Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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The association between pain catastrophizing and chronic fatigue in the general population: the HUNT Pain Study

Master's thesis in Clinical Health Science - Pain and Palliative Care
Supervisor: Tormod Landmark

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Abstract

Introduction: Fatigue and pain are common complaints in the community and may have many of the same underlying mechanisms. Pain catastrophizing is a predictor of adverse pain-related outcomes, but the relation to fatigue is not fully investigated. The aim of this study is to firstly investigate the association between pain catastrophizing and feeling of energy in the general population and the second aim is to see if pain catastrophizing is related to the occurrence of chronic fatigue.

Method: In the population-based HUNT pain study, a random sample of 6419 participants were invited to answer questions about how much energy they had during the last week, using the SF-8 vitality scale, every three months over a year. Multiple linear regression and logistic regression analyses were used to investigate the association between pain catastrophizing and individuals' tendency to report energy over one year, and the association with chronic fatigue, respectively. Chronic fatigue was defined as a mean score of less than 2 which indicates reports of a little energy or less most of the time.

Results: The current sample (n=3965) consisted of individuals answering about the required variables and possible confounders. A significant association was found between pain catastrophizing and energy levels of the general population even after controlling for age, sex, organ-specific diseases, mental health, and pain intensity (β=0.04, 95% CI: 0.03-0.05). In the general population, 10% was defined as having chronic fatigue and odds increasing by 1.2 (95% CI: 1.1-1.3) for every unit increase in pain catastrophizing.

Conclusion: This study indicates that there is an association between pain catastrophizing and energy levels, and the association is even more apparent with chronic fatigue. According to models explaining fatigue and pain, pain catastrophizing may strengthen an imbalance of costs versus benefits in goal-directed behaviour. Moreover, it is proposed that fatigue can be included in the vicious circle described by the fear-avoidance model as a consequence of catastrophizing and maintaining pain.

Sammendrag

Introduksjon: Utmattelse og smerte er utbredte plager i samfunnet og kan ha mange av de samme underliggende mekanismene. Verstefallstenkning om smerte er en prediktor for negative smerterelaterte konsekvenser, men sammenhengen med utmattelse er ikke fullstendig undersøkt. Det første formålet med studien er å undersøke sammenhengen mellom verstefallstekning om smerte og følelsen av overskudd i den generelle befolkningen, og det andre formålet er å se om verstefallstenkning om smerte er relatert til forekomsten av kronisk utmattelse.

Metode: I den populasjonsbaserte studien smerte-HUNT ble et tilfeldig utvalg på 6419 deltagere invitert til å svare på spørsmål om hvor mye overskudd de hadde siste uken, ved bruk av SF-8 vitalitetsskala, hver tredje måned over ett år. Multiple lineære og logiske regresjonsanalyser ble brukt for å undersøke henholdsvis sammenhengen mellom verstefallstenkning og personers tendens til å rapportere overskudd over ett år, og assosiasjonen med kronisk utmattelse. Kronisk utmattelse ble definert som en gjennomsnittsscore på mindre enn 2 som indikerer rapportering av litt overskudd eller mindre over tid.

Resultater: Utvalget i studien (n=3965) bestod av personer som hadde svart på de nødvendige variablene og mulige konfundere. Det ble funnet en signifikant sammenheng mellom verstefallstenkning om smerte og overskudd i den generelle befolkningen, selv etter å ha kontrollert for alder, kjønn, organspesifikke sykdommer, mental helse og smerteintensitet (β=0.04, 95% CI: 0.03-0.05). I den generelle befolkningen ble 10% definert som å ha kronisk utmattelse og odds økende med 1.2 (95% CI: 1.1-1.3) for hver enhet økning i verstefallstenkning om smerte.

Konklusjon: Denne studien indikerer at det er en sammenheng mellom verstefallstekning om smerte og overskudd, og sammenhengen er enda mer tydelig med kronisk utmattelse. Ifølge forklaringsmodeller for utmattelse og smerte kan verstefalltenkning om smerte mulig forsterke ubalansen mellom kostnader og nytte i målrettet adferd. Det foreslåes at utmattelse kan inkluderes i den onde sirkelen beskrevet i frykt-unngåelsesmodellen som en konsekvens av verstefallstenking og opprettholdelse av smerte.

Acknowledgement

First of all, I wish to sincerely thank my supervisor Tormod Landmark for exceptional guidance and patience with me during this period. Also, a sincere thanks to my partner, family, and friends for their support during my studies and helping me finalise this thesis.

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Abbreviations

CBT	Cognitive behavioural therapy
CFS	Chronic Fatigue Syndrome
CI	Confidence interval
CSQ	Coping Strategies Questionnaire
FSS	Fatigue Severity Scale
GLM	General Linear Models
GP	General practitioner
HUNT	The Nord-Trøndelag Health Study
IASP	International Association of the Study of Pain
ICC	Intra-class Correlation Coefficients
MHI-5	Mental Health Inventory-5
OR	Odds ratio
PCS	Pain Catastrophizing Scale
Q-Q-plot	Quantile-quantile plot
REK	Regional Committee for Medical and Health Research Ethics
SD	Standard deviation
SF-8	Short form-8
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

1.0 Introduction

1.1 Fatigue

Fatigue is a common symptom in the community (van't Leven et al., 2010) and it is among the most frequent patient-reported causes for seeking primary health care (Finley et al., 2018). People suffering from chronic fatigue, lasting more than six months, have a significant functional impairment and have unwanted consequences as impaired social relations and many are unable to work (Bombardier & Buchwald, 1996; Sharpe et al., 1991). Fatigue as a symptom is highly associated with impaired quality of life across different medical conditions (Abrahams et al., 2018; Komaroff et al., 1996). Women, the ones with children, and people from lower educational or occupational groups appear to have higher levels of fatigue (Jason, Jordan et al., 1999).

The interest of fatigue in science and in history has been varying due to different attitudes in the society and illnesses. The first indication of fatigue is found in the medical literature in the 1870s referred to as overwork due to loss of mental energy (Rabinbach, 1990). This is connected to the Industrial Revolution in the middle of the 18th century and a change from aspects of work being in high control and task-oriented to lower control and time-oriented work (Hockey, 2013). As a name to this gap between demand and control, neurasthenia, or "over-taxing of the nerves", was defined as an illness in the late industrial period and was the first acceptance of fatigue as a medical condition (Hockey, 2013). After this, research in fatigue was related to tendencies in the society, such as focusing on work and psychology (Hockey, 2013). Late in the 1980s the Epstein-Barr virus syndrome increased the focus on fatigue. This was later renamed to chronic fatigue syndrome (CFS) (Wesseley, 1997).

Fatigue is defined as an overwhelming sense of tiredness or exhaustion, and lack of energy, associated with impaired physical and/or cognitive functioning (Shen et al., 2006). Other definitions are focusing on the imbalance capacity and resources needed (Aaronson et al., 1999). Fatigue is documented to be a symptom related to many chronic and life-threatening diseases such as cancer and multiple sclerosis (Morrow, 2007; Bertoli & Tecchio, 2020) as well in psychiatric diseases (Ghanean et al., 2018). In addition, it is also a common complaint among healthy individuals (Kangas & Montgomery, 2011). About 0.2-0.4% of the general population have chronic fatigue syndrome (Nacul et al., 2011; Jason, Richman et al., 1999), meaning fatigue lasting at least six months including additional symptoms such as impaired memory or concentration, sleep disturbance, muscle pain etc (Fukuda et al., 1994). To determine this diagnosis there are strong exclusion criteria and if another medical or psychiatric cause of chronic fatigue is found, the person will be excluded from having the diagnosis (Fukuda et al., 1994).

Fatigue is often divided into two dimensions; physical fatigue which includes exhaustion, weakness, tiredness, and mental fatigue, which causes problems with cognitive functions such as memory, attention, and concentration (Stone & Minton, 2008). The term can also be divided into, acute and chronic fatigue. Acute fatigue or short-term fatigue has a normal protective function in the body. It lasts under three months, has usually a clearly

identifiable cause and will withdraw with rest or by treating the underlying condition (Jason et al., 2010). Chronic fatigue is an abnormal, more persistent, fatigue. The debut is gradual, it persists over time and is normally multifactorial in aetiology. It is generally not relieved with normal resting. It affects the quality of life and daily activities negatively (Aaronson et al., 1999). Chronic fatigue usually starts with decreased physical activity levels. Many cancer patients report inference on the activities they used to do; they lose control over some parts of what their lives used to consist of. Further, it may contribute to the feeling of loneliness and/or isolation. This negative spiral will further decrease their distressing position (Flechtner & Bottomley, 2003).

The prevalence of chronic fatigue varies widely from around 3-30% in other studies (Jason, Jordan et al., 1999; Loge et al., 1998; Wesseley, Chalder et al., 1997; van't Leven et al., 2010). The prevalence of fatigue in a population will depend on the cut-offs used (Lerdal et al., 2005), samples that are studied and methods used (Jason, Jordan et al., 1999). In the general population, the fatigue score is normally distributed, meaning it ranges from no fatigue to high levels of fatigue (Lerdal et al., 2005). After the pandemic of coronavirus disease (COVID-19) the prevalence of fatigue has increased. Chronic fatigue is a known symptom in the aftermath of infectious diseases (White et al., 2001; Seet et al., 2001; Hanevik et al., 2014). Persons who report symptoms weeks and months after the initial acute illness of COVID-19 have been termed "long haulers" or described as having "long-COVID" (Baig, 2020). The World Health Organization (WHO) proposed to name the condition "post-COVID-19 condition". It is described as "the condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" (Soriano et al., 2022). The global prevalence of post-COVID-19 condition is approximately 43% of the ones infected and fatigue is the most prevalent sequela (Chen et al., 2022). The global situation in February 2023 is over 765 million confirmed cases, and in Norway 1.4 million cases (World Health Organization, 2023). It is important with further research on risk factors for developing post-COVID-19 condition, because of the implications for screening and appropriate treatment (Chen et al., 2022).

1.2 Pain

Throughout the years several theories of pain have been evolved. The first description of pain is from over 3000 years ago in an ancient medical book from Chinese medicine. Pain was believed to be a result of an imbalance between yin and yang (Chen, 2011). Descartes "hard wire system" is from the 17th century. At that time, the body was seen as a machine, and it was stated that the pain signal was transferred through a tubular structure from the periphery to the brain (Weiner, 2001). Melzark & Wall (1965) were the first to describe a modulation of pain in their "gate-control theory" and a more complex theory compared to the mechanic theory of Descartes (Fornasari, 2012; Weiner, 2001). The theory includes a more multidimensional experience consisting of sensory, affective, and cognitive components (Melzark & Wall, 1965). In later years new models for understanding chronic pain have been developed, such as the neuro matrix of the brain by Melzack (2001). This model describes pain as a multidimensional experience, produced by the output of a widely distributed neural network or pattern rather than directly by a sensory input by injury or pathology.

The prevalence of chronic pain is estimated to be high, about 30% in the Norwegian adult population (Landmark et al., 2013). Chronic pain is pain lasting for more than three months (Treede et al., 2015). It negatively affects many aspects of quality of life such as function at work, self-esteem, and daily activities (Hegarty & Wall, 2014; Breivik et al., 2006). The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). This definition is illustrating that pain is a personal experience and not the same as tissue damage.

1.3 The relationship between fatigue and pain

Fatigue and pain have several components in common. They both are subjective complaints and caused by several factors both of physical and psychological nature. Fatigue is a common complaint for people with chronic pain and can be an additional source of disability (Affleck et al., 2001). Of patients with fibromyalgia, 75% report fatigue (McNallen et al., 2013). Fatigue in chronic pain patients can reduce their ability to fully engage in treatment because of their mental and physical fatigue, especially regarding treatments aimed at increasing physical activity (Vlaeyen & Linton, 2012). Due to a systematic review of the coexistence of pain and fatigue by Fishbain and colleagues (2003), it is found in prospective studies that fatigue is developed after the pain onset. This is indicating that chronic pain might cause fatigue. Fatigue is more likely to occur when the pain is more intense and present for a longer time (Fishbain et al., 2003). Fatigue and pain are among the most frequent patient-reported causes for seeking primary health care, and therefore it is clinically important to obtain a further understanding (Finley et al., 2018).

The biopsychosocial model has been responsible for the most comprehensive basis for understanding and treating chronic pain (Gatchel et al., 2007). This model evaluates the whole person, acknowledging both the physical and mental facets, and considers the biological, psychological, and social components of pain and illness (Bevers et al., 2016). Since both pain and fatigue have many of the same underlying mechanisms it is suggested that fatigue may be conceptualised as a network model such as the biopsychosocial model (Geenen & Dures, 2019). Biological factors like pain, low physical activity and sleep disturbance are associated with fatigue (Geenen & Dures, 2019). Psychosocial factors play a significant role in development and maintenance of pain (Edwards et al., 2016). The same in fatigue, stress and psychological management are psychological factors associated with fatigue in patients with rheumatoid arthritis (Geenen & Dures, 2019). Lower socioeconomic status is one social component involved in both chronic pain and chronic fatigue (Gatchel et al., 2007; Jason, Jordan et al; 1999). Social support is correlated with lower fatigue levels in the same patient group (Geenen & Dures, 2019).

For better understanding of fatigue in chronic pain, new models have been developed. Van Damme and colleagues (2018) proposes that fatigue occurs because of an imbalance of the costs-benefit trade-off connected to goal-directed behaviour. They propose three

different pathways that this costs-benefits trade-off will be affected by chronic pain. The first is through increased demand of effort to maintain a goal-directed behaviour, the second is through higher expected pain during goal pursuit and the last through lower expecting reward of an activity (Van Damme et al., 2018). Executive control is a central component of the model in evaluating the expected effort. This refers to the ability to coordinate thoughts and action and still being able to obtain goal-directed behaviour. The prefrontal cortex is central in this function due to the function of planning and evaluating consequences (Miller & Wallis, 2009). To overrule the automatic tendency to stop or avoid behaviour, executive control is required (Miyake et al., 2000). Both chronic pain and fatigue is related to compromised executive control (Moriarty et al., 2011; Van der Linden et al., 2003). This can lead to a circle of maintained fatigue. Established theories as the fear-avoidance model can explain the elevated pain expectations for a task to interpret pain in an excessively negative way (Vlaeyen & Linton, 2012). This this can further lead to fatigue due to an imbalanced costs-benefit trade-off.

The fear-avoidance model describes how interpretation of pain as fearful may cause a vicious circle leading to increased disability and maintained pain (Vlaeyen & Linton, 2000). For those who interpret pain as threatening; avoidance, hypervigilance, disuse, depression, and disability may follow (Vlaeyen & Linton, 2000). When fear is low when experiencing pain, activity levels are maintained leading to faster recovery (Vlaeyen & Linton, 2000). Avoidance strategies have been associated with fatigue severity, dysfunction, and greater pain (Nater et al., 2006). High levels of fear avoidance are found in 40% of patients with fibromyalgia (Turk et al., 2004) and even though the literature is indicating that fear avoidance is prevalent in CFS, the prevalence data is not clear (Nijs et al., 2013).

1.4 Coping and catastrophizing

Coping and beliefs are central parts of the complexity in fatigue and pain. Coping is defined as purposeful strategies that people use to manage stressful events (Lazarus & Folkman, 1984). Attributions about the causes of an illness or the symptoms are important in how the patient responds to the illness (Sensky et al., 1996). The attribution or beliefs serve as a lens for interpreting the meaning of events and making decisions about how to react to them (Lazarus & Folkman, 1984). The believes about causes of chronic fatigue syndrome as a virus, and less about their own behaviour or influence, causes impaired functioning and increased symptoms (Sharpe et al., 1992; Cathebras et al., 1995). Avoidance strategies for dealing with both fatigue and pain are, as mentioned, shown to have negative impact. The catastrophizing aspect is important to consider in fatigue because of the well-known theory of fear-avoidance in pain and the consequences related (Vlaeyen & Linton, 2000). When overestimating the potential threat of a symptom, there is an increased possibility of higher emotional distress and intensity of the symptom experienced (Sullivan et al., 2001; Severeijns et al., 2002). This is called catastrophizing. The term catastrophizing was first coined by Ellis in the 1960s (Petrini & Arendt-Nielsen, 2020) and described as the tendency to overestimate the perceived threat and the seriousness of the potential consequences of the threat. This can be related to symptoms like pain and fatigue. Fatigue catastrophizing is the tendency to engage in negative catastrophic perceptions regarding one's subjective experience of fatigue (Kangas & Montgomery, 2011). Catastrophizing according to the symptom of

fatigue is related to the severity of fatigue for chronic and life-threatening diseases, including CFS and fibromyalgia (Lukkahatai & Saligan, 2013). The same association is found in a healthy student sample (Kangas & Montgomery, 2011).

1.5 Pain catastrophizing

In relation to pain, catastrophizing has a significant role. Pain catastrophizing is defined as an exaggerated negative orientation towards pain and has been established as an important predictor of adverse pain-related outcomes (Martinez-Calderon et al., 2019). In an acute painful stimulation, pain catastrophizing contributes to a more intense pain experience and increases emotional distress (Sullivan et al., 2001). Also, in chronic pain conditions an association of catastrophic thinking and suffering from the disease is found (Edwards et al, 2006). Pain catastrophizing is considered one of the most important predictors of pain chronicity and disability (Petrini & Arendt-Nielsen, 2020).

Pain catastrophizing is a construct divided into three dimensions; rumination ("I can't stop thinking about how much it hurts"), magnification ("I worry that something serious may happen") and helplessness ("It's awful and I feel that it overwhelms me") (Sullivan et al., 1995). Although anxiety, depression, and catastrophizing are related to each other, pain catastrophizing has been reported to be the strongest psychological factor associated with the pain experience (Sullivan et al., 2001). The catastrophizing subscale of Coping Strategies Questionnaire (CSQ) and The Pain Catastrophizing Scale (PCS) are widely used measuring tools for pain catastrophizing across different medical conditions and age groups (Sullivan et al., 2001; Leung, 2012).

Most of the research examining the relationship between pain catastrophizing and pain has a cross-sectional design. Therefore, it is natural to consider that intense pain can cause catastrophic thinking, and not the other way around. Studies with prospective design have investigated this and pain catastrophizing prospectively predicted pain rating even though the patients were in a pain-free state (Sullivan & Neish, 1998; Sullivan et al., 1995). Catastrophizing of pain is also found to prospectively predicts depressive symptoms, and that catastrophic thinking might contribute to the development or maintenance of anxiety, fear or depression associated with pain (Keefe et al., 1989).

Pain catastrophizing is believed to be associated with activation in the brain structures that are involved in processing attentional and emotional aspects of pain (Gracely et al., 2004). Attention to pain symptoms appears to be one of the main mechanisms increasing the physical and emotional distress for individuals who are pain catastrophizing. Especially rumination has been shown to be highly correlated with pain outcomes (Sullivan et al., 1998). Sullivan and colleagues (1997) found that pain catastrophizing individuals may be impaired in their ability to divert attention away from pain. It is also argued that because of the activation of brain areas involving example attention it could be beneficial with interventions based on alteration of attention and to modify the perceived threat (Gutiérrez et al., 2023). Reduced descending inhibitory control is related to pain catastrophizing (Goodin et al., 2009).

Pain catastrophizing seems to mediate the relation between neuroticism and pain intensity (Affleck et al., 1992). Neuroticism is defined as the tendency to experience frequent, intense negative emotions associated with a sense of uncontrollability in response to stress (Barlow, 2014). This means that catastrophizing will have many of the same characteristics, especially due to the perception of for example threat (Barlow et al., 2014). Also, the personality feature neuroticism is found to be related to pain catastrophizing, and vigilance to pain and fear of movement (Goubert et al., 2004). Neuroticism is negatively correlated with subjective well-being in comparison to extraversion and agreeability that are positively correlated (Steel et al., 2008).

The role of relatively stable personality-based traits versus situational state characteristics when pain is experienced has been discussed and researched (Fishbain et al., 2006; Turner & Aaron, 2001). In the Pain Catastrophizing Scale, the subjects are asked to recall past painful experiences when they feel pain. Because of this, it is considered that this is measuring trait-based pain catastrophizing (Sullivan et al., 1995). The stability of pain catastrophizing scores over time is shown to be high (Keefe et al., 1989). Other studies with a longitudinal design argue that because of the changes in pain and pain catastrophizing are associated, pain catastrophizing should be considered a situational state (Lape et al., 2020; Wade et al., 2012).

Some individuals may also be triggered by a stressful event because of a predisposing biological or psychological characteristic, referred to as diathesis. The diathesis-stress framework postulates that the interaction of both diathesis and stress is responsible for the development of a disease (Banks & Kerns, 1996). It is proposed that pain catastrophizing is predisposing character, but it can be amplified under stressful situations (Turner & Aaron, 2001). Pain catastrophizing can therefore be a diathesis that in highly stressed situations, such as high pain intensity, can lead to disability. Differences in pain catastrophizing may manifest as early as in adolescent age (Bedard et al., 1997). Experiencing significant life events such as severe accidents, abuse and other traumas can make individuals more prone to orient to bodily signals as catastrophic or frightful (Tsur & Talmon, 2023).

Pain catastrophizing has a communicative function due to how it is expressed. Also, it is important to consider the complexity of pain behaviour and the fact that it goes two ways (Boersma et al., 2020). It is shown that patients who report more negative and demanding interpersonal behaviours also report higher levels of pain catastrophizing (Ryum et al., 2020). On the other hand, social support with beneficial relationships can contribute to better coping of chronic illness (Parker & Wright, 1997). As the evidence exposes, pain catastrophizing is a modifiable characteristic (Schütze et al., 2018). Reductions in catastrophizing have been shown to prospectively predict reductions in pain and disability (Sullivan et al., 2006; Adams et al., 2007). A systematic review found that cognitive behavioural therapy (CBT) has the best evidence for individuals with high levels of catastrophizing (Schütze et al., 2018). To give a successful treatment to patients with chronic fatigue syndrome, it should be focused on improving coping skills and reducing catastrophic thinking in addition to increasing activity and work on comorbidities like sleep, pain, and depression (Afari & Buchwald, 2003).

1.6 Pain catastrophizing and fatigue

The role of pain catastrophizing in fatigue is still not fully investigated. A few studies in the general population are made and the most of them in patient samples (Lukkahatai & Saligan, 2013). Association of pain catastrophizing and lack of energy and/or tiredness is found in the Dutch general population (Severeijns et al., 2002) and some findings show no association (Thompson et al., 2020). As described earlier, the biopsychosocial model is used in understanding and treating both fatigue and pain. Pain catastrophizing can be explained in this model as a psychological factor. Fewer catastrophizing cognitions correlates with less fatigue (Van Hoogmoed et al., 2010), in addition to low neuroticism and low helplessness (Jump et al., 2004; Nicklin et al., 2010). Pain catastrophizing is also a central part of the fear-avoidance model through the interpretation of the pain experience. When the pain experience is interpreted as fearful, as for individuals who catastrophize, this may contribute to the vicious circle of avoidance and probable increased disability and maintained pain (Vlaeyen & Linton, 2000). In non-catastrophizing patients, the fear experienced will be low and activity levels maintained leading to faster recovery from the pain (Vlaeyen & Linton, 2000).

One might expect that pain catastrophizing will contribute to increasing the possible costs of an activity due to the costs-benefit trade-off. Especially the expected pain will be increased due to catastrophic thinking in chronic pain patients leading to an interpretation of pain in a negative way (Sullivan et al., 2001). It hypothesised that pain catastrophizing can be a contributing factor to fatigue. This may be through all the three dimensions of pain catastrophizing (rumination, magnification, and helplessness) that will cause an imbalance of the costs-benefit trade-off leading to fatigue. The same model can be used for people without chronic pain because when they feel pain, situational, this is the same path of behaviour which may lead to fatigue.

1.7 Research question

To summarise, the relationship of fatigue and pain is complex and in need of a better understanding. Catastrophizing is related to both pain and fatigue, but the role of pain catastrophizing in fatigue is not entirely investigated, which can be relevant to models explaining the relationship between pain and fatigue.

The aim of this study is to firstly investigate the linear association of pain catastrophizing and reported feelings of energy levels in the general population. The second aim is to see if the association of pain catastrophizing is related to the occurrence of chronic fatigue.

2.0 Method

2.1 Participants

This study was a longitudinal study that was a part of a larger epidemiological study called the Nord-Trøndelag Health (HUNT) study. So far, four studies have been completed, HUNT1 in 1984-86, HUNT2 in 1995-97, HUNT3 in 2006-08, and HUNT4 in 2017-2019 (Krokstad et al., 2013; Åsvold et al., 2023). The participant rate has been respectively 89%, 70%, 54%, and 54% (Åsvold et al., 2023). The HUNT study covered a range of health-related topics through repeated surveys with questionnaires, interviews, clinical examinations, laboratory measurements, and storage of biological samples. The HUNT study is conducted in the northern part of Trøndelag county in Norway and 123 004 residents in Nord-Trøndelag have participated in at least one of the HUNT studies (Åsvold et al., 2023). The population in Nord Trøndelag is homogenous (97% Caucasian) with demographic characteristics like the average of the Norwegian population, except for a lower average income and educational level. The country is mostly rural and sparsely populated (Krokstad et al., 2013).

A random sample (n=6419) from the third wave, HUNT3, was asked to participate in a sub-study of pain called the HUNT pain study. Participants were asked to answer questions about pain and associated characteristics (Landmark et al., 2012). The sub-study of pain was completed in 2012. The HUNT pain study included five questionnaires with three months intervals in the first year and annual questionnaires for the three additional years. The current sample (n=3965) consisted of individuals answering about energy levels and pain catastrophizing, and questions about several potential confounders. The questions included in this study are from the five questionnaires over the first year of the HUNT pain study. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK). Figure 1 illustrates the process of study inclusion.

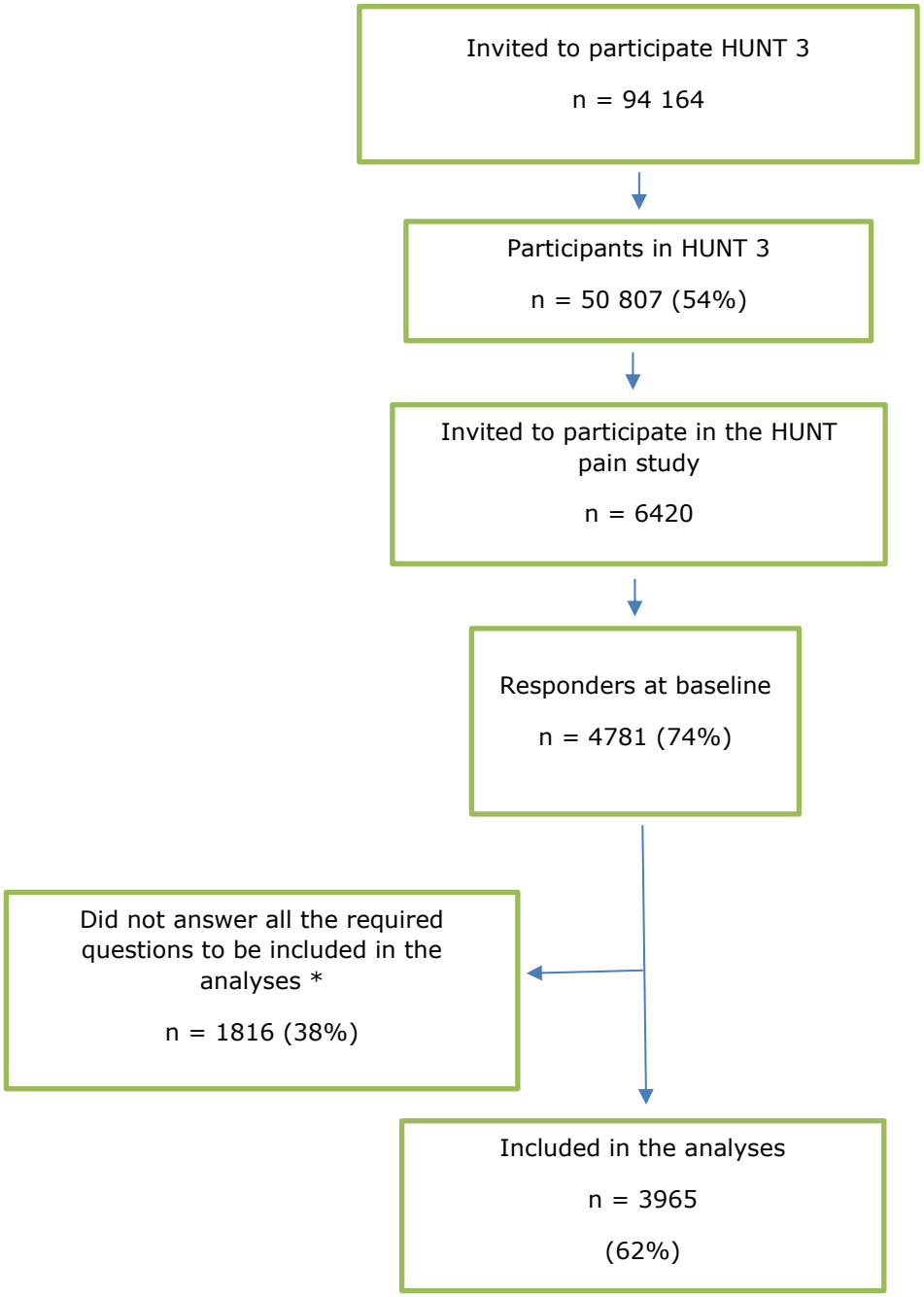

Figure 1: Flow chart illustrating the process of study inclusion of the HUNT pain study and the current study. * Variables: sex, age, organ-specific diseases, pain catastrophizing (CSQ), energy levels (SF-8), pain intensity (SF-8), mental health (MHI-5).

2.3 Measures

Energy levels

The energy levels of the sample were assessed using SF-8 vitality scale (Ware et al., 2001) which is worded: «During the last week, how much energy did you have?» Responses were given in five categories ranging from "Very much", "Quite a lot", "Some", "Little" and "None". This question was repeated every three months over a 12-months period. The mean value of the five scores was used to give a measure of each individual's overall energy level over one year. In that way, a high score indicated a relatively consistent report of moderate or much energy, a medium score may indicate variations in energy level or a consistent report of moderate energy, and a low score indicated a relatively consistent report of little energy, indicating chronic fatigue. The cut-off for chronic fatigue score <2 was chosen as this included the lowest fourth of the possible scores of the scale corresponding to previous suggestions for identifying fatigue (Lerdal et al., 2005). Moreover, by scoring lower than two on the mean of the five questionnaires, a participant would have at least one response of "None" energy and the rest with a "Little", or several responses of no energy and one response with more, both including a particulate low level of energy during one year follow-up period.

Pain catastrophizing

Pain catastrophizing was assessed using the two-item version of the catastrophizing subscale of the Coping Strategies Questionnaire (CSQ) at baseline. The scale measured subjective evaluations of helplessness and threat when experiencing pain (Rosenstiel & Keefe, 1989). The questions included were "When I'm in pain it is terrible, and I feel like it's never going to get any better" and "When I'm in pain it feels like I can't stand it anymore". The items were rated on a 7-point Likert scale from 0 = "never do" to 6 = "always do that". The two scores were added together, and higher scores indicated higher levels of pain catastrophizing. The two-item version of CSQ has a strong association with the full scale and is sensitive to change due to pre- to post-treatment, but not to the same degree as the full scale (Jensen et al., 2003). High levels of the catastrophizing scale of the CQS are associated with higher levels of physical and emotional distress related to their pain condition (Keefe et al., 1989).

2.4 Possible confounders

Pain intensity was assessed by the question; "How much bodily pain have you had during the last week?". Responses were provided on a 6-point verbal rating scale ("none," "very mild," "mild," "moderate", "severe" or "very severe"). Baseline data was used. The item was administered as part of the SF-8 health survey (Ware et al., 2001). The higher score, the higher the pain intensity.

Mental health was measured with the Mental Health Inventory - 5 (MHI-5) for measuring mental distress and mental disorder. This measurement is widely used not only in psychiatric surveys but also in surveys of general health (Strand et al., 2003). The answer alternatives on the two questions that pin out the positive in mental health of the last week ("felt happy" and "felt calm and harmonious") were reverse coded so a high score indicated better mental health and a low score indicated poorer mental health.

Information about *organ-specific diseases* was measured by self-report by enquiring about the presence of the following conditions during the past year: heart disease, lung disease, cancer, gastrointestinal disease, kidney disease, neurological disease, osteoarthritis, arthritis (rheumatoid arthritis, psoriasis arthritis and Bechterew's disease) and diabetes. Self-reports of these chronic diseases are found to be accurate (Kriegsman et al., 1996). Responses at baseline were categorized into three; "no organ-specific disease", "one organ-specific disease" or "two or more organ-specific diseases".

2.5 Statistical analyses

The variables of the study were summarized for descriptive purposes using means and SD for the continuous variables and frequencies for categorical variables. The association between pain catastrophizing and individuals' energy levels over one year in the general population was measured using a series of multiple linear regression in the statistical software program SPSS (Statistical Package for the Social Sciences) using General Linear Models (GLM). Fatigue was included as the dependent variable and pain catastrophizing as the independent variable. Age, sex, and organ-specific diseases were added as potential confounders in the second step, then pain intensity was added in the fourth, and mental health was included in the last adjusted model. To see if the assumptions for linear regression were fulfilled the continuous variables were plotted against the dependent variable to check the linear relationship and Q-Q plots were used to check if the residuals were normally distributed. Then the Pearson correlations between the variables were computed evaluating their bivariate association. A coefficient from 0.10 to <30 is considered as small, medium as 0.30 to <0.50, and 0.50 to 1.0 as large (Cohen, 1992). The assumption of homoscedasticity was checked by inspecting the residuals in a scatterplot against the predicted values. There were no clear deviations from homoscedasticity. An interaction term between pain intensity and pain catastrophizing was constructed and in a sensitivity analysis. The same linear regressions were done for the group with chronic pain (n=2228) and for the sample of the study with pain catastrophizing after 12 months as the independent variable. Logistic regression in GLM was used to investigate the association between pain catastrophizing and chronic fatigue defined as scoring <2 on the five questionnaires over a year. These analyses were done using similar steps to account for confounding of age, sex, organ-specific diseases, pain intensity and mental health.

3.0 Results

3.1 Characteristics of the study sample

The majority (57%) of the study sample were women (n=1698) and the mean age of the sample was 55 years (SD=12.89). In total, 23% were in the youngest group (19-44), 54% middle-aged (45-65), and 23% in the oldest age group (65 and older). At baseline, 75% (n=2215) reported not having any organ-specific diseases and 7% (n=205) of the sample had 2 or more organ-specific diseases. The mean energy level was 2.8 (SD=0.78). The mean pain catastrophizing score was 2.8 (SD=2.63). On mental health, the sample mean was 25.5 (SD=3.48). Keeping in mind that a higher score on this measure indicates better mental health. Further characteristics of the sample are illustrated in Table 1.

Table 1: Characteristics of the study sample (n=3965)

Categorical variables	**N**	**%**
Sex (men)	1267	43
Sex (women)	1698	57
No organ-specific disease	2215	75
One organ-specific disease	545	18
≥ 2 organ-specific diseases	205	7

Continuous variables (scale)	**Mean**	**SD**
Energy level (1-5)	2.8	0.78
Age (20-96)	54.5	12.89
Pain catastrophizing (0-12)	2.8	2.63
Mental health (5-30)	25.5	3.48
Pain intensity (1-6)	2.8	1.36

Table 1: Characteristics of the study sample.

Figure 2 describes the mean energy level of the sample over one year. It shows almost a normal distribution meaning the main part of the sample scored in the middle of the scale indicating moderate energy levels most of the time, or fluctuation in the energy levels. Mean and median were approximately the same. Calculation of intraclass correlation coefficient (ICC) was 0.6 meaning their answers' consistency was quite high and had some variation of the answers. This indicates moderate consistency (Koo & Li, 2016). Of the sample, 10% scored below the cut-off for chronic fatigue which was defined as <2.

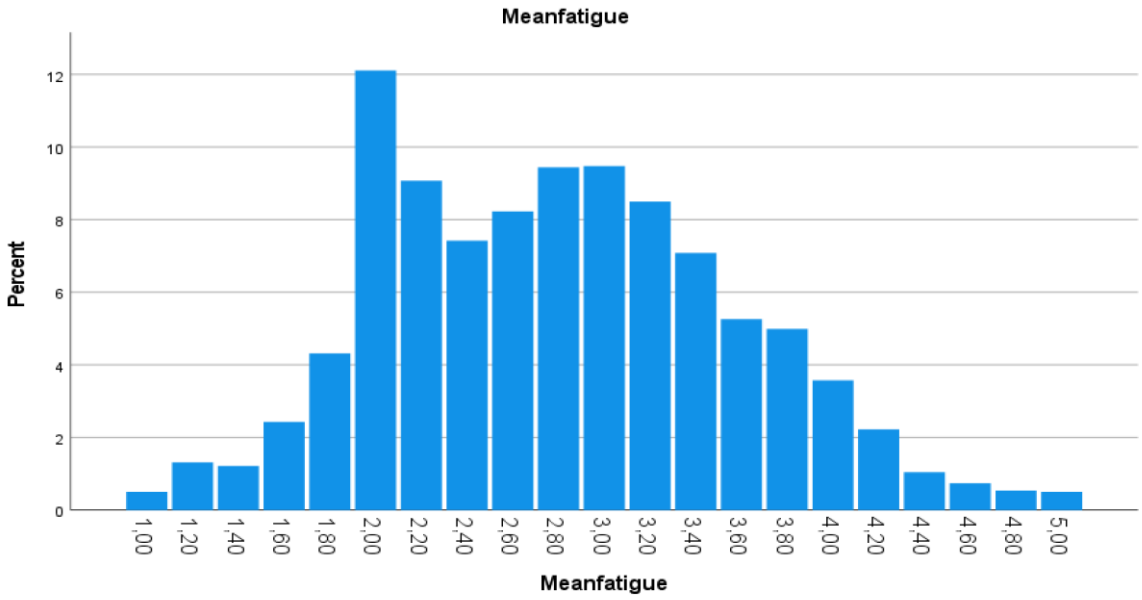

Figure 2: Bar chart showing energy levels of the sample over one year. Mean fatigue refers to energy levels.

3.2 Associations between pain catastrophizing and energy level

The Pearson correlations coefficients among the continuous variables are presented in table 2. Energy level showed moderate correlation with pain catastrophizing (r=0.45), mental health (r=-0.54), and pain intensity (r=0.53). Pain catastrophizing showed a moderate correlation to pain intensity (r=0.57) indicating the importance of including it as a potential confounder in the further analyses. The negative correlations of mental health are explained by the fact that higher scores indicate better mental health. Pain catastrophizing showed a moderate association with mental health (r=-0.35).

Table 2: Pearson correlations between energy level, pain catastrophizing, mental health, and pain intensity.

	Energy level (FS-8)	**Pain catastrophizing (CSQ)**	**Mental health (MHI-5)**	**Pain intensity (FS-8)**
Energy level (FS-8)	-	0.45	-0.54	0.53
Pain catastrophizing (CSQ)		-	-0.35	0.57
Mental health (MHI-5)			-	-0.34
Pain intensity (FS-8)				-

Table 2: Bivariate Pearson correlation coefficients between continuous variables.

The results of the regression analysis with energy level as the dependent variable are summarised in table 3. The beta value for crude analyses was 0.13 (95% CI: 0.12-0.14). This value indicates the mean increase of energy level for one unit increase of pain catastrophizing when the data is unadjusted. When adjusted for age, sex, and organ-specific diseases the beta value decreased to 0.12 (95% CI: 0.11-0.13) and it further decreased to 0.06 (95% CI: 0.05-0.07) when additionally adjusted for pain intensity. When additionally adjusted for mental health the beta value was 0.04 (95% CI:0.03-0.05). In separate analyses similar results were found in individuals with chronic pain, lasting over six months (β=0.04, 95% CI: 0.02-0.05). Significant association was found when pain catastrophizing after 12 months was the independent variable.

Table 3: Associations between pain catastrophizing and energy levels measured with repeated questionnaires every three months in the general population (n=3965).

Variables and steps	β	95% CI
Step 1		
Pain catastrophizing*	0.13	0.12 – 0.14
Step 2		
Pain catastrophizing*	0.12	0.11 – 0.13
Step 3		
Pain catastrophizing*	0.06	0.05 – 0.07
Step 4		
Pain catastrophizing*	0.04	0.03 – 0.05

Table 3: Associations between pain catastrophizing and energy levels. Step 1: crude. Step 2: adjusted for age, sex, and organ-specific diseases. Step 3: adjusted for age, sex, organ-specific diseases, and pain intensity. Step 4: adjusted for age, sex, organ-specific diseases, pain intensity and mental health. *Pain catastrophizing was scaled 0-12.

When analyzing the association between pain catastrophizing and the prevalence of chronic fatigue, the crude odds ratio (OR) was 1.50 (95% CI: 1.39-1.62). This indicates that the odds for chronic fatigue. When adjusted for age, sex and organ-specific disease OR decreased to 1.48 (95% CI: 1.37-1.60). When additionally adjusted for pain intensity OR further decreased to 1.26 (95% CI: 1.16-1.37). In the last step, when adjusted for age, sex, organ-specific disease, pain intensity and mental health OR=1.21 (95% CI: 1.11-1.31). The results of the regression analysis for sample with chronic fatigue is summarised in table 4.

Table 4: Associations between pain catastrophizing and chronic fatigue measured with repeated questionnaires every three months in the general population (n=3965).

Variables and steps	Odds ratio	95% CI
Step 1		
Pain catastrophizing*	1.50	1.39 – 1.62
Step 2		
Pain catastrophizing*	1.48	1.37 – 1.60
Step 3		
Pain catastrophizing*	1.26	1.16 – 1.37
Step 4		
Pain catastrophizing*	1.21	1.11 – 1.31

Table 4: Associations between pain catastrophizing and chronic fatigue. Step 1: crude. Step 2: adjusted for age, sex, and organ-specific diseases. Step 3: adjusted for age, sex, organ-specific diseases, and pain intensity. Step 4: adjusted for age, sex, organ-specific diseases, pain intensity and mental health. *Pain catastrophizing was scaled 0-12.

3.0 Discussion

Associations between pain catastrophizing and energy levels were evaluated in a population-based sample. A significant association was found even after controlling for age, sex, organ-specific diseases, pain intensity and mental health, although adjusting for pain intensity attenuated the association notably. The same association was found in the group with chronic pain. The energy levels of the sample were approximately normally distributed and 10% were defined as having chronic fatigue. The association was even more salient for chronic fatigue, with odds increasing by 1.2 for every unit increase in pain catastrophizing.

These findings are in line with other studies that have investigated the association between catastrophizing and fatigue. The majority of the studies focused on the association between fatigue catastrophizing and fatigue (Lukkahatai & Saligan, 2013) and fewer on pain catastrophizing in association to fatigue. As a general concept, catastrophizing can be related to different symptoms, and it is described as the tendency to overestimate the potential threat of a symptom and the seriousness of the potential consequences of the threat (Petrini & Arendt-Nielsen, 2020). In this setting, it will be due to the symptoms of either fatigue or pain. In the upcoming section, the results will be discussed in relation to other studies on respectively pain catastrophizing and fatigue catastrophizing.

3.1 Association between pain catastrophizing and fatigue

This is one of few studies to investigate the association between pain catastrophizing and fatigue in the general population. In a sample of patients with fibromyalgia, a significant association between pain catastrophizing and fatigue was found (Aaron, 1999). The study used catastrophizing subscale of CSQ. Findings in this current study are in contrast to a study on a sample of patients with persistent pain and fatigue in a physiotherapy environment where no significant associations were found (Thompson et al., 2020). Both physical and mental fatigue was assessed using Chalder Fatigue Scale. A study from the Dutch general population found a significant association between pain catastrophizing and vitality (feelings of energy and tiredness) but stronger associations for those with pain than those without pain (Severeijns et al., 2002). While the current study shows the same associations in the sample of chronic pain and the general population. A limitation of earlier studies from the general population is a lack of control for depression and the medical seriousness of pain complaints (Severeijns et al., 2002).

3.2 Association of fatigue catastrophizing and fatigue

The association of fatigue catastrophizing and fatigue is better documented in the literature. A systematic review by Lukkahatai & Saligan (2013) was looking into the association between catastrophizing and fatigue, including different measuring tools both for pain- and fatigue catastrophizing. Different measures for fatigue and pain catastrophizing were used, also different from the ones in this current study. In a sample of healthy students, an association was found between fatigue catastrophizing and fatigue severity (Kangas & Montgomery, 2011). For patients with CFS, higher fatigue catastrophizing was associated with higher levels of fatigue (Petrie et al., 1995). It is important to emphasize that this applies to fatigue catastrophizing. However, fatigue and pain catastrophizing are likely to be related. As presented earlier the same thoughts and beliefs are included but for different symptoms, and it is naturally to assume the same characteristics are involved in both types of catastrophizing. The personality trait neuroticism is involved in both variants of catastrophizing (Kangas & Montgomery, 2011; Affleck et al., 1992) and may also be linked to pain-related fear and avoidance (Vlaeyen & Linton, 2000).

Most of the literature on catastrophizing is focused on patient samples. If these studies are longitudinal designed, it is because of a follow-up around treatment. Among cancer patients, pre-treatment fatigue catastrophizing is associated with post-treatment fatigue severity (Jacobsen et al., 2004; Goedendorp et al., 2013; Andrykowski et al., 2010; Donovan et al., 2007). In patients with multiple sclerosis the findings are mixed (Bol et al., 2010; Skerrett & Moss-Morris, 2006).

3.3 Pain catastrophizing and fatigue according to explanatory models

The findings from this study may contribute to explaining the relationship between pain and fatigue. In this section, the findings will be further explained considering the mentioned, fear-avoidance model, and the model of costs-benefit trade-off. The fear-avoidance model emphasizes how pain-related fear, pain catastrophizing, and avoidance can lead to a vicious cycle of adverse coping strategies which might lead to further inactivity, deconditioning, depression, and more pain (Vlaeyen & Linton, 2000). In that

way, pain catastrophizing can increase or maintain fatigue through activity avoidance patterns and the disuse following. Fear of movement predicts avoidance in patients with CFS (Silver et al., 2002) and avoidance strategies are associated with lower energy levels and pain severity (Nater et al., 2006). Pain catastrophizing can act as a promoter of inactivity in fibromyalgia patients (Gutiérrez et al., 2023). Therefore, the fear-avoidance model is relevant in explaining the link between pain catastrophizing and fatigue, as it emphasizes the role of negative coping strategies, depression and deconditioning in maintaining pain and exacerbating fatigue.

Although pain catastrophizing or avoidance of potentially harmful movements can be functional in an acute stage, it can become dysfunctional when the pain problem persists (Crombez et al., 2012). Avoidance can lead to isolation and inactivity, making the discrepancy between the current situation and the desired end goal even greater and requiring extra effort and resources to solve the problem (Crombez et al., 2012). This can explain why pain catastrophizing can lead to fatigue, as the effort requested for an activity becomes even higher to reach, resulting in an unbalanced costs-benefit trade-off. Negative thoughts, as pain catastrophizing, may reduce the expected reward and the weight of the benefits associated with the behaviour, inducing reduced motivation and increasing fatigue. Fatigue is believed to have a signal value for motivation control, meaning a mechanism resolving conflicts between current goals and other desired actions (Hockey, 2013). Moreover, depression and deconditioning may not follow from avoidance in all individuals who catastrophize about pain. In this current study, the association was maintained even after controlling for mental health and pain intensity. Therefore, understanding the impact of pain catastrophizing on energy levels and motivation can be valuable not only for those with chronic pain, deconditioning or depression but also for others dealing with negative thoughts around pain.

The degree to which pain behaviour is related to stable traits (Vlaeyen & Linton, 2000; Keefe et al., 1989; Dumenci et al., 2020) or more situational behaviour depended upon the motivational context they are in (Van Damme et al., 2012) is debated. The fact that the association between pain catastrophizing and the energy levels over one year remained significant, even after controlling for pain intensity, leaning more against that it is related to a trait. People high in neuroticism seem to be high in pain catastrophizing (Affleck et al., 1992). The perception of reward may be influenced by neuroticism, as individuals with this trait tend to respond negatively to different stressors and hold the belief that they lack the ability to cope with challenging events (Barlow et al., 2014). This increases the weight of the cost and reduces the expected reward thus causing fatigue in the same way as explained earlier. Also, individuals with this trait tends to focus on the problems, and therefore competing goals will increase during attempts to solving the problems with pain. When pain relief is the most dominant goal, the individuals become more sensitive to related information, probably increasing hypervigilance (Notebaert et al., 2011), and the attention is drawn to pain relief at the cost efforts in pursuing other goals (Crombez et al., 2008). The other way around, because of the decreased executive control when in fatigue (Van der Linden et al., 2003) it will be even harder to overrule the tendency to stop or avoid pain catastrophizing and other maladaptive coping strategies. This may lead to increased effort for a task and contributes to continuing the

downward spiral of fatigue. Both the physical fatigue, through weakness and tiredness, and the mental fatigue through less executive control, may probably contribute to this.

In the previous sections mainly the psychological part of the biopsychosocial model is discussed. In this model pain catastrophizing can be described as a shared factor between pain and fatigue. Biological mechanisms contributing to the association between pain catastrophizing and fatigue may be seen from studies of plasticity in the nervous system. An overlap between psychiatric disorders, fatigue, and pain is found due to the same neurotransmitters in different brain regions being operative (Clauw, 2010). The same physiological mechanisms may be related to central nervous system sensory amplification as seen in central sensitisation of pain (Clauw, 2010). The association found between pain catastrophizing and energy levels can thus be due to sensory amplification. Central sensitization significantly predicts fatigue independently of the presence of pain (Druce & McBeth, 2019).

The association between pain catastrophizing and fatigue may also be related to social mechanisms. Catastrophizing may be views as an attempt to elicit social support and pain catastrophizing can be related to interpersonal problems (Ryum et al., 2020). Communication may therefore play an essential role in pain catastrophizing and the lack of effective communication can lead to development of pathological patterns and coping strategies, ultimately leading to learned helplessness. Learnt helplessness is linked to fatigue because the benefits of pursuing effortful goals will be reduced and over time increasing the costs required, in addition to reducing the individual's control in the situation (Hockey, 2013). Therefore, it is important to consider both biological and social factors in the relationship between pain catastrophizing and fatigue.

3.4 Methodological considerations

In the following sections possible bias will be discussed due to the selection of participants, the way the study variables were measured and confounding. Additionally, some considerations of the study will be discussed.

Selection bias

Selection bias is a systematic error that refers to procedures used to select participants and factors influencing the study participation (Rothman, 2002). Participants in HUNT 3 were not fully representing the population in the rest of Norway because both the oldest and the youngest were underrepresented (Langhammer et al., 2012). Also, men in all age groups were more likely to not participate in the study. The non-participants had lower socioeconomic status, higher mortality, and higher prevalence of several chronic diseases. They also had a higher prevalence of musculoskeletal pain (Langhammer et al., 2012). In addition, several of the same factors were associated with the participants in the longitudinal HUNT pain study. The loss to follow-up was therefore a limitation that may have reduced the representativeness of the estimates. External validity or generalizability refers to the extent the findings of the study have to other settings and contexts (Rothman, 2002). In addition to the mentioned characteristics of the non-participants, the geographic area of Nord-Trønderlag where the HUNT study was

conducted, has no large city. Therefore, the generalizability of the result to other cultures and countries should be interpreted with caution. When assessing associations, as in this thesis, representativeness is less important (Galea & Tracy, 2007). In scientific inference, the goal is often to infer abstract theories rather than finding one conclusion for one specific population (Rothman, 2002). Some selection bias, through self-selection, in the HUNT pain study was probably because those with pain could have been more likely to participate, which could lead to an overrepresentation of individuals with pain. The results in this study were adjusted for potential confounding factors to minimise the impact of selection bias.

Information bias

Information bias is the measuring error or misclassification due to either the exposure or the outcome (Rothman, 2002). The data collected in this study collected only information of "lack of energy", whereas the definition of fatigue includes a sense of tiredness/exhaustion and impaired physical and/or cognitive functioning (Shen et al., 2006). This is a limitation of the study, but we can assume that if the lack of energy is strong enough, it will affect mental and physical function, making it an adequate measure of fatigue. This is a non-differential misclassification meaning it is unrelated to the exposure (Rothman, 2002). Another possible non-differential misclassification is due to the cut-off for chronic fatigue. The cut-off was estimated to be <2 (scaled 1-5) and 10% was defined as having chronic fatigue. This was for targeting the group with consistently low energy levels over a year. However, a wide range of prevalence for chronic fatigue according to different cut-offs, countries, and settings has been published (Lerdal et al., 2005; Jason, Jordan et al., 1999). For instance, the Fatigue Severity Scale (FSS) is measuring the impact of disabling fatigue on daily functioning (Krupp et al., 1989), which is different from comparing a scale of levels of energy over a year. In other studies, the prevalence of chronic fatigue in the general population in the UK is found to be 9% and in Germany 6% (Skapinakis et al., 2000; Martin et al., 2007). In primary care in the UK the prevalence is 10% (Wesseley, Chalder et al., 1997) which can indicate an adequate cut-off. The highest prevalence that has been measured is in the Netherlands at 30% (van't Leven et al., 2010). If the cut-off was set higher, the association could be affected due to lower association found.

In this study, brief measures were used. Pain catastrophizing is a construct of three dimensions; rumination, magnification, and helplessness (Sullivan et al., 1995). While a two-item scale may not fully capture the entire construct, it has been found to have a strong association with the full scale and is sensitive to change, and therefore can provide adequately valid estimates of the helplessness dimension (Jensen et al., 2003). These brief versions of the full scale are useful in epidemiological studies due to the few questions per variable assessed (Jensen et al., 2003) and therefore easy to include in a large study such as the HUNT study focusing on many different factors. It is worth noting that the helplessness dimension of pain catastrophizing is linked to pain experience in subgroups with chronic pain (Sullivan et al., 2001). Therefore, despite the limitations of the two-item scale, it can still provide valuable insight of pain catastrophizing. This large sample size will assure that random error to a smaller degree will influence the results (Rothman, 2002), and therefore will to a large degree compensate for any precision lost due to any precision lost due to brief measures.

Confounding factors

Confounding is referred to as confusion, or mixing, of effects due to a common cause. This leads to bias if the effect of the exposure is mixed with the effect of another variable (Rothman, 2002). Confounding has been handled in this study with statistical procedures through multivariate analyses. Age, sex, organ-specific diseases, pain intensity and mental health were included to be confounding factors in the association between pain catastrophizing and fatigue. Pain intensity was considered as a confounder in this study but is not obvious that it is so, as it can be a part of the causal pathway from exposure to disease, known as a causal intermediate (Rothman, 2002). That is different from a confounder due to a causal intermediate is affected by the exposure. Explained like this, pain catastrophizing (as an exposure) can lead to higher pain intensity (Sullivan et al., 2001) and the greater the pain intensity, the more likely the chance of experiencing fatigue (the "disease") (Liao & Ferrell, 2000). A confounder cannot be affected by the exposure due to its definition or criteria (Rothman, 2002). The same can be with mental health due to the strong association between pain catastrophizing and depression (Edwards et al., 2011) and it seems to be pain catastrophizing affecting depressive symptoms (Glette et al., 2021). Thus, it may be argued that the models including pain intensity and mental health may have been over-adjusted (Schisterman et al., 2009). Organ-specific diseases were controlled for in that way comorbidity is highly related to fatigue and it is highly unlikely that pain catastrophizing is the cause (Komaroff et al., 1996). Due to the etiological relationship between insomnia symptoms and pain (Finan et al., 2013), sleep difficulties could also have been included as a confounder, but it was considered more likely a causal intermediate as pain catastrophizing may disrupt sleep in a direct way.

Considerations of the study

There are various weaknesses or improvements that could have been made in this study. Optimally, separate regression analyses should have been conducted for the group without chronic pain, in addition to the analyses for chronic pain, to estimate difference between the groups. For a more consistent measure of pain catastrophizing, a mean of the pain catastrophizing score at baseline and after 12 months could have been used. However, in this study, only baseline data was used to decrease the loss of responders when using both measures. The same analyses were done with the pain catastrophizing score after 12 months as the independent variable, and the association was still significant. In the analyses of pain catastrophizing the two items of the CSQ scale were added together (0-12) and not from 0-6, which could have made it easier to interpret the results. Despite these weaknesses, the study has some strengths. The large sample size provides enough power to find associations of different variables and adjust for the wanted confounders. The frequency of the follow up about the energy levels of the sample was repeated every three months over a 12-months period compared to other studies on the general population that only has one (Kangas & Montgomery, 2011; Severeijns et al., 2002). This gave the opportunity to identify a group with chronic fatigue with a higher precision.

3.5 Clinical implications

Our findings shows that it is an association between pain catastrophizing and fatigue in the general population and even more prominent for those with chronic fatigue. Even though this is not a clinical study, it can provide information about factors involved in illness and therefore it is worthwhile to explore how findings from this study potentially could impact quality of life. The threshold of identifying a minimal clinical difference in the importance of quality of life appears to be half standard deviation (SD) difference or more (Norman et al., 2003). SD for energy level was 0.78 (divided in two is 0.39). The beta-value for pain catastrophizing was 0.04. For the general population this means to reach a clinically significant difference one needs to move 10 steps on catastrophizing scale. That means a clinically significant difference in energy levels may be indicated between those who score at the lowest and the highest end of the scale which runs from 0-12. When identifying individuals with higher end of the catastrophizing scale, for example in primary care, the need to plan an integrative treatment plan to prevent or treat fatigue should therefore be appraised. The association between pain catastrophizing and chronic fatigue was more apparent and addressing pain catastrophizing should be considered among patients with chronic fatigue, in particular when pain is a comorbid symptom.

Even though the clinically meaningful difference is not that large for the general population, the findings could have significance on public health. It is argued that public health significance is more valuable than statistical significance when interpreting epidemiological findings (Kraemer, 2010). Pain catastrophizing and avoidance can be underlying transdiagnostic mechanisms for an occurring pain problem (Linton, 2013). Findings from this current study suggest that pain catastrophizing is an underlying mechanism also in fatigue, and especially in chronic fatigue. Treatment targeting the underlying mechanisms, that can be potent drivers in chronification process, can be meaningful (Linton, 2013). From a public health point of view, working on these negative thoughts about pain, in group or individual level, could lead to a difference in the degree of energy levels for a significant proportion of the population.

In the logistic regression analyses the information is simplified when a cut-off is used. However, the cut-off for chronic fatigue gives more clinical relevance due to the public health significance because different levels of pain catastrophizing give an increased probability for having chronic fatigue. It is harder to interpret the linear association in term of clinical relevance because comparing the different levels of energy runs from high to no energy. It may be argued that a change from high levels of energy to normal levels of energy is not clinically relevant, but a change from normal to a little energy is.

The results from this study do not provide concrete implications on the longer term, however including pain catastrophizing as a preventive action could be useful, also when reducing the burden of fatigue. Most chronic fatigue and chronic pain patients are treated in primary health care services, commonly by the patient's GP. Patients could benefit from a broader approach to the psychological symptoms in preventing chronic fatigue in these patient groups. Other preventive approaches could be to have easier access to primary health care services or focus on public health prevention programs. The

programs could have included teaching pain coping strategies, including techniques for reducing pain catastrophizing. Pain catastrophizing is a modifiable factor and multimodal treatments combining CBT and exercise may work best for reducing pain catastrophizing (Schütze et al., 2018). Cognitive behaviour therapy (CBT) on the maintaining factors of CFS in several controlled trials showed to lead to a reduction in fatigue (Whiting et al., 2001). This includes outcome variables as coping strategies. For people with CFS, a decrease in pain severity was associated with an improvement in fatigue severity (Knoop et al., 2007). The benefit of both preventive and treatment point of view is to target other potential consequences of pain catastrophizing like pain, sleep problems, and depression (Martinez-Calderon et al., 2019; Campbell et al., 2015; Glette et al., 2021)

Because of the huge prevalence of post-COVID 19-condition, there is a large group at risk of developing chronic fatigue in addition to the ones already suffering from fatigue as a sequela of the infection. Studies show that psychological factors such as stress and fear are involved in developing post-COVID-19 fatigue in addition to pain as a symptom of the condition (Rudroff et al., 2020). This is indicating an importance of screening and potentially treating pain catastrophizing for post-COVID-19 fatigue.

3.4 Future research

The cross-sectional design of this study limits the ability to establish causal relationships or determine risks. Prospective studies are needed for identifying risks because it occurs before onset of the disease (Kraemer et al., 1997). Preventive strategies could be useful if pain catastrophizing is a factor occurring before fatigue. A longitudinal study is needed to assess whether changes in pain catastrophizing can explain changes in fatigue. In general, the future research on fatigue and pain should aim to identify potential mechanisms involved for identifying possible targets for treatment in individual and population levels. In line with this, further research is needed to examine the role of pain catastrophizing in post-COVID-19 fatigue because of the potential improvement of quality of life for those affected.

4.0 Conclusion

This study shows that pain catastrophizing is associated with energy levels in the general population, even after controlling for factors related to fatigue and health. In the general population, 10% was defined as having chronic fatigue and the association was even more prominent when cut-off for chronic fatigue was made. According to models explaining fatigue and pain, pain catastrophizing may strengthen an imbalance of costs versus benefits in goal-directed behaviour. Moreover, it is proposed that fatigue can be included in the vicious circle described by the fear-avoidance model as a consequence of catastrophizing and maintaining pain. Due to the large prevalence of fatigue as a sequela after COVID-19 infection the findings can indicate clinical relevance. To better assess the causal relationship of pain catastrophizing and fatigue longitudinal studies are needed.

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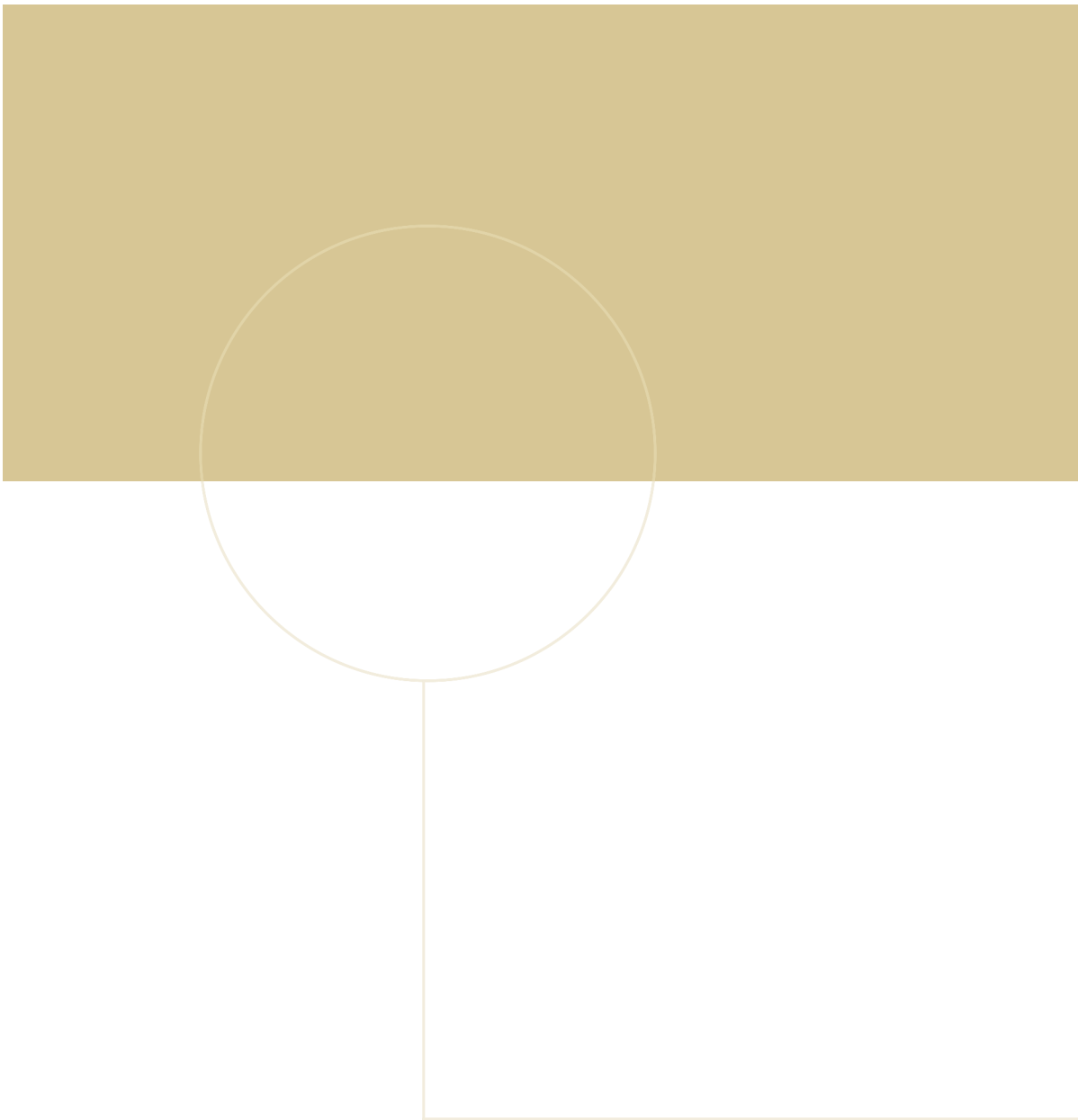

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