurring sleep problems. Multiple health conditions, such as asthma, angina pectoris, low back problems, and depression, were reported more often by those with recurring sleep problems than by those sleeping normally. Recurring sleep problems were associated with more use of sleep and pain medications.

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