Risk factors for development and maintenance of chronic whiplash

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Scientific environment

This PhD project was carried out at the Department of Public Mental Health, Norwegian Institute of Public Health (NIPH), Bergen, Norway, in collaboration with the Department of Clinical Science, the University of Bergen (UiB), Bergen, Norway.

My main supervisor has been Børge Sivertsen at the Department of Public Mental Health, NIPH. Ingvard Wilhelmsen at the Department of Clinical Science, UiB, and Jens Christoffer Skogen at the Department of Public Mental Health, NIPH, have been my co-supervisors.

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Part of the PhD project was carried out during a research stay at the Department of Psychological Medicine at the University of Auckland, New Zealand.

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During my PhD period I have also been a student in EPINOR, a National Research School of Population Based Epidemiology.

EPINOR

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List of abbreviations

Conditions
CFS: Chronic Fatigue Syndrome
FSS: Functional Somatic Syndromes
LBP: Low Back Pain
MUS: Medically Unexplained Symptoms
PTSD: Post-traumatic Stress Disorder
WAD: Whiplash Associated Disorder

Therapy
APT: Adaptive Pacing Therapy
BT: Behavioral Therapy
CBT: Cognitive-Behavioral Therapy
GET: Graded Exercise Therapy
GP: General Practitioner
MRI: Magnetic Resonance Imaging

Instruments
CSQ: the Coping Strategies Questionnaire
GHQ: General Health Questionnaire
HADS: The Hospital Anxiety and Depression Scale
IES: Impact of Event Scale
IEQ: Injustice Experience Questionnaire
MSPQ: Modified Somatic Perceptions Questionnaire
NDI: Neck Disability Index
SNQ: Standardized Nordic Questionnaire
VPMI: Vanderbilt Pain Management Inventory

Statistics, methods and data
CI: Confidence Interval
HUNT (1, 2, 3): Nord-Trøndelag Health Study (wave one, two and three)
OR: Odds Ratio
RCT: Randomized Controlled Trials
ROC: Receiver Operating Characteristics curve

Institutions
NIPH: Norwegian Institute of Public Health
NTNU: Norwegian University of Science and Technology
REC: Regional Committees for Medical and Health Research Ethics
UiB: University of Bergen

Various
BMI: Body Mass Index
DSM: Diagnostic and Statistical Manual of Mental Disorders

GBD: Global Burden of Disease
ROM: Range of motion
QTF: Quebec Task Force
YLD: Years Lived with Disability

Abstract

Background: After experiencing whiplash accidents, most individuals recover rapidly. Others, however, develop chronic whiplash, a condition characterized by long lasting neck pain, somatic complaints and symptoms of anxiety and depression. Individuals with chronic whiplash report the condition to reduce their quality of life and ability to work.

As most individuals recover from whiplash accidents without needing medical attention, identifying those at risk of chronic complaints, and in need of treatment, is important. Factors related to the whiplash accident, like speed and extent of damage to the cars, as well as findings from clinical imaging seem poorly correlated with outcome. Previous research indicates that socio-demographic factors, pre-injury somatic and mental health as well as coping might be associated with prognosis. However, as existing literature remains inconclusive, and much of the research is based on retrospectively collected data, more evidence is needed.

Aim: The overall aim of the thesis was to investigate whether socio-demographic factors, pre- and post-injury health, use of health care and medications, and early coping preferences are associated with outcome after whiplash accidents.

Method: In study one and two data from two waves of the large, Norwegian population-based Nord-Trøndelag Health Study (HUNT2 and HUNT3) was used. Study one investigated whether socio-demographic variables (such as age, gender, education) and health related variables (such as perceived health, health behavior and use of health-services, musculoskeletal complaints, somatic complaints, medical diagnoses and anxiety and depression) measured before the accident were associated with development of chronic whiplash.

Study two investigated whether socio-demographic and health-related variables measured in individuals with whiplash were associated with recovery.

Study three used prospective data from Denmark, following individuals with acute whiplash for a year. Coping and health care preferences reported during the first few days following the whiplash accident were described. The associations between early health care/coping preferences and outcome (neck pain/reduced capability to work) one year later were investigated.

Results: The three studies in this thesis show that: Poor pre-injury health, both mental and somatic, is associated with development of chronic whiplash (study one). Similar health complaints reported among individuals with whiplash are associated with non-recovery from the condition (study two). A high use of health care services and medications before the injury is associated with increased risk of developing chronic whiplash (study one). High use of health care and medications among individuals with whiplash is associated with non-recovery (study two).

Patients' coping preferences in the acute phase after whiplash injuries are associated with outcome in whiplash (study three): Reporting passive coping preferences and need of health care increase the risk of neck pain and reduced capability to work one year later. Individuals who prefer active coping and want to keep living as normal have a better prognosis.

Conclusion: Chronic whiplash is a complex condition characterized by a broad range of complaints. Clinical imaging and accident related factors seem to be poor predictors of outcome. Poor pre-injury health and use of health services and medications are associated with subsequent chronic whiplash. Similar variables in individuals with whiplash are associated with non-recovery. Preferring use of health care and passive coping after whiplash is associated with non-recovery. As such chronic whiplash resembles functional somatic syndromes.

Knowledge of prognostic factors might aid identification of individuals at risk of an adverse prognosis after whiplash, enabling earlier treatment for those most in need. However, health care in whiplash is often ineffective and might itself increase the risk of poor recovery. More research on treatment of whiplash is needed; in particular on

whether targeting prognostic factors like those identified in this thesis can improve recovery.

List of publications included in thesis

Myrtveit, S. M., Wilhelmsen, I., Petrie, K. J., Skogen, J. C., & Sivertsen, B. (2013): What characterizes individuals developing chronic whiplash?: the Nord-Trøndelag Health Study (HUNT). Journal of Psychosomatic Research, 74(5), 393-400.

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Myrtveit, S. M., Carstensen, T., Kasch, H., Ørnbøl E., & Frostholm, L. (2015): Initial health care and coping preferences are associated with outcome 1 year after whiplash trauma: a multicentre 1-year follow-up study, BMJ Open, 5(3), e007239

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Contents

1. Background

1.1 Chronic pain and muscoloskeletal disorders

Chronic pain and musculoskeletal disorders are common worldwide [1], and can impede quality of social and working life [2]. Musculoskeletal disorders are globally the second most common cause of disability (as measured by years lived with disability (YLDs)[1]) [1], and from 1990 to 2010 the disability due to musculoskeletal disorders increased by 45% [1]. The most frequent musculoskeletal disorders are back and neck pain (global prevalence of 9.2% and 4.8% respectively) [1, 3]. Other important musculoskeletal conditions include osteoarthritis, rheumatoid arthritis, gout, low bone mineral density [1, 3], fibromyalgia [4] and whiplash [5].

Disability due to pain is especially common in Norway and other Western countries [6]. A survey of chronic pain in Europe found that about one in five adults experience chronic pain of moderate to severe intensity [2]. In Norway as many as 75% of adults experience pain or complaints from the musculoskeletal system in the course of one month [7]. Musculoskeletal conditions lead to great societal costs [7, 8] and are the most common cause of sick leave [9] and disability pension [8] in Norway.

In Europe around 40% of individuals with chronic pain report inadequate pain management [2]. Chronic pain conditions are multifactorial, and physical, mental and experienced health as well as psycho-social and demographic variables can influence outcome [10, 11]. In many chronic pain conditions there is poor correlation between clinical presentation and objective findings. For as many as 85% of patients with low back pain (LBP), no specific pathogenetic mechanism can be found [12]. At the same time, magnetic resonance imaging (MRI) shows substantial abnormalities in 30-60%

[1] For the GBD 2010: "YLDs per person from a sequela are equal to the prevalence of the sequel multiplied by the disability weight for the health state associated with that sequela. YLDs for a disease or injury are the sum of the YLDs for each sequela associated with the disease or injury." (1. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2013. **380**(9859): p. 2163-2196.)

of individuals with no back pain [13, 14], and in about 30% of individuals with no neck pain [15].

Though clinical imaging and other objective methods often correlate poorly with symptoms and outcome in musculoskeletal conditions, other factors (for instance mental and general health, psycho-social and demographic variables [10, 11]) might predict recovery and be targets for intervention. These factors might not have caused the pain in the first place, but can be predisposing or maintaining factors. In patients with chronic pain, gender, experienced health, and belief in return to work have been found to be strong predictors of vocational rehabilitation [11], and behavioral (BT) and cognitive-behavioral therapy (CBT) can sometimes reduce pain and distress and improve daily functioning [16]. A study from Norway found a combination of peer support, modified work load and a media campaign aiming to improve pain beliefs to result in decreased pain intensity and less sickness absence for individuals with LBP [17]. Also information about the nature of pain, provided in a manner designed to reduce fear, seems associated with less sickness absence in patients with LBP [18].

Whiplash accidents can in some individuals result in substantial chronic pain [19]. Few factors related to the accident seem to be of prognostic importance [19] and there is poor correlation between MRI findings and outcome [20-24]. In contrast to many other musculoskeletal conditions, whiplash has a specific and obvious cause and time of onset. Chronic whiplash might thus provide a valuable opportunity for studying how both pre- and post injury socio-demographic and health related factors are associated with the development and maintenance of musculoskeletal pain. The aim of this thesis was to evaluate whether socio-demographic and health related variables self-reported before or after the whiplash accident are of prognostic importance in whiplash.

1.2 Whiplash

1.2.1 Definition and history

The term “whiplash” was first introduced by Crowe in 1928, at the annual meeting of the Western Ortopaedic Association, San Francisco [25]. Crow drew attention to injuries related to a lash-like effect of the cervical spine in motor vehicle accidents, but later regretted introducing the term; the term spread and became widely used while he found himself at loss to know exactly what happened to the patients suffering from this condition and how to cure them [26]. Prior to this, the syndrome “railway spine” had been diagnosed in persons injured in train accidents [27].

In the literature the term whiplash has been used to describe the mechanism of the injury, the injury itself, the various clinical manifestations as well as symptoms and signs reported after the injury [28]. In 1995, the Quebec Task Force (QTF) agreed on a definition of whiplash [29]:

“Whiplash is an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear-end or side-impact motor vehicle collisions, but can also occur during diving or other mishaps. The impact may result in bony or soft-tissue injuries (whiplash injury) which in turn might lead to a variety of clinical manifestations (Whiplash-Associated Disorders (WAD)).”

A five-level grading system has been introduced, grading whiplash injuries according to clinical presentation from WAD0 to WAD4 (See Table 1). As most whiplash injuries are classified as WAD2 or lower [30, 31], whiplash injures are mainly considered to be soft tissue injures of the neck. Injuries of grade 4 (and grade 0) are often excluded from research, also by the QTF (WAD0 was not considered as no disorder manifests, WAD4 was not in the mandate for the QTF) [29].

The importance of the WAD-classification has been debated as the grade assigned to a patient has been shown to be associated [32, 33] modestly associated [19, 34] and not associated [31, 35] with outcome after whiplash injuries.

Table 1: Clinical classification of Whiplash-Associated Disorders by the Quebec Task Force [29]

Grade	Clinical presentation
0	No complaints about neck, no physical signs
1	Neck complaints; pain, stiffness, tenderness, no physical signs
2	Neck complaints and musculoskeletal signs; decreased range of motion or tender points
3	Neck complaints and neurological signs; decreased or absent tendon reflexes, weakness, sensory deficits
4	Neck complaints and fracture or dislocation

In concordance with previous research [36-39], chronic complaints following whiplash (by the QTF called WAD) will in this thesis be called "chronic whiplash". Two of the studies presented in this thesis are based on self-reported information on whiplash, with no possibility of WAD-classification. As mentioned above, WAD grades 0-2 are most common, and there is no reason to believe this to be different in the samples investigated in this thesis. In the thesis' third study, individuals were recruited from GPs and emergency units after whiplash car accidents, and individuals with no symptoms (WAD0) and fractions or dislocations (WAD4) were excluded [40].

1.2.2 Diagnosing whiplash

The Whiplash diagnosis is based on the patient's symptoms, physical examination and mechanism of injury [41, 42]. Medical imaging such as MRI is usually not needed [42] or even justified in patients where severe injury is not suspected, due to the infrequency of abnormalities detected, the lack of prognostic value, and the cost of the procedure [24]. Smaller lesions after whiplash can usually not be detected using clinically available diagnostic modalities [41, 43], and even when they can be, findings are often unassociated with symptoms [20-23]. When medical history or clinical presentation suggests fractures or other serious structural damage, medical imaging should be used [41, 42].

1.2.3 Incidence

In Sweden in 2003, the annual incidence of acute whiplash trauma was 4.2 per 1,000 inhabitants [44]. In the same study, the annual incidence of WAD grades one to three was 3.2 per 1,000 [44]. In Norway, the yearly incidence of whiplash trauma has been

estimated to be somewhat lower; 2.6 per 1,000 (based on the data used for study one and two in this thesis, the Nord-Trøndelag Health Study (HUNT), wave two, collected in 1995-1997) [45]. The possibility of underreport in this sample has been discussed [45]. Population-based estimates from Canada suggest that 0.81 adults per 1,000 will present with whiplash injuries of important severity per year [46]. The incidence of *chronic* whiplash varies greatly between countries, but has in general increased over the past 30 years in Western countries [5].

1.3 Acute whiplash

In the acute phase after whiplash accidents, individuals commonly report pain in neck, shoulders and head [30, 47-49]. In some individuals mental health is also affected; symptoms of anxiety and depression are reported, as well as phobia of traveling in a car [47].

Most individuals recover rapidly during the acute phase [29], and the greater part of improvement seems to occur during the first three months [40, 46]. Later, symptom reporting remains unaltered with further passage of time [46, 50]. Individuals who still display symptoms or disability at six months are defined as chronic [29].

1.4 Chronic whiplash

1.4.1 Development of chronic whiplash

In 2008 a review investigating course and prognostic factors for neck pain in whiplash reported that around 50% still report symptoms one year after a whiplash injury [19]. However, the proportion developing persistent complaints varies greatly [41]; from 98% recovered within a year [51] to 70% still reporting symptoms after 15 years [52]. The differences in prognosis are likely related to multiple factors. Some disparity might be due to different cut-offs or measures selected to represent recovery [41, 53].

Also, study samples are derived from different populations [41]. The prognosis after whiplash might for instance differ between population-based samples and samples

recruited from health services, as well as with the insurance or compensation system under which individuals are allowed to claim benefits [53]. Studies based on data related to insurance processes report varying prognosis; From 31% [30] to 98% recovered within a year [51], and 51.7% within two years [54]. Studies investigating participants recruited from primary care or emergency units also vary, from, for example, 20% [55] to 35% [46] not recovered at 6 months, 24% [56] to 50% not recovered within a year [35], or even 82% not recovered within 11 years [50] and 70% not recovered within 15 years [52].

The importance of cultural differences in whiplash is highlighted as prognosis varies substantially between countries [5]. In for instance Canada [46] and Norway [57] persistent problems are common, while in Greece [58] and Lithuania [59] almost everyone recovers. Frequency of chronicity might be associated with degree of public knowledge of potential chronic problems and the expectation of whiplash injuries being more or less malign [36, 60, 61]. This is thoroughly discussed in the whiplash literature [62] and is more closely covered in the Discussion of this thesis.

1.4.2 Complaints

Pain

As in the acute phase, pain is frequently reported in chronic whiplash. Neck pain is the most common complaint [30, 46, 50, 52, 63], and also the symptom most commonly reported to significantly affect health [30].

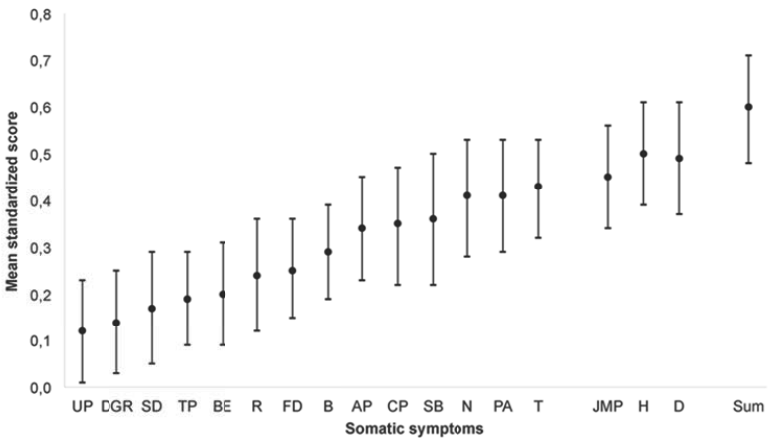
Other pain symptoms, like headache and pain in shoulders [30, 50, 63, 64] and back [52] are also commonly reported. Individuals with whiplash experience pain in both central and distal body parts [65] and report a higher number of painful locations and higher pain intensity than individuals with chronic pain from other causes [65].

Other somatic symptoms

In addition to pain symptoms, individuals with chronic whiplash experience a wide range of somatic symptoms, across body parts and organ systems [66], e.g. abdominal pain, nausea, dizziness, tiredness [67], fatigue and sleep disturbances [64].

A population-based study from Norway investigated the reported level of a wide range of somatic symptoms [67]: As displayed in Figure 1, individuals with chronic whiplash reported more of all 17 somatic symptoms investigated than individuals with no whiplash.

Figure 1: Mean difference in somatic symptoms reported compared between individuals reporting chronic whiplash and individuals reporting no chronic whiplash. Reprinted with permission [67]



Abbreviations: UP=Urination problems, DGR=Discomfort in genital region, SD=Skin discoloring, TP=Tongue plaque, BE=Burning eyes, R=Regurgitation, FD=Frequent defecation, B=Bloating, AP=Abdominal pain, CP=Chest pain, SB=Shortness of breath, N=Nausea, PA=Paresthesia, T=Tiredness, JMP=Joint and muscle pain, H=Headache, D=Dizziness

Mental health

Psychological aspects seem more pronounced in chronic whiplash than in the acute phase. Individuals with chronic whiplash have been found to report elevated levels of anxiety and depression [63, 66] as well as more symptoms of somatization, obsessive compulsive disorders, hostility [63], post-traumatic stress disorder (PTSD) and travel anxiety [68]. Compared to individuals that recover, individuals with persisting symptoms are more likely to have axis 1 psychiatric diagnoses (as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria) [69].

However, findings on mental health are conflicting. Based on cross sectional data, individuals reporting a recent whiplash injury report symptoms of anxiety and depression no different than individuals with no whiplash trauma, while those reporting an older whiplash injury (or no time specification) report elevated symptom levels (as measured by the Hospital Anxiety and Depression Scale (HADS)) [45].

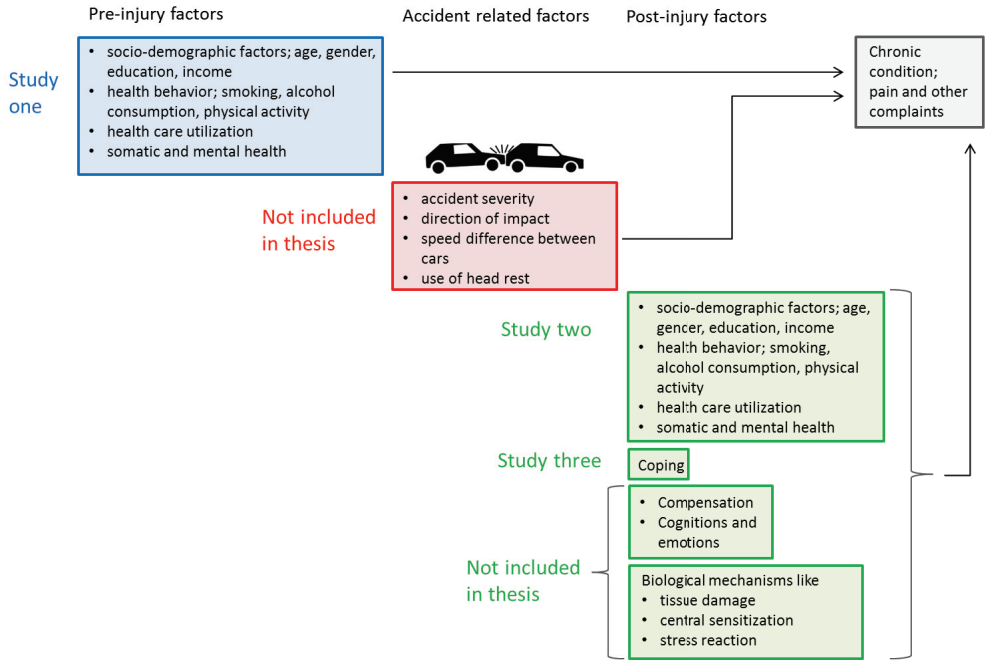
1.4.3 Capability to work

After whiplash injuries some individuals experience reduced capability to work. About one in three report sick-leave due to the accident [30], and most individuals seem to need less than a week off from work [46]. Around 10% are on sick leave for over a month, and 3% for over three months (participants recruited through insurance companies) [30]. In Canada, around 35% still modify their work and leisure activities at six months [46]. In Denmark, around 10% of patients recruited thought primary health services after whiplash received temporary health benefits one year later - versus 3% of marched controls [70]. Other Danish data (participants recruited from emergency units) showed that over 90% had returned to usual level of activity/work after a year [71]. Based on the evidence above, one might argue that symptoms remain longer than reduced function, and that individuals despite reporting considerable complaints, often are able to keep working.

1.5 Risk factors for chronic whiplash

Multiple factors seem to affect the development of chronic complaints after whiplash. An overview of potential prognostic factors and mechanisms involved in the development of chronic complaints are presented in Figure 2. The main focus of this thesis lies on self-reported pre- and post-injury predictors (predisposing and maintaining factors) of chronic complaints.

Figure 2: Factors related to the development of chronic complaints after whiplash



Study one investigates pre-injury factors, study two similar factors reported after the accident and study three investigates early coping. Please note that the figure is not complete and none of the studies cover all topics of relevance.

1.5.1 Pre-injury factors: Socio-demographic variables

Gender

There are conflicting findings on the prognostic importance of gender. Some reviews have found a modest association between gender and outcome after whiplash [19, 32], others report consistent evidence of female gender being associated with [53] or unassociated with [72] adverse prognosis. In original articles female gender has for instance been found associated with lower likelihood of recovery [49, 51], persistent neck pain [31, 73, 74], disability/disabling pain [35, 44] and psychological

consequences [73, 75]. Other studies have found gender to be unassociated with recovery [34, 54, 56, 71, 76-78].

Age

Findings on age are also inconclusive. One systematic review concludes that older age is associated with delayed recovery [53], others disagree [32, 72]. In original articles age has been found to be both associated [51, 56, 79-82] and unassociated [34, 44, 49, 54, 71, 73, 77, 78] with delayed recovery. In most studies identifying age as prognostic, the effects are modest [19], suggesting that age does not play a major role in outcome.

Work-situation, income and education

A review investigating risk factors for persistent problems after whiplash concludes that low education increases the risk of persistent problems [32]. Other reviews report insufficient [72] or inconsistent [53] information on the importance of education. In original articles, education has been found associated with disability [44, 73], anxiety and neck pain [73] at follow-up. Others have found low level of education to predict poor recovery [49, 83], or to be unassociated with outcome [35].

A review from 2001 states that there is inconsistent evidence on the importance of income and work activities [53]. Multiple original articles, some published after this review, have investigated such variables. In some studies, part-time employment is associated with lower likelihood of recovery [49, 51]. Receiving unemployment benefits, social assistance or sickness benefits before the accident has been found associated with negative change in provisional status after whiplash [70]. Other studies have found employment status [54, 77], income [73, 77], and social support [76] to be unassociated with outcome.

Family situation

Reviews have not found consistent information on the importance of family related variables [53]. In original articles, married status and a larger number of dependents have been found associated with lower likelihood of recovery [51]. Family-situation

(single/divorced/widowed versus in relationship) has been found unassociated with outcome [35].

1.5.2 Pre-injury factors: Health and health behavior

Pre-injury health

The prognostic importance of pre-injury health and pain is disagreed on. One review reports varying findings [19], one concludes on pre-injury health and pain being unassociated with outcome [53] and one states that a history of neck-pain indicates a small but significantly increased risk of chronic whiplash [32].

A population-based study collecting information among individuals who had never experienced whiplash found that poor health, both physical and mental, was associated with whiplash and neck pain 11 years later [84]. Examples from other original articles show that pre-injury neck pain [31, 44], general musculoskeletal complaints [79], a history of widespread pain [34], more depression, and axis 1 psychiatric diagnoses [69] as well as pre-injury use of health care (GPs and hospitalization) and medications (weekly use of analgesics) [84] are associated with adverse prognosis after whiplash. However, findings are not consistent. High psychological distress (several psychological distress factors) has been shown to predict neck pain but not capability to work [83]. A study found pre-injury widespread pain to predict persistent symptoms after whiplash, while general pre-collision health and neck pain did not [34]. Pre-injury neck pain [49, 76, 85], widespread pain [76] or pre-injury psychiatric factors [79] have all been shown to be unassociated with outcome.

Individuals with continued pain after whiplash have been found to underreport pre-injury pain symptoms [86]. Information on pre-collision health collected post-injury is thus at risk of misclassification bias, potentially contributing to the varying findings on the prognostic importance on pre-injury health [19].

Pre-injury health behavior

Few studies have investigated the prognostic importance of pre-injury health behavior in whiplash. A review from 2008 found no studies investigating the effect of pre-injury

physical fitness or exercise on outcome [19]. Potentially related to physical fitness, BMI has been found both associated [78] and unassociated [71] with prognosis.

1.5.3 Accident related factors

The prognostic importance of factors related to the actual accident has been studied widely, and seem to be of surprisingly little importance. It should be noted that most studies investigating collision related factors rely on self-reported information, and there might be inaccuracies related to recall and estimations. Collision related factors are not included in the studies in this thesis (apart from as potential confounding factors in study three), but findings from previous literature are presented briefly here.

Reviews have found collision related factors (position in the vehicle [19], awareness of impending collision [19, 32], direction of collision [19, 32, 72], being the driver or front passenger [32] and whether the vehicle was stationary when hit [32]) unassociated with adverse prognosis. One review states that there is insufficient evidence to conclude on the importance of head-rest and seat-belt [72]. Later reviews have concluded that not wearing a seat-belt predicts persistent complaints [32] while use/type of headrest does not [19].

Examples from follow-up studies show that use of head rest or seat belt, seating position, whether the seat belt was broken [73], head position on impact [73, 81], speed [34, 71, 78, 81], anticipation of the collision, lack of head-rest [34] and direction of collision [34, 35, 44, 78, 85] are unassociated with persistent complaints. Also studies with a cross-sectional design [87] and shorter follow-up times [48] have found accident related factors unassociated with symptom report. Findings are, however, mixed. Some studies find that being in a vehicle other than a car [34, 51], being a passenger, collision with a moving object and colliding head-on or side-ways [51] are associated with lower likelihood of recovery. Also, individuals who reported their collision as medium or high severity are at increased risk of persistent neck pain [34]. This was, however, found in a study where neither speed, direction nor use of head-rest was of importance [34], potentially implying that individual interpretation of severity is of greater importance than the actual forces involved.

A placebo study from Germany reported that around 20% of volunteers exposed to a placebo collision almost completely lacking biomechanical stress, developed "whiplash like" symptoms within a few days [88]. Perturbations of daily living have been shown to be similar to those experienced in low velocity whiplash accidents [89] further implying that actual forces might be of limited importance.

1.5.4 Post-injury factors: Tissue damage and biological mechanisms

The kinematics[2] and kinetics[3] of rear-end car collisions have been investigated in studies involving dummies, human cadavers, volunteers and computer models [43]. The whiplash neck movement can sometimes exceed physiological limits and might lead to structural injury to for instance zygapophysial joints and capsules [41, 43, 91], anterior longitudinal ligaments and discs, muscles [43], nerve roots and dorsal root ganglia [43, 92]. The development of chronic pain might further be related to stress response systems [93, 94], dysregulation of the hypothalamus-pituitary-adrenal axis [94, 95] and augmented central pain processing [96, 97] (list not complete).

Some studies find structural changes in muscles of individuals with chronic whiplash when using MRI [98]. For instance more fatty infiltrate in and a larger cross sectional area of the neck extensor muscles has been shown in females with chronic whiplash compared to health controls [23, 99]. Other MRI studies find no significant differences between individuals with whiplash and healthy volunteers [20-22]. When morphological changes are detected, there is often little [100] or no correlation between these and clinical symptoms [20-23]. In general it seems that clinically available imaging technics fail to detect tissue damage in whiplash [43]. Tissue damage might very well exist, but is not yet clinically useful in predicting chronic symptoms. Biological mechanisms and findings are beyond the scope of this thesis.

[2] Kinematics: "branch of physics and a subdivision of classical mechanics concerned with the geometrically possible motion of a body or system of bodies without consideration of the forces involved (*i.e.,* causes and effects of the motions)" (90. Taboola. *Encyclopaedia Britannica Online.* 12.02.2014].)

[3] Kinetics: "branch of classical mechanics that concerns the effect of forces and torques on the motion of bodies having mass." (90. Ibid.)

1.5.5 Post injury factors: Initial complaints and clinical findings

The predictive importance of initial complaints and clinical findings has been investigated in multiple studies. Systematic reviews report consistent evidence that high initial pain [19, 32, 53, 72], a greater number of symptoms, more parts of body in pain and pain-related limitations [19] predict persistent problems.

Examples from original articles show that high initial neck pain [49, 56, 73, 74, 76, 81, 82], a greater number of symptoms [76, 81], impaired neck movement [80, 82] as well as high scores on the Neck Disability Index (NDI) [34, 76, 78, 80] and the Function Rating Index (FRI) [54] are associated with poor recovery. Other studies report that range of movement (ROM) is unassociated with chronic disability [76], and that pain intensity and ROM do not to predict sick leave [101].

As the WAD-classification is based on complaints and clinical findings, studies showing the WAD grading to be associated [32, 33, 44] or modestly associated [19, 34] with outcome suggest that early complaints and clinical findings are of prognostic importance, while studies finding the WAD grading unassociated with outcome [31, 35] do not.

1.5.6 Post-injury factors: Cognitions and emotions

Early psychological factors

The research evidence is mixed with regards to whether early emotions related to the accident are of prognostic importance. Some reviews state strong evidence of acute psychological response being unassociated with outcome [72] while others find post-injury psychological distress to predict recovery [19].

Examples from original articles show that emotional distress has been found associated with subsequent neck pain [31] and post-traumatic stress disorder (PTSD) [68]. Rumination is associated with psychological consequences one year post-injury [75]. Individuals with high level of general psychological distress (as measured by the General Health Questionnaire (GHQ)) after the accident have increased risk of chronic disability [76] and persistent neck pain [34]. Stress reaction (measured by the Impact

of Event Scale (IES) [102]) has been found associated with subsequent symptom report [48] and disability (NDI) [80]. Injury-related changes in psychological and cognitive functioning (i.e. nervousness and impaired focused attention) are also associated with adverse prognosis [82]. Also helplessness[4] is associated with neck pain, as well as perceived disability and anxiety and depression at follow-up after whiplash [73].

Expectations

Positive expectations are associated with better health outcomes in a range of conditions, including locomotor pain [11], low back pain and myocardial infarction [104]. The strength of association depends on the clinical condition and measures used [104]. In whiplash, expectations predict both development of chronic disability [76, 105] and recovery [106, 107]. Individuals with mild pain are more likely to expect complete recovery [105], but the association between expectations and disability remains after controlling for severity of physical and mental symptoms [105].

Coping

Coping can be defined as purposeful efforts to manage stress. In the field of chronic pain, some researchers categorize coping efforts into active and passive dimensions [108, 109]. Active coping refers to coping strategies where an individual tries to do something active to remove or relive the stressor (here: pain), or attempts to control pain or function in spite of pain. Passive coping refers to strategies that keep an individual from directly addressing the stressor (such as withdrawal), and involves giving responsibility for pain management to an outside source and/or allowing other areas of life to be adversely affected by the pain [108, 109].

After a whiplash accident individuals have to cope with a stressful, potentially life-threatening event, in addition to the early physical complaints resulting from the accident. Reviews show that the way individuals cope is associated with recovery also in whiplash [19, 107]. While active coping often is found to be unassociated with

[4] Helplessness generally refers to a psychological state in which individuals believe their efforts to be ineffective (103. Maier, S.F. and M.E. Seligman, *Learned helplessness: Theory and evidence.* Journal of experimental psychology: general, 1976. **105**(1): p. 3.)

outcome [110-112], most studies agree that passive coping is associated with an adverse prognosis [76, 110-112]. In the first few weeks post-injury, individuals who seek palliative relief, experience fear, annoyance, anger or feel inadequate but do not share their concerns or fear with others are at risk of developing chronic whiplash [110]. High scores on “distraction”, “reinterpretation”, “praying and hoping” [113], “catastrophizing” (more thoroughly discussed below) [113, 114] and low scores on "control of pain" [114] are associated with persistent symptoms. Individuals who recover from whiplash use more active problem-solving coping strategies than individuals who remain symptomatic [114].

Coping style may affect recovery from whiplash injury through issues of compliance; whiplash patients who have a low active and a high passive coping style are less likely to attend an active exercise-based rehabilitation program and more likely to use prescription medications in the first 3 weeks following injury [115].

The importance of coping seems to increase from the acute phase and throughout the first year; as time passes individuals use a higher number of different coping strategies, and the proportion of variance in disability explained by coping gets larger [116].

Catastrophizing and perceived injustice

Research indicates that catastrophizing and perceived injustice might predict prolonged pain and disability after whiplash [117]. Pain catastrophizing can be defined as an exaggerated negative orientation to actual or anticipated pain. It comprises elements of helplessness, rumination and magnification [118].

Catastrophizing is associated with heightened pain experience across a broad range of pain conditions [118]. Also in whiplash this seems to be the case. In multiple cross-sectional studies, catastrophizing has been found associated with adverse outcomes, for instance pain [119], disability [116, 120] and sensory hypersensitivity [121]. A prospective study investigating some participants with whiplash injuries and some with musculoskeletal problems due to occupational accidents found high scores on pain catastrophizing to predict pain at the one year follow-up [122]. This association

remained significant after controlling for initial pain severity, depression and fear of movement and re-injury [122].

Catastrophizing correlates highly with perceived injustice [117, 122], another predictor of outcome after whiplash. In the context of painful injury, perceived injustice can be measured using the Injustice Experience Questionnaire (IEQ), a construct comprising cognitive appraisal of severity of the condition, perceived irreparability of loss, a sense of unfairness, and blame (amongst more) [122]. In whiplash, perceived injustice (as measured by the IEQ) seems relatively low the first three months. Then, between three and six months, perceived injustice scores become elevated in individuals that do not recover [55]. In individuals having been through a 7 week rehabilitation program after whiplash injury, post-treatment perceived injustice (IEQ) is a significant predictor of not having returned to work, of higher levels of pain and of use of narcotics one year later [123]. A prospective study on individuals with musculoskeletal injuries (occupational injuries and whiplash), high scores in perceived injustice predicts work disability one year later, also after controlling for initial pain severity, catastrophizing, and pain-related fears [122].

Perceived injustice might be important when considering how and why blame affects recovery from whiplash [124]. A recent prospective study found individuals who were responsible for the accident to be twice as likely to recover as those not responsible [35], and resentment is associated with both psychological and emotional dysfunction and quality of life after whiplash [125].

1.5.7 Post-injury mechanisms: Compensation and litigation

Many of those who seek compensation after whiplash are distressed by the slowness and obscurity of the proceedings, as well as dissatisfied with the outcome [68]. Legal problems are reported as stressful and a constant reminder of the accidents' physical, psychological, and social consequences [68]. Settlement, even if unsatisfactory, can be a relief from stress, enabling people to put the past behind them and concentrate on the future [68].

Compared to individuals that recover, individuals with persistent symptom after whiplash are more likely to have claimed compensation and less likely to report a resolution to the claim [34]. Claiming compensation predicts persistent neck pain [75], and claim closure is associated with higher report of recovery [54]. Time to claim closure is a potential proxy of recovery, and is associated with pain intensity, functioning and depressive symptomatology in both tort[5] and no-fault compensations systems [127].

In Saskatchewan, Canada, the importance of compensation in whiplash was investigated as a natural experiment. In January 1995, the previously used tort compensation system for traffic injuries, which included payment for pain and suffering, was changed to a no-fault system which did not include such payments [128]. Despite an increase in number of vehicle-damage claims and total kilometers driven, after the change to the no-fault system, the incidence of whiplash claims dropped by 28% and the median time to claim closure dropped by more than 200 days [128]. These findings indicate that type of insurance system impacts frequency and duration of whiplash claims, and that claimants recover faster when no compensation for pain and suffering is available [128].

Even though an association between compensation processes and recovery has been shown in multiple studies, other studies have found little or no association between outcome and the initiation of a lawsuit [71], litigation processes [129] or prolonged compensation proceedings [68]. A review from 2003 provides strong evidence of compensation being unassociated with prognosis [72]. A different review from 2001 concludes that "it is becoming obvious that the insurance and compensation systems have a large impact on recovery from acute whiplash injuries" [53(page E445)]. This statement was however based on findings from only one study ([128]).

[5] Tort: "A wrongful act or an infringement of a right (other than under contract) leading to legal liability" (126. *Oxford Dictionaries*. Available from: http://www.oxforddictionaries.com/definition/english/tort.).

1.5.8 The presence of multiple risk factors

The risk of chronic problems after whiplash seems affected by the number of separate risk factors present [76]: When investigating risk factors like baseline pain, number of symptoms, passive coping and predicted time to recovery, a dose-like response relationship has been found; as the number of risk factors increases, so does the proportion of participants with chronic disability.

1.6 In summary – few conclusions

As evident by the research presented above, there is still uncertainty around the predictive importance of many proposed risk factors. This might for instance be related to different measures and cut-offs used to define chronic whiplash and recovery, samples being derived from different populations (country, cultural differences, insurance systems, population-based samples or participants recruited from police records or health services), changes over time as well as recall[6] and publication bias[7].

The two latest reviews investigating risk factors after whiplash were published in 2009. One review concludes that low education, female gender, a history of pre-injury neck pain, baseline neck pain, baseline headache, catastrophizing, WAD grade two or three, and no use of seat-belt are significant predictors of outcome [32]. This review, however, also investigated publication bias, and found only the predictive importance of baseline neck pain, WAD grade, headache and no postsecondary education to be robust to publication bias [32]. The other review presents results from the Bone- and Joint decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders and found no scientifically admissible studies examining the prognostic importance of

[6] Recall bias: When diagnosis (here the accident or chronic whiplash) effects reporting, e.g. by improving memory (enhancing sensitivity among cases), by provoking false memory of exposure (reducing specificity among cases) or by the disease itself clouding memory (130. Rothman, K.J. and S.L. Greenland, T. L., *Modern Epidemiology, Chapter 8*, in *Modern Epidemiology*. 2008, Lippincot WIlliams & Wilkins: Philadelphia. p. 111.)

[7] Publication bias: Bias with regards to what is more likely to be published, e.g. significance bias (preferential submission and acceptance of significant associations), size bias (preferential submission and acceptance of larger studies) and suppression bias (when certain types of results are intentionally not submitted) (131. Rothman, K.J. and S.L. Greenland, T. L., *Modern Epidemiology, Chapter 33*, in *Modern Epidemiology*. 2008, Lippincot WIlliams & Wilkins: Philadelphia. p. 678.)

psychological or social factors after whiplash [5]. This review states the need for studies investigating these factors as well as personal factors such as premorbid conditions and collision related factors [5].

1.7 Avenues for further research

Previous research has identified several areas where more information is needed. There is for instance, lacking evidence regarding the prognostic importance of socio-demographic factors, pre- and post-injury health and health behavior, compensation and early coping in whiplash.

When information on pre-injury health and health behavior is collected after the injury (retrospectively[8]), reporting of exposure might be affected by the event/outcome and the information subject to recall and report bias [132]. Further, as the role of compensation systems and litigations is still unclear, research investigating other factors should be conducted unrelated to such processes. The importance of socio-demographic, pre- and post-injury health and health behavior should therefore be investigated in large, prospective[9], population-based studies, unassociated with compensation processes.

Conclusions on the prognostic importance of early coping are also lacking. Most studies investigating coping after whiplash have collected the information used around three to six weeks post-injury [76, 110-112]. To the best of our knowledge, only one study has investigated coping within one week of the accident [74]. Later, coping might already have been affected by for instance on-going pain or health services, and in whiplash, coping has indeed been shown to change over time [116]. Early coping should be investigated in clinical studies recruiting participants straight from the first-line services, minimizing time from accident to participation. To further reduce the

[8] Retrospectively with respect to the recording of the exposure (132. Rothman, K.J. and S.L. Greenland, T. L., *Modern Epidemiology, Chapter 6*, in *Modern Epidemiology*. 2008, Lippincot WIlliams & Wilkins: Philadelphia. p. 96.)

[9] Prospective with respect to recording of exposure; when exposure measure cannot be influenced by the disease (outcome/event) (132. Ibid.)

risk of confounding, also this research should be conducted unrelated to compensation and litigation processes.

2. Aim

The overall aim of the thesis was to investigate factors associated with development of, and recovery from, chronic whiplash.

Study one and two

Using data from two waves of the large, Norwegian population-based Nord-Trøndelag Health Study (HUNT), the aims were to:

- investigate whether socio-demographic variables (such as age, gender, education) and health related variables (such as perceived health, health behavior and use of health-services, musculoskeletal complaints, somatic complaints, medical diagnoses and anxiety and depression) measured before the accident are associated with development of chronic whiplash (study one)

- investigate whether socio-demographic and health-related variables measured in individuals with whiplash are associated with recovery (study two)

Study three

Using prospective data from Denmark (individuals with acute whiplash followed for a year), the aims were to:

- describe which coping and health care preferences participants report during the first few days following the whiplash accident

- determine whether these early health care and coping preferences are associated with neck pain and reduced capability to work one year later

3. Methods

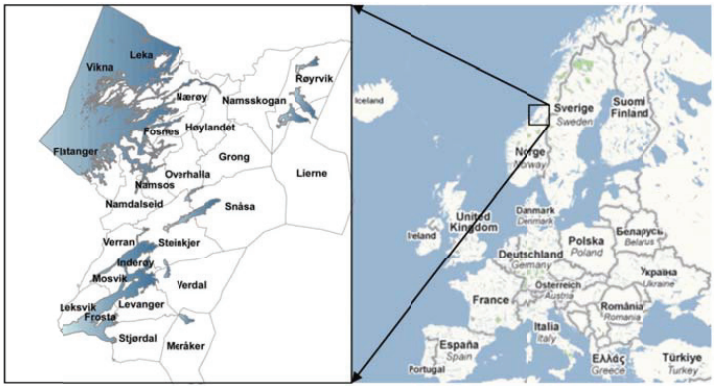
3.1 Study design, population and variables

Study one and two are based on data from two waves of the Nord-Trøndelag Health Study (HUNT), HUNT2 and HUNT3. Study three is based on prospective data from Denmark.

3.1.1 Study one and two, HUNT Data

HUNT consists of three large, population-based surveys conducted in Nord-Trøndelag [133, 134]. Nord-Trøndelag is one of Norway's 19 counties and is located in the middle of the country (see Figure 3). Nord-Trøndelag is mostly rural and sparsely populated. The education attainment and level of income is somewhat lower than the Norwegian average [133, 135]. In most other respects, including economy, industry, age distribution, mortality and morbidity, Nord-Trøndelag is fairly representative for Norway in general [135]. Around 127,000 people reside in Nord-Trøndelag. The population is stable (net out migration of 0.3% per year (1996-2000)) and homogenous (less than 3% non-Caucasian) making the county suitable for epidemiological studies [135, 136].

Figure 3: The HUNT study area, 24 municipalities in Nord-Trøndelag County, Norway. Taken from [134], reprinted with permission



The first wave of HUNT was conducted in 1984-1986 [133]. Data was collected using questionnaires, interviews and clinical examination [133]. All inhabitants over 20 years of age were invited, and in total 89.3% (n=77,212) participated [134]. The design applied in HUNT1 was in large repeated in the two following waves, HUNT2 and HUNT3 [134]. For each wave, both new and previous participants were invited, resulting in a large data-base of partly repeated-measure information.

The second wave of HUNT, HUNT2 was conducted in 1995-1997 [136]. The main objectives in HUNT2 were large public health issues like cardiovascular disease and mental health [135]. Among the 94,194 individuals (aged 20 years and older) that were invited, 66.7% of men (n=30,860) and 75.5% of women (n=35,280) participated [135]. Participation was age-dependent, with the highest participation in the age group 60-69 for both genders [135].

The third wave of HUNT was conducted from 2006 to 2008 [133, 136]. Among the 93,860 individuals invited, 50,807 (54.1%) participated [134]. In HUNT3 nonparticipants had lower socioeconomic status, higher mortality and higher prevalence of several chronic diseases [137].

The participation rate declined from HUNT1 to HUNT3. In all waves, more women than men participated [134]. In this thesis, data from HUNT2 and HUNT3 was used (no data from HUNT1 used). In total, 33,117 individuals participated in both HUNT2 and HUNT3 and were eligible for our analyses.

3.1.2 Study three, Danish Pain Data

The third study is based on data from a two-center study conducted by the Danish Pain Research Centre, Aarhus University Hospital and the Back Research Centre, Odense University Hospital. Data was collected from April 2001 to June 2003 [40]. The catchment area included the former four counties of Viborg, Aarhus, Vejle, and Funen, and covered 1.7 million inhabitants in 2001.

Patients consulting emergency units or general practitioners (GPs) with acute neck pain after whiplash accidents were invited to participate and informed about the study

in a written invitation. Patients aged 18-70 years experiencing neck pain within 72 hours after being exposed to a rear-end or side-impact car collision were included. Patients were not included if they [40]:

- could not be examined within 10 days post-accident
- had insufficient knowledge of Danish
- had fractures, dislocations, amnesia or unconsciousness in relation to the accident (WAD4 hereby excluded)
- had injuries other than the whiplash injury or displayed no symptoms (WAD0 hereby excluded)
- had significant pre-collision physical or psychiatric disorder, significant self-reported pre-injury neck pain (during the preceding 6 months)
- suffered from alcohol or drug abuse

In total, 1,495 participants were assessed for eligibility. Among these, 740 joined the study, 200 declined, 7 were excluded due to protocol violations and 548 were ineligible (22.6% could not be examined within 10 days after the collision, 17.7% had injuries other than the whiplash injury) [83, 113].

Among the 200 subjects declining participation there were significantly more men than among the participants. The 55 subjects lost to follow-up did not differ from those completing the study with respect to gender but they were younger, more likely to be students or unemployed and more likely to report pre-collision unspecified pain. More detailed information on inclusion, exclusion and differences between groups has been published elsewhere [83, 113].

Two randomized controlled trials (RCTs) were performed within the study population [40, 138]. The first study compared the effect of three intervention strategies after acute whiplash injury; immobilization, "act-as-usual" and active mobilization [40]. The second evaluated whether education of patients communicated by a specially trained nurse was superior to giving patients a pamphlet after whiplash injury [138]. As no significant differences on outcome measures (pain intensity, disability, and

capability to work) was observed in any of the trials, no further reference will be made to these RCTs.

3.2 Study variables

The main variables used in the articles included in this thesis are presented in table 2 below.

Table 2: Overview of studies; population, baseline information and outcome

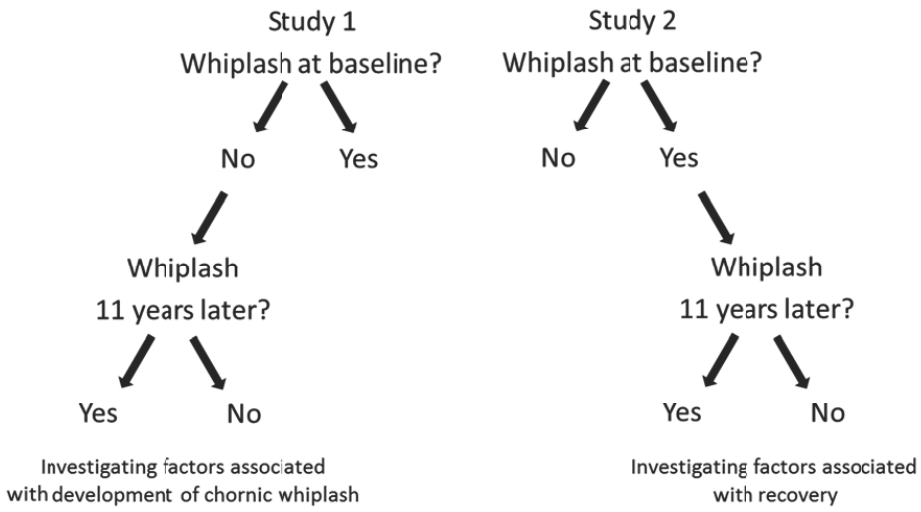
Study	Data used	Sample	Main baseline information	Outcome
Study 1	HUNT2 and HUNT3	Individuals with no whiplash	Socio-demographic and health-related variables	Chronic whiplash (developed) 11 years later
Study 2	HUNT2 and HUNT3	Individuals with whiplash	Socio-demographic and health-related variables	Chronic whiplash (non-recovery) 11 years later
Study 3	Danish Pain Data	Individuals with acute whiplash	Health care and coping preferences	Neck pain and capability to work one year later

3.2.1 Outcome and grouping variable, study one and two; Chronic whiplash

In the first two studies the outcome-variable was self-reported chronic whiplash. In HUNT2 and HUNT3 participants were asked: “Have you ever experienced a whiplash injury”. Participants also indicated their age at time of their last whiplash injury (HUNT2)/ their first whiplash injury (HUNT3).

In study one, individuals who had not experienced whiplash in HUNT2 were followed in HUNT3 after 11 years. Individuals who reported whiplash in HUNT2 were excluded (n=899). In HUNT3, the n=30,008 participants who had reported no whiplash in HUNT2 were classified into those who had developed chronic whiplash and those who had not (see Figure 4). Chronic whiplash was defined as having experienced a whiplash injury more than 1 year ago (excluding individuals possibly still in the acute phase of injury) and reporting neck-pain.

Figure 4: Study set-up. Study one; individuals *without* whiplash in HUNT2 were followed to HUNT3 and categorized as either having developed chronic whiplash or having not developed chronic whiplash. Study two; individuals *with* whiplash in HUNT2 were followed to HUNT3 and categorized as either having recovered or having not recovered



In study two, individuals reporting whiplash in HUNT2 (n=899) were followed up in HUNT3 11 years later. In HUNT3 participants were again asked if they had experienced whiplash, the time of the injury and if they had experienced at least 3 consecutive months of neck pain during the last year. Individuals reporting neck pain as well as a whiplash injury more than one year ago were set as having chronic whiplash. Individuals reporting no whiplash and individuals reporting whiplash but no neck pain were coded as recovered.

As whiplash was self-reported, there was no medical confirmation and no possibility for WAD-classification. More information on these issues is available in the Discussion, under Strengths and limitations.

3.2.2 Variables potentially associated with outcome, study one and two

All information on potential predictors was measured at baseline (HUNT2). In study one, information was therefore collected before the injury, in study two, information was collected in individuals with whiplash.

Sociodemographic variables

Information on gender, age and marital status was obtained for each participant. Participants were asked whether they currently received "sick pay", "rehabilitation benefits", "disability pension" or "unemployment benefits". The validity of self-reported rehabilitation benefits [139] and disability pension [139, 140], has been found to be good, the validity of self-reported sick leave, somewhat lower [140-142]. For the analyses, "sick pay" and "rehabilitation benefits" were labelled "Short-term health related benefits" while "disability pension" was labelled "Long-term health related benefits".

Self-rated health

Self-rated health/global health was evaluated by the question "How would you describe you present health?". The response options were "very good", "good", "not all good" and "poor". These were dichotomized into good (very good, good) and poor (not all good, poor). Self-rated health has been found to be a valid health measure appropriate for use in general health surveys [143].

Somatic health

Musculoskeletal complaints were measured using an instrument adapted from the Standardized Nordic Questionnaire (SNQ) [144]: Participants were asked if they had experienced musculoskeletal pain or stiffness for a minimum of three consecutive months during the last year, in any of the following areas: "neck", "shoulders", "elbows", "wrists, hands", "chest, abdomen", "upper back", "lower back", "hips", "knees" and/or "ankles/feet". The number of reported complaints was summarized for each individual in a count variable.

In study one pre-injury musculoskeletal complaints were investigated as potentially associated with developing whiplash. Neck pain was therefore included in the count variable for musculoskeletal complaints, giving a variable ranging from zero to ten. In study two, however, all participants had whiplash, and neck pain was used to define the whiplash group. Neck pain was therefore excluded from the count variable, giving a count variable ranging from zero to nine.

Somatic symptoms/complaints were evaluated by asking to what degree participants had been bothered by "nausea", "heartburn", "diarrhea", "constipation", "palpitations" or "breathlessness" during the last year. Response options were "not bothered", "bothered some" or "bothered a lot". The last two categories were grouped together. A dichotomous variable was created, grouping individuals as reporting zero to two complaints or more than two complaints.

Somatic diagnoses: Participants were asked to indicate whether they suffered from or had suffered from certain somatic diseases; "cardiac infarction", "angina pectoris", "stroke", "asthma", "diabetes", "osteoporosis", "fibromyalgia", "arthrosis", "spondylarthritis", "other musculoskeletal disorder" or "epilepsy". Positive responses were counted for each participant.

Mental health

Symptoms of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS) [145]. HADS is a widely used self-report questionnaire considered valid for both clinical settings and the general population [146-148]. The scale can be divided into one anxiety subscale (HADS-A) and one depression subscale (HADS-D), each containing seven items. In this study, two dichotomous variables were created, one for depression and one for anxiety, using the recommended cut-off of eight (>=8) [147, 148]. When using this cut-off, the sensitivity and specificity of both subscales are about 0.8 [148].

Participants not responding to items on any of the scales were excluded from the analyses. Participants responding to items on anxiety but not answering for depression

were classified as having no depression. Participants responding to items on depression but not answering for anxiety were classified as having no anxiety.

In study one comorbid anxiety and depression was investigated. A new variable was constructed and individuals reporting a HADS-score of eight or higher on both depression and anxiety in HUNT2 were classified as having comorbid anxiety and depression.

Health-related behavior

Smoking: Based on the question "Do you smoke cigarettes/cigars/pipe daily?" participants were grouped as smokers or non-smokers.

Alcohol consumption: Amount of alcohol consumption was assessed using two questions: "Do you abstain from alcohol?" and "What is your normal consumption of alcoholic beverages over a two week period?". Participants not giving information on amount of alcohol were set as having no consumption if they reported to abstain from alcohol. As in previous studies [149] a cut-off value of 15 units was used and participants were grouped as having "no consumption", "moderate consumption", or "high consumption".

Physical activity: Participants were asked how often, and for how long, they engaged in both light and intense leisure-time physical activity. A dichotomous variable was created, grouping individuals performing physical activity and those not.

Use of health-services and medications

Participants were asked if they had visited a "general practitioner (GP)", "company physician", "doctor at hospital", "other doctor", "physiotherapist", "chiropractor", "homeopath" or a "other treatment provider (naturopath, reflexologist, healer, psychic etc.)" during the last year. They were also asked whether they had been admitted to the hospital during the last five years. A count-variable was created, displaying the total number of different health-services visited for each individual.

Participants were asked how many months during the last year they had used different medications and supplements; "cod-liver", "medications for allergy", "pain-killers",

"asthma medication", "heart medication", "anti-depressants", "iron-supplements", "sedatives", "sleeping-pills", "vitamin-D" and "others". A count-variable was constructed, representing the total number of medications used for at least one month for each individual. Individuals not answering were classified as not using medications.

3.2.3 Outcome variables, study three; Neck pain and capability to work

In study three, individuals with complaints of acute whiplash were recruited from emergency units and GP's after whiplash accidents. Therefore, no self-reported information on whiplash accidents was needed. At follow-up twelve months later, two outcomes, neck pain and capability to work, were measured.

Neck pain

Participants were presented with the statement: "This is your assessment of your average neck pain the last week" and could rank their pain on a visual analogue 11-point box scale. Zero represented no neck pain and ten the worst imaginable pain.

Capability to work

During the last month of the follow-up year patients were asked to register days with sick leave or reduced working hours due to the accident in a calendar [40]. As in previous research [83] a dichotomous variable was created, dividing individuals with unaffected work capability from individuals reporting reduced work capability due to whiplash.

The follow-up questionnaires were completed by 672 participants of whom 529 responded to the outcome neck pain (overall response rate: 78.7%). The response rate was higher for work capability (n=651, overall response rate: 96.9%), as non-responders were contacted by phone and asked about this specific item [83].

3.2.4 Variables potentially associated with outcome, study three

Sociodemographic variables

Information on age, gender and education was obtained for each participant. Education was assessed as a dichotomous variable, grouping individuals having completed compulsory education only and individuals with higher education.

Collision related factors; speed difference and extent of damage to car

Participants reported estimated speed of the two cars involved. As in previous research [83, 113], the speed categories for each car was 0, 0-30, 30-80, 80-110 and 110 km/h or more. From this information, estimated speed-difference of the cars (delta speed) was calculated.

Participants also rated the extent of damage to the car as 0-30%, 30-50%, 50-80% or 80-100%. From speed difference and % damage to car, a dichotomous variable was created; “Not severe collision” and “Severe collision”. If the speed difference exceeded 30 km/h this was defined as a risk factor, as was 50% or more damage to the car. Individuals were only grouped in “Not severe collision” if they were neither at risk in terms of delta speed or extent of car damage.

Neck pain at baseline

Neck pain at baseline was investigated using the statement: “This is your assessment of your average neck pain since the accident”. Participants were asked to indicate their level of neck pain on a visual analogue eleven-point box scale where zero represented no neck pain and ten the worst imaginable pain, the same scale used when investigating neck pain as an outcome.

Coping and health care preferences

At baseline participants were presented with a list of 13 health care and coping preferences and were asked to indicate which options they believed could help them get better. The options provided were:

- Keep living as normal
- Changing lifestyle
- Changing diet

Grouped as active coping preferences

- Taking it easy
- Sickness absence
- Taking medications
- Being referred to a specialist
- Further medical investigations
- Being referred to a physiotherapist/chiropractor
- Surgery
- Being referred to a psychologist
- Talking to a doctor about symptoms
- Having a doctor explain what is wrong

Grouped as health care and passive coping preferences

For each coping preference participants could indicate: “right”, “mostly right”, “mostly wrong”, “wrong” and “cannot answer”. A dichotomous variable was created for each option, grouping “right” and “mostly right” as “agreeing” and “mostly wrong” and “wrong” as “not agreeing”. Participants could indicate multiple preferences, so the groups are not mutually exclusive.

The coping preferences were grouped as active preferences (“keep living as normal”, “changing lifestyle” and “changing diet”) and passive preferences (“taking it easy”, “sickness absence”, “taking medications”, “being referred to a specialist”, “further medical investigations”, “being referred to a physiotherapist/chiropractor”, “surgery”, “being referred to a psychologist”, “talking to a doctor about symptoms” and “having a doctor explain what is wrong”). The items “surgery”, “change of diet”, “being referred to a psychologist”, and “having the doctor explain what is wrong” were not used in the final analyses. The item “having the doctor explain what is wrong” was excluded as it was largely overlapping with the item “talking to a doctor about symptoms”. The other three items were excluded due to too low n for meaningful analyses (n=10, n=43, n=28 respectively).

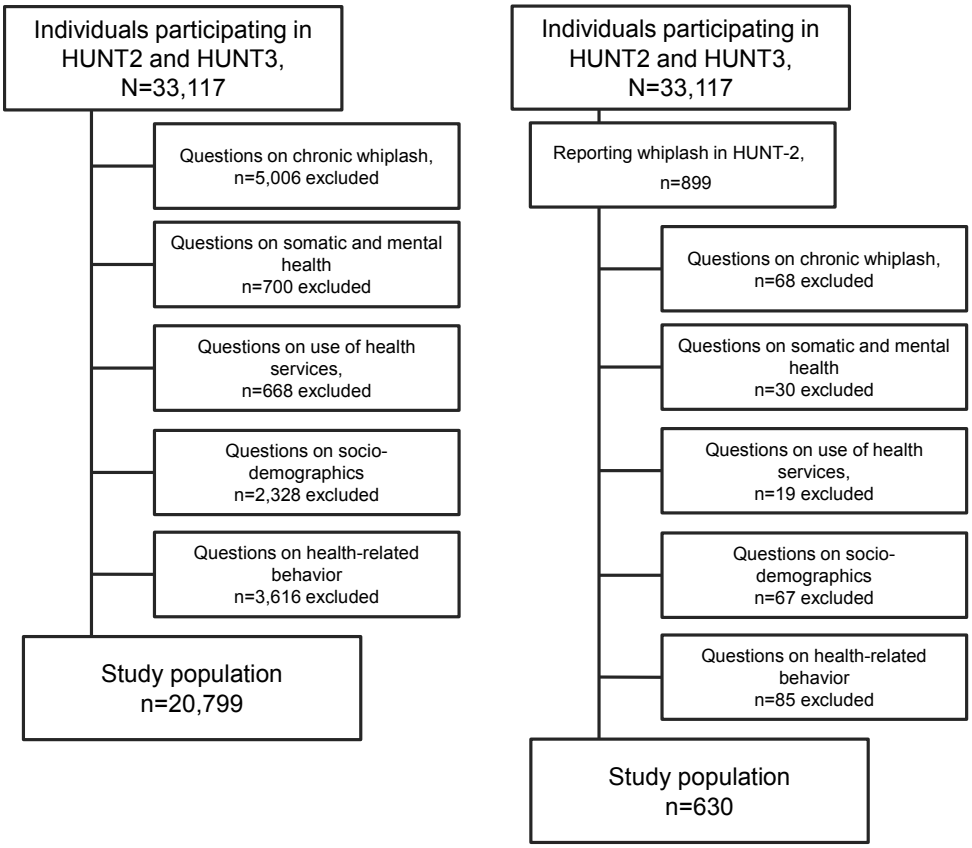
The list used to assess coping and health care preferences in this study is not part of any validated coping instrument. It does, however, contain items similar to those used in other inventories, for instance the Vanderbilt Pain Management Inventory (VPMI) [108]. Multiple validated measures have been used to evaluate coping in whiplash, for instance the Coping Strategies Questionnaire (CSQ) [76, 114, 116] and the 11-item [111] and 18-item VPMI [115]. Most of these instruments, however, contain a high number of items. Coping has been found important in whiplash when using complex measures, also in the data applied in this study, using the 31-item CSQ [113]. As it might be difficult to prioritize complex and time-consuming screening tools in primary care, we aimed to determine whether simpler measures are associated with outcome after whiplash. Also in contrast to most instruments and previous research, we evaluate coping and health care *preferences*, not actual coping.

3.3 Handling missing data

In study one and two listwise deletion was used to handle missing data. Where nothing else is stated under description of the variables above, individuals not answering were excluded from the sample (see Figure 5).

In study one, missing data was also handled using multiple missing imputation in Stata 11 [150]. Five new datasets were created using the *mi impute* command, with the *mvn* parameterization, indicating arbitrary missing pattern. The analyses investigating the associations with whiplash were run in each of the new datasets, and the results were combined to produce estimates and confidence intervals. As the findings did not differ substantially between the original and the imputed datasets, findings from the original set are presented in the article.

Figure 5: Individuals included and excluded (due to missing information), in study one and study two. Adapted from study one [151] and two [152], reprinted with permission



3.4 Study design

All three studies included in this thesis are longitudinal. In study one the baseline information was collected before the whiplash accident. The accident could therefore not affect the reported baseline information, and the study is said to be prospective. At baseline in study two and three, the whiplash accident had already happened, and will therefore affect the baseline report. However, all individuals studied have experienced a whiplash accident, and as the associations of interest are between characteristics in individuals with (acute) whiplash and outcome (recovery/neck pain/reduced capability

to work), these studies can also be said to be prospective. Prospective studies have the advantage of collecting the information on exposure before the outcome, thus avoiding the risk of outcome affecting the recording of exposure, for instance by influencing recall [132].

3.5 Statistical analyses

3.5.1 Statistical analyses, study one

Baseline characteristics (HUNT2, before the injury) were compared between participants reporting chronic whiplash in HUNT3 and those not, using Pearson's chi-squared test and independent samples t-tests. Logistic regression analyses [153] were used to examine the relationship between baseline variables and subsequent chronic whiplash[10], and odds ratio (OR) estimates were produced. Precision of the estimated associations were assessed by 95% confidence intervals (CI).

Potential confounders like female gender, age, marital status and receipt of benefits were taken into account. To be a confounder, a variable must (necessary but not sufficient characteristics) [154]:

1. be associated with the exposure
2. be associated with the outcome
3. not lie on the causal pathway between exposure and outcome

In this study, most potential confounders were unassociated with outcome, and only results from crude analysis were presented.

As mentioned above, missing information was handled using listwise deletion and multiple missing imputation. All analyses were conducted using Stata 11 [150].

[10] Considering the regression function E(Y|X=x), the dependent variable Y is here chronic whiplash (developed versus not developed), the independent variable X is the potential predictive factors measured at baseline, pre-injury.

3.5.2 Statistical analyses, study two

Using Pearson's chi-square tests and independent samples t-tests, characteristics reported at baseline (HUNT2) were compared between individuals recovered (n=431) and individuals still suffering from chronic whiplash (n=199) in HUNT3. Logistic regression analyses were used to examine the relationship between baseline variables (HUNT2) and non-recovery (HUNT3)[11], and OR estimates were produced. The precision of the estimated associations were indicated by 95% confidence intervals (CI).

As in study one, as most potential confounders were unrelated to recovery, only crude estimates were presented. Missing information was handled using listwise deletion. The analyses were conducted using Stata11 [150].

3.5.3 Statistical analyses, study three

Participants' mean level of neck pain at follow-up was calculated, as was the percentage reporting reduced capability to work. Multiple regression models were used to investigate whether coping preferences at baseline were associated with outcome at follow-up. To avoid over-fitting, the number of parameters in a linear regression model should not exceed N/15. In this study 529 individuals responded to the item on neck pain at follow-up, giving at most 529/15≈35. In a logistic regression model, 10 to 15 cases for each explanatory parameter should be estimated [155]. In this study 98 individuals reporting reduced capability to work at follow-up, giving between at most 98/10≈10 and 98/15≈7 parameters.

As neck pain was a continuous variable, linear regression analyses were used for analyzing this outcome. For the dichotomous variable work capability, logistic regression analyses were used. The selection of potential explanatory variables was made a-priori, based on our hypotheses build upon rational, theoretical choices and previous research [19, 32]. Analyses were adjusted for socio-demographic variables

[11] Considering the regression function E(Y|X=x), the dependent variable Y is here chronic whiplash (recovered versus non-recovered), the independent variable X is the potential predictive factors measured at baseline, post-injury.

(age, gender, education), neck pain at baseline and accident severity, all in a linear fashion. Multiple linear regression analyses were used for neck pain and multiple logistic regression analyses for capability to work.

Bonferroni's method of taking multiple testing into account was used [156]; the required p-value of 0.05 was divided by number of regression analyses (20). Results presenting a p-value below 0.0025 were considered to be statistically significant.

Assumptions regarding the linear regression model were assessed by means of regression diagnostics: To investigate model fit of the logistic regression model, the Hosmer-Lemeshow fit statistic was used [157]. For discrimination the area under the Receiver Operating Characteristic curve[12] was evaluated [159, 160]. Distribution of residuals was assessed by inspection of a series of scatter plots of residuals and each of the explanatory variables and of residuals and fitted values. Histograms and QQ-plot was inspected to assess normality of the residuals. None of the plots gave rise to concern.

The analyses for study three were conducted using Stata12 [161].

[12] Receiver Operating Characteristics curve (ROC) is a plot of sensitivity against 1-specificity. The name is derived from the curve's original use in radar signal detection. The ROC curve can also be used to quantify how well a predictor based on a number of variables (e.g. based on the linear predictor from a logistic regression model) discriminated between individuals with and without a certain outcome. (158. B. R. Kirkwood, J.A.C.S., *Essential Meical Statistics, Chapter 36*. 2003, Blackwell Science. p. 432-433.)

3.6 Ethics

The HUNT2 and HUNT3 surveys were both approved by the Regional Committees for Medical and Health Research Ethics (REC) and the Norwegian Data Inspectorate. Written consent was obtained from all participants. For study one and two no new information was gathered, no new participants were recruited and there was no communication between researchers and participants. Both study one and two were approved by REC (2012/788/REK) and the HUNT research committee. The projects were conducted in line with the Helsinki II declaration.

Upon data-collection for study three, patients signed a written consent. The study was approved by the local ethical committees and conducted in accordance with the Helsinki II declaration.

In all three studies, data used was anonymous, and no individual person could be identified.

4. Results

Results from the three articles will be only briefly presented here. For further details, please refer to study one, two and three printed at the back of the thesis.

4.1 Factors associated with development of chronic whiplash, study one

Outcome; chronic whiplash: Among the 20,799 individuals reporting no whiplash in HUNT2, 199 (1.0%) developed chronic whiplash during the eleven year follow-up period.

Socio-demographic variables: Age and gender did not affect the risk of developing chronic whiplash. Compared with being married, being separated or divorced increased the risk of subsequent chronic whiplash by approximately 54%. Individuals who received short term health-related benefits were at increased risk of developing chronic whiplash whereas long-term health related benefits and unemployment benefits were unassociated with outcome

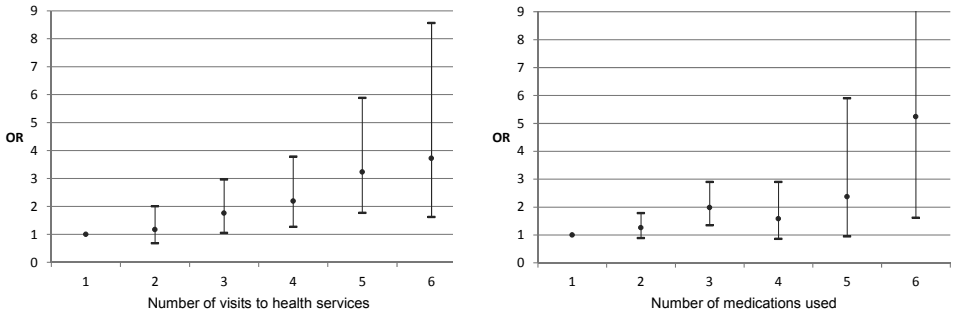
Health-related variables: In general, individuals reporting chronic whiplash in HUNT3 reported worse health at baseline (HUNT2) than those not developing chronic whiplash. The strongest risk factor for developing chronic whiplash was poor self-rated health at baseline (OR=2.26, $p<0.001$). Musculoskeletal pain (OR=1.21, $p<0.001$), somatic complaints (OR=2.09, $p<0.001$), anxiety (OR=1.93, $p<0.001$) and comorbid anxiety and depression (OR=2.06, $p=0.003$) were also significantly associated with subsequent chronic whiplash. Depression was borderline significant (OR=1.53, $p=0.050$). Individuals who reported to have been kept from working due to pain were at risk of developing chronic whiplash (OR=2.31, $p<0.001$).

Individuals who used many different medications/supplements and visited a high number of health-care services at baseline had significantly higher risk of subsequent chronic whiplash; individuals who developed chronic whiplash reported more visits to their GP, hospital doctors, physiotherapists, alternative therapists and more hospital

admissions at baseline. This group also used significantly more analgesics and sedatives and more medications for allergies and asthma. The odds of subsequent chronic whiplash increased alongside number of health-services visited and number of medications used (see Figure 6).

Individuals who were physically active at baseline, had reduced risk of developing chronic whiplash (p=0.009). Alcohol consumption and smoking were unassociated with outcome.

Figure 6: Association between use of health services and use of medications at baseline and subsequent chronic whiplash (odds ratio (point estimate and 95%CI)). Adapted from study one [151], reprinted with permission



4.2 Factors associated with non-recovery from whiplash, study two

Outcome; non-recovery: Among the 630 individuals reporting whiplash in HUNT, 199 (31.6 %) still reported whiplash in HUNT2, while 431 had recovered.

Socio-demographic variables: Female gender increased the risk of still reporting chronic whiplash in HUNT3 (OR=1.50, p=0.018). Compared to being married, being separated or divorced also increased the risk (OR=1.90, p=0.015). Age and receipt of benefits were not significantly associated with outcome.

Health-related variables: Poor self-rated health at baseline was the strongest risk factor for non-recovery, with an OR=3.12, p<0.001. Symptoms of anxiety also increased the risk substantially (OR=1.70, p=0.007) while symptoms of depression were

unassociated with outcome. Somatic complaints (OR=2.38, p<0.001), musculoskeletal pain (OR=1.21, p<0.001) and comorbid somatic diagnoses (OR=1.26, p=0.021) increased the risk of non-recovery.

Individuals who visited multiple different health-care services (OR=1.18, p=0.003) or used a high number of medications (OR=1.24, p<0.001) were also at risk of non-recovery from chronic whiplash. Alcohol consumption, smoking and physical activity were unassociated with outcome.

4.3 The prognostic importance of health care and coping preferences, study three

Outcome; neck pain and capability to work: Twelve months post-injury, the mean level of reported neck pain was 2.92 (95%CI: 2.66-3.18, range 0-10). Reduced capability to work was reported by 98 participants (15.1%).

Health care and coping preferences: At baseline, almost all participants (91.0%) reported that they wanted to "keep living as normal". However, only 10.8% reported "keep living as normal" as their only preference – most individuals reported other preferences as well. Participants commonly believed that "being referred to a physiotherapist/ chiropractor" (62.3%), "talking to a doctor about symptoms" (54.3%), "taking it easy" (44.5%) and "further medical investigations" (36.6%) could be helpful. For more details on reported preferences, see table 3 below.

Both outcome measures were significantly associated with multiple health care and coping preferences, as detailed in Table 3. Neck pain was most strongly associated with "taking medications" (mean difference =1.24, p<0.001) and "sickness absence" (mean difference=1.18, p<0.001). Preferring "being referred to a physiotherapist/ chiropractor" was also associated with neck pain at follow-up (mean difference=0.65, p=0.040).

Table 3: Treatment and coping preferences (n=740); number of participants reporting each preference, and the associations between coping and health care preferences and neck pain and reduced capability work, fully adjusted models, adapted from study three [162]

	Patients agreeing n (%)	Neck pain, linear regression Mean difference (95%CI))	p-values	Reduced capability to work, logistic regression OR (95%CI))	p-values
Active coping preferences					
Keep living as normal	673 (91.0)	-0.55 (-1.82-0.72)	0.393	1.23 (0.27-5.59)	0.786
*Keep living as normal – only***	80 (10.8)	**-1.62 (-2.39- -0.84)**	**<0.001***	**0.09 (0.01-0.64)**	**0.017**
Changing lifestyle	63 (8.5)	-0.46 (-1.39-0.46)	0.323	**0.11 (0.01-0.78)**	**0.028**
Passive coping preferences, including health care					
Taking it easy	329 (44.5)	0.44 (-0.08-0.96)	0.096	1.62 (0.99-2.67)	0.057
Sickness absence	144 (19.5)	**1.18 (0.53-1.82)**	**<0.001***	**3.05 (1.80-5.17)**	**<0.001***
Taking medications	181 (24.5)	**1.24 (0.67-1.82)**	**<0.001***	**3.53 (2.13-5.86)**	**<0.001***
Being referred to a specialist	214 (28.9)	0.47 (-0.14-1.08)	0.127	**1.98 (1.15-3.41)**	**0.014**
Further medical investigations	271 (36.6)	0.03 (-0.52-0.58)	0.918	1.53 (0.93-2.53)	0.097
Talking to a doctor about symptoms	402 (54.3)	0.08 (-0.45-0.61)	0.771	1.45 (0.86-2.44)	0.160
Being referred to a physiotherapist/chiropractor	461 (62.3)	**0.65 (0.03-1.28)**	**0.040**	**3.03 (1.33-6.91)**	**0.008**

Adjusted for socio-demographic variables (Age, gender, education (dichotomous variable)), neck pain at baseline and accident severity (dichotomous variable)
Statistically significant associations marked in bold
*significant also after Bonferroni correction (p<0.0025)
**Individuals reporting wanting to keep living as normal – and no other preferences
Mean difference: Indicating the preference was associated with a x higher mean level of neck pain

Reduced working capability was most strongly associated with "taking medications" (OR=3.53, p<0.001), "sickness absence" (OR=3.05, p<0.001) and "being referred to a physiotherapist/chiropractor" (OR=3.03, p=0.008). Preferring referral to a specialist also raised the risk of reduced capability to work at follow-up (OR=1.98, p=0.014).

The preferences "taking it easy", "talking to a doctor about symptoms", "further medical investigations" and "keep living as normal" were not associated with neither neck pain nor reduced work capability at follow-up. However, reporting "keep living as normal" as the only preference was protective, both with regards to neck pain (mean difference=-1.62, p<0.001) and reduced work capability (OR=0.09, p=0.017). Participants who believed that a change of lifestyle could make them better, were protected against reduced work capability at twelve months (OR=0.11, p=0.028).

After Bonferroni correction for multiple testing, preferring sickness absence and medications remained significant risk factors of both neck pain and reduced work capability at follow-up. Preferring to “keep living as normal” *only* remained protective against neck pain.

5. Discussion

5.1 Summary of findings

In short, the three studies in this thesis show that

1. Poor pre-injury health, both mental and somatic, is associated with increased risk of developing chronic whiplash (study one). Similar health complaints reported among individuals with whiplash are associated with non-recovery from the condition (study two).

2. A high use of health care services and medications before the injury is associated with increased risk of developing chronic whiplash (study one). High use of health care and medications among individuals with whiplash is associated with non-recovery (study two).

3. Patients` coping preferences in the acute phase after whiplash injuries are associated with outcome in whiplash (study three). Reporting need of health care and passive coping preferences increase the risk of neck pain and reduced capability to work one year later. Individuals who prefer active coping and want to keep living as normal have a better prognosis.

5.2 Interpretation of findings

Neck pain in the general population

Globally, neck pain is the fourth most common cause of YLDs [1]. In the adult population, 12-month prevalence estimates range from 30% to 50% (Results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders) [163]. In Norway, more than 30% of adults report neck pain within the last year and 14% report neck pain lasting for more than six months [164].

The development of chronic pain after whiplash must be interpreted in the light of the high prevalence of pain in the general population. This is highlighted in a study from Lithuania [165]: among individuals who had experienced whiplash, neck pain was

reported by 35% and headache by 53% (one to three years post-injury). In age- and sex-matched controls, neck pain was reported by 33% and headache by 50%. This might indicate that the prevalence of neck pain does not vary as much between countries as does the prevalence of attribution of neck pain to a whiplash accident. The importance of attribution is further discussed below.

The prognostic importance of sociodemographic factors and health related behavior

In this thesis, age was unassociated with both development of chronic whiplash and non-recovery. Female gender was unassociated with development of chronic whiplash, but associated with non-recovery. As discussed above, findings on the prognostic importance of age and gender in whiplash vary in the literature [53, 72].

The lacking prognostic importance of age and gender found for chronic whiplash in this thesis, stands in contrast to findings from other musculoskeletal conditions. For instance, the prevalence of neck pain in general peaks in the middle ages [163], and the prevalence of back pain and chronic widespread pain increases with higher age [166, 167]. Regardless of etiology, neck pain in the general population is more common in women than men [163], and in girls than boys [168]. Indeed, the prevalence of most common forms of pain, including chronic widespread pain [167], is higher among women than men [169]. There are multiple theories as to why women experience more pain then men, for instance women seem to display enhanced sensitivity to experimentally induced pain [169].

Though not associated with development of chronic whiplash, gender was found associated with recovery in this thesis. This might be related to health care: There is evidence of gender differences in pain treatment [169], and physicians have been found to request more laboratory tests for males, while proposing nonspecific diagnoses and asking psychological questions more often when seeing women [170]. Further in depth discussion of gender differences in pain and pain treatment is beyond the scope of this thesis.

Unemployment benefits and long term health related benefits were found to be unassociated with outcome. Receiving short term health-related benefits was associated with development of chronic whiplash but not with non-recovery. Compared to married individuals, individuals that were separated or divorced were more likely to develop chronic whiplash and to experience non-recovery. This is (apart from the findings on unemployment and long term health related benefits) in line with findings from other musculoskeletal conditions. For instance, urban areas with a high rate of referrals to pain clinics have a higher proportion of single households with children and a higher percentage of people in need of benefits [171]. Socioeconomic differences seem to affect pain in all age groups; pain is found to be more common among children in families with low education and low income [172], and education, type of work and marital status seems associated with pain in aging employees [173].

As mentioned in the introduction, the prognostic importance of health behavior has not received much attention in the whiplash literature, and this thesis provides new evidence on such factors. Smoking and alcohol consumption was found to be unassociated with outcome. Individuals who were physically active before the accident were less likely to develop chronic whiplash, while non- recovery was unassociated with physical activity. Research on pain unrelated to whiplash has found smoking to increase the risk of both sciatic, back and neck pain [174, 175], while exercise and alcohol consumptions has been found unassociated with back and neck pain [174].

The prognostic importance of pre-collision somatic and mental health

In this thesis, pre-injury somatic health (both somatic and musculoskeletal complaints) was found to be associated with development of chronic whiplash as well as non-recovery. Previous research has found pre-injury pain to be associated with outcome [31, 34, 44, 79], but (as discussed above) findings are inconsistent, and reviews have reached different conclusions [19, 32, 53].

Symptoms of anxiety were also found to be associated with development of chronic whiplash and non-recovery. Depression was borderline significantly associated with development of chronic whiplash, but unassociated with recovery. Some previous

studies have found pre-injury mental health to be associated with outcome in whiplash [69, 84], others have not [79].

The findings from this thesis indicate that individuals with poor mental (symptoms of anxiety) and somatic health are at increased risk of developing chronic whiplash. One explanation for this could be that individuals with poor health are more likely to experience car accidents, for instance due to concentration problems or because they are less watchful and vigilant in traffic (due to the disease itself, or due to medications). In study one, individuals developing chronic whiplash reported a higher use of medications at baseline, and use of sedatives was associated with development of chronic whiplash. However, as most whiplash accidents are rear-end car collisions, reduced concentration and attention of the victim might not be a satisfactory explanation for the increased risk. Also, individuals with chronic whiplash have been shown to be safe divers in experiments [176]. In study two, physical and mental health as well as use of medications (analgesics and asthma medications) was associated with non-recovery among individuals who already had whiplash, an association that increased risk of experiencing a car accident cannot explain.

The prognostic importance of pre-injury health might be an expression of vulnerability for chronic pain; some individuals might be more likely to experience pain and other symptoms both before and after car accidents. This theory is supported by a study from 2006, where individuals high in somatic awareness (as measured by the modified somatic perceptions questionnaire (MSPQ)) were at increased risk of persistent symptoms [34]. The importance of somatic awareness is further supported in this thesis as subjective, global health was found to be more strongly associated with outcome than reported symptom load. One might hypothesize that the collision can be a trigger for predisposing factors to ignite the development of health disabilities.

The importance of anxiety might be understood in relation to processes of attribution and fear avoidance: Attributing symptoms to an accident can make them seem more serious and troublesome [177, 178]. Anxiety related to causal beliefs, as well as fear avoidance, might contribute to continued experience of symptoms after whiplash

[179]. Attribution is discussed in more depth below. Further, the collision and related anxieties might function as stressors, throwing the body out of allostatic balance and activating stress responses [180]. Prolonged stress can potentially lead to fatigue, reduced function of the immune system, depression as well as altered perception of pain [180, 181]. A further in depth discussion of stress and pain is beyond the scope of this thesis.

Poor psychological health is a risk factor for neck pain unrelated to whiplash [163]. In general, physical symptoms seem associated with both anxiety and depression [182], and especially individuals with symptoms that remain medically unexplained after initial evaluation are at increased risk of both depression and anxiety [183]. Why depression seem to be of less importance in whiplash than other musculoskeletal conditions could not be investigated in this thesis, but is an interesting topic for further research.

Many studies investigating the prognostic importance of pre-injury health are based on post-injury reporting [34, 49, 76, 85]. The findings might therefore be complicated by recall and report bias. Individuals with continued pain after motor vehicle accidents have been found to underreported pre-injury pain symptoms [86]. A study investigating individuals with back pain after whiplash found that 52% had a history of back pain [87]. Of these, 27% did not report previous pain when asked, but the pain history was noted by GP's or specialists. Among the individuals that reported their low back pain to be caused by the accident, 41% of females and 54% of males had a history of previous back pain [87]. Individuals with continued pain after whiplash accidents have also been found to underreport pre-injury psychological distress [86].

Underreport of pre-injury health problems seems strongest in individuals perceiving the accident as someone else`s fault and in individuals filing compensation claim [86]. In Saskatchewan, Canada, individuals claiming in a tort[13] system were more likely to

[13] Under the tort system used in Canada up to January 1995, individuals injured in motor vehicle collisions could sue for pain and suffering. This possibility was eliminated with the change to a no-fault system (128. Cassidy, J.D., L.J. Carroll, P. Cote, M. Lemstra, A. Berglund and A. Nygren, *Effect of eliminating compensation for pain and suffering on the outcome of insurance claims for whiplash injury.* N Engl J Med, 2000. **342**(16): p. 1179-86..)

report never having experienced neck pain before the injury than individuals claiming in a no-fault system [128]. In Norway a history of neck pain was found in reports from doctor or physiotherapist - but not mentioned and partly denied by the patients - in eight of 27 cases submitted for assessment of medical invalidity after traffic accidents [184]. These findings highlight the importance of investigating pre-injury health in prospective studies unrelated to compensation processes.

The prognostic importance of use of health care and medications

In study one, visiting more health care services and using more medications were associated with development of chronic whiplash. In study two, increased use of health care services and medications was associated with lower likelihood of recovery. A high use of medications and health care services might solely be the result of poor health, thereby merely expressing the association between poor health and adverse outcome after whiplash. However, in study three, individuals reporting that they wanted to see a physiotherapist or take medications after the accident were at increased risk of both neck pain and reduced capability to work - also after adjusting for accident severity and baseline neck pain.

In addition to reflecting the health situation, health care use might be a separate risk factor for poor recovery. In pain patients (not related to whiplash), iatrogenic factors such as over-investigation, inappropriate information and advice, misdiagnosis, over-treatment and inappropriate prescription of medication are common [185]. Clinicians who promote frequent visits might unwittingly encourage patients to cope passively with their pain [186]. Multiple studies have shown that high use of health care after whiplash accidents is associated with both development of symptoms and delayed recovery [19, 151, 152, 187, 188]. Even after controlling for injury severity and pre- and post-injury pain, individuals with low utilization of health care recover faster [186]. This will be further discussed under Treatment. A high use of health care and medications can also bee seen as a passive way of coping. Coping is discussed further below.

The prognostic importance of coping preferences

In study three, participants preferring passive coping strategies were at increased risk of both neck pain and reduced capability to work at follow-up. As discussed above, several studies have found passive coping to be associated with an adverse prognosis [76, 110-112]. A study based on the data used in study three in this thesis also found coping to be important for outcome; individuals with high scores on "distraction", "reinterpretation" and "catastrophizing" at three months were at increased risk of considerable neck pain twelve months after the accident [113].

The findings from this thesis add to previous research as information on coping preferences was collected within ten days post-accident. Most previous studies have collected data on coping at later time points [76, 110-113]. In study three of this thesis, coping preferences are not the result of living with chronic symptoms, or already having experienced certain coping options as beneficial or ineffective with regards to whiplash. Also, the risk of preferences already being affected by health services is reduced. Coping preferences were further measured before coping efforts had actually taken place. Most previous studies investigate coping methods currently used [74, 76, 110-112], while study three investigates intentions to cope, or beliefs about what might be helpful.

It seems likely that injury severity and baseline neck pain would be associated with both coping preferences and recovery. As described above, pre-injury physical, mental and self-rated health, as well as use of health care and medications, are associated with recovery. Individuals with poor pre-injury health might be more likely to indicate need of health care after whiplash accidents due to experience and expectations. Some of the associations found in this study could thus be explained if individuals with better pre-collision health are more likely to recover and less likely to indicate the need of health services. To account for this potential confounding, analyses were adjusted for baseline pain and accident severity. Preferring sickness absence, taking medications and being referred to a physiotherapist/chiropractor or a specialist remained significantly associated with outcome after adjustment, indicating that coping

preferences not only reflects a more severe injury. This is supported by previous findings [112].

Patients' initial coping preferences might be affected by personal and psychological factors. In whiplash [76, 105-107] as well as in other conditions [11, 104], expectations are associated with outcome. Individuals with negative illness perceptions [189] and catastrophizing [32, 116, 117, 119-121] are more likely to develop chronic symptoms after whiplash accidents. Individuals expecting and fearing whiplash to have lasting consequences might also be more likely to feel the need of health care.

The importance of expectations has been studied in whiplash, under the bio-psycho-social model, a model recognizing that both physical, psychological and social factors might affect the presentation of somatic symptoms [62]. As discussed above, studies from different countries report very different outcomes after whiplash; in some countries like Lithuania [59], and Greece [58] chronic whiplash hardly occurs, in others, for instance Canada [46] and Norway [57], chronic complaints after whiplash are common. Research suggests that these prevalence differences might be related to lay people expectations of outcome after whiplash: Study participants were recruited from local companies in Canada, Germany, Lithuania and Greece. Individuals who had never experienced a whiplash injury and had no family member who had experienced such an injury were invited to participate. Participants were asked to report what symptoms they would expect to experience after a whiplash injury, and how long they believed each symptom would persist [36, 60, 61]. In all countries the expected symptoms resembled the symptom profiles reported in acute whiplash [36, 60, 61]. However, the expected symptom duration varied; in Canada, around 50% anticipated symptoms to last for months or years, while in Germany [61], Greece [36], and Lithuania [60] few subjects expected any symptoms likely to persist. The authors argue that in some countries, a lack of expectation for persisting symptoms may in part determine a low prevalence of chronic whiplash.

In study three, wanting to keep living as normal was unassociated with neck pain or capability to work. However, individuals reporting wanting to keep living as normal as

their only coping preference, were less likely to report neck pain and reduced capability to work one year later (the latter association not significant after Bonferroni's correction for multiple tests). Most previous studies on whiplash have not found active coping to be protective [110-112], but for other pain patients, active coping seems associated with better psychological adjustment [108], and less depression and disability at follow-up [190].

Coping styles have been suggested to affect recovery through issues of compliance and choice of therapy; individuals high in passive coping and low in active coping during the first week after the injury have been found to be more likely to take medications and less likely to attend active therapy [115]. In line with our results, this suggests that early passive coping preferences should be taken into account in clinical settings and in future intervention studies, as these may otherwise impede attempts to engage patients actively in treatment.

Treatment

Finding effective treatment for chronic whiplash patients, as well as preventing patients with acute whiplash from developing chronic problems, has proven difficult [41]. The layperson impression of preferred treatment after whiplash might be the traditional whiplash neck collar, but already in 1995, the Quebeck Task Force stated that prolonged periods of rest and the use of collars might be detrimental to recovery [191]. A randomized treatment trial from 1998 showed that act-as-usual (act as usual, no neck collars or sick leave) gave better outcomes than immobilization (14 days of sick leave and neck collars) [192]. Similarly, active treatment (frequently repeated active submaximal movements) has been found more effective in reducing pain than initial rest, recommended use of a soft collar and gradual self-mobilization [193]. Further, individuals receiving psychological intervention in addition to physical therapy have higher return-to-work rates than individuals receiving physical therapy alone, with the most marked benefit seen among individuals with psychological risk factors [194]. A systematic review from 2001 gave the cautious conclusion that active treatment seems beneficial over passive treatment [195]. However, the quality of the studies included was low, and only three were of acceptable validity [195].

A prospective study from 2008 found no difference in the rate of persistent neck-pain between a no-follow-up regimen (recommendations to act as usual only) and the multiple-follow-up regimen proposed by the Quebec Task Force (follow-up week one, three, six and twelve and at one year, with analgesics and physiotherapy in case of discomfort/stiffness) [31]. A more recent randomized controlled trial found that multidisciplinary treatment (medications, physiotherapy and seeing a psychologist according to individual presentation) did not give benefit over usual care (participants were free to pursue care from health practitioners of their choice or as monitored by the insurer, for instance care from general practitioners, physiotherapists or chiropractors) [196]. Individuals with acute whiplash do not recover faster when part of additional-exercise groups (compared to those with regular treatment) [114]. Further, in individual with acute whiplash, immobilization, "act-as usual" and mobilization have similar effects regarding prevention of pain, disability and capability to work (based on the same data used in study three of this thesis) [40]. Also in patients with chronic whiplash, treatment is difficult; individually tailored physiotherapy exercise programs do not reduce pain more than simple advice alone [197].

These findings seen alongside the discussion above, indicates that treatment after whiplash in not only inefficient, but might actually increase the risk of poor recovery - rising fundamental questions on how to meet patients after whiplash accidents.

Functional somatic syndromes

Whiplash patients experience considerable symptom load without a clear pato-biological explanation. Accident related factors and medical imaging are of limited prognostic importance while pre-injury health as well as coping preferences and expectations seem important for outcome. Following this, whiplash resembles, and has been suggested to be one of the wide range of conditions referred to as functional somatic syndromes (FSS) [178, 198]. Various names have been used for these conditions, for instance somatization, somatoform disorders and medically unexplained symptoms (MUS) [198]. In the following discussion, the terms functional somatic syndromes (FSS) will be used.

FSS are “characterized more by symptoms, suffering and disability than by disease-specific, demonstrable tissue abnormality” [178]. Multiple chemical sensitivity, the Gulf war syndrome, chronic fatigue syndrome (CFS), irritable bowel syndrome and fibromyalgia (amongst others) have been proposed to be FSS [178, 198, 199]. Diffuse or non-specific complaints like fatigue, sleep difficulties, headache, nausea and other gastro-intestinal symptoms, muscle and joint pain as well as symptoms of anxiety and depression are often reported in FSS [178]. Such complaints are common also in the general population [163, 200, 201], and in primary-care medically unexplained symptoms (MUS) are more common than medically explained symptoms [202]. Different FSS have remarkably similar symptom profiles [198]. Symptoms typical for one condition are prevalent in others [203], and many individuals could be diagnosed with more than one condition [198, 204, 205]. As such the conditions categorized as FSS have many similarities which may be of importance when trying to understand the different conditions and develop adequate treatment.

Gulf War Syndorome

Lessons from one particular FSS, the Gulf War Syndrome, might be especially useful when considering chronic whiplash. Serving in the Gulf War has been found associated with increased symptom burden and decreased well-being. Symptoms like fatigue, headache, numbness [206, 207], post-traumatic stress, and limb weakness [206] are commonly reported, and Gulf War veterans report more somatic symptoms than veterans having served other places [206, 207]. The symptom profile is wide; out of a list of 35 symptoms, Gulf War veterans report 33 significantly more often than other veterans (list of 35 current and long-term symptoms from different body regions, e.g. fatigue, joint pain, headache, wheezing, diarrhea) [207]. Despite the increased symptom report, no physical examination, laboratory, or serologic findings could identify Gulf War veterans [207], and pin pointing “what is wrong” is difficult [208]. Further, there is no evidence of increased disease related mortality among Gulf War veterans [209]. As in whiplash, the Gulf War Syndrome thus has a specific time of onset and a distinct exposure (though more long-lasting and multi-factorial than for whiplash) resulting in suffering and a wide symptom profile but few bio-pathological findings or explanations.

Attribution and other prognostic fators

In the Gulf War syndrome, attribution has been proposed to be an important factor in the development and maintenance of chronic symptoms. When experiencing somatic symptoms, most people tend to search for external or environmental explanations for the symptoms, rather than search for attributions internal to oneself [210]. Thus, it might be natural for a returning citizen to attribute the novel symptom to war experiences, and for a whiplash victim to attribute it to the accident. Such attribution can make recovery less likely [211], potentially as symptoms caused by a specific injury or exposure can seem to the patient to have a more "sinister and irreparable underlying pathology" [177]. Attribution of symptoms might amplify them, making them seem more intense, noxious and troublesome [212]. It has been suggested that the more convinced patients are that their symptoms are serious and pathogenic, the more intense, prolonged and disabling the symptoms become [178]. The role of attribution in Gulf War syndrome is highlighted in a study showing that, among Gulf War veterans, the variable most strongly associated with believing one had Gulf War syndrome was knowing someone else with Gulf War syndrome [213]. Attribution also seems important in other FSS [211, 214]. For instance, patients with CFS attribute a wider range of everyday somatic symptoms to their disorder, and believe the consequences of their disorder to be more serious, than do individuals with the more clearly defined condition rheumatoid arthritis [215]. Also in whiplash attributions are believed to be of importance [62], and it has been argued that fear avoidance and illness beliefs might contribute to the chronic course [78, 179].

In addition to attribution, factors like sensitization, attention [211], the belief that one is sick, negative expectations about the future course of the disease, the sick role and stressful events all seem to influence prognosis in FSS [178]. The negative consequences related to prolonged stress response might also be of importance, and for instance irritable bowel syndrome is thought to be associated with stress [180]. In FSS frequent testing and visits to doctors can provide little reassurance but heighten worry and anxiety [178]. Symptoms might be amplified by becoming a patient [179], and once a person is labeled as ill, he or she can be regarded and treated in ways that make

recovery more difficult [178]. These considerations support our findings and discussion on whiplash above.

Further, somatic distress and medically unexplained symptoms are endemic to everyday life, and social and cultural characteristics of each era seem to shape the expression, interpretation and attribution of such symptoms [178]. In whiplash this might aid the understanding of the strongly varying incidence over time and between countries.

Treating FSS

Multiple treatment strategies have been proposed for FSS, and extensive research efforts are put into determining which might be effective. In CFS, cognitive behavioral therapy (CBT) [216, 217], graded exercise therapy (GET) [217-219], and adaptive pacing therapy (APT) [220] are proposed strategies. Challenging and changing fatigue-related cognitions, achievement and maintenance of a basic (and increasing) amount of physical activity, as well as planning rehabilitation (work or other) are central components of CBT in CFS [217]. GET aims to help the patient return to appropriate physical activities, to reverse deconditioning and reduce fatigue and disability [219]. APT is based on the theory of CFS being a condition with an irreversibly reduced and finite amount of energy. It aims to give optimum adaption to CFS, by helping patient plan and pace activity [220].

A randomized trial from 2011 published in the Lancet investigated the effect of CBT, APT and GET compared to specialist medical care (providing explanation of the syndrome, advice to avoid extreme activity and rest, specific advice to self-help and symptomatic pharmacology (for insomnia, pain and mood)) on CFS [221]. Compared to specialist medical care alone, patients receiving CBT and GET had lower fatigue and higher functioning at follow-up one year later in the trial. ATP did neither reduce fatigue nor increase functioning. This might be due to ATP encouraging adaptation to the illness [220], while CBT and GET encourages gradual increase in activity with the aim of improving the condition [218]. Changes in beliefs about avoidance of activity and exercise have been shown associated with better outcomes in CFS [222].

How a psychological treatment such as CBT contributes to a physical improvement is not yet known, and though CBT and GET can lead to moderately improved outcomes in CFS [216, 217, 221], they cannot be said to be a cure; despite good outcomes with CBT, few patients cross the threshold for "normal" fatigue [216]. The failure of treatment to completely cure patients with FSS is a further addition to the similarities between chronic whiplash and FSS.

5.3 Strengths and limitations

5.3.1 Strenghts

Strenghts common for all three studies

The major advantage of all three studies is the prospective follow-up design. The participants were asked about symptoms, thoughts and beliefs *now*, at multiple time points. The exposure was recorded before outcome, thereby avoiding problems related to recall-bias [132]. This might be particularly important when investigating the prognostic importance of pre-injury factors on outcome after whiplash accidents, as in study one; Previous research has shown that individuals with acute back or neck pain after motor vehicle accidents tend to under report pain symptoms, as well as drug and alcohol use, and psychological distress experienced before the injury [86].

All three studies have large sample sizes. The response rate in HUNT3 was only 54.1% [134], but for HUNT2 it was higher (71.2%) [135]. The number of individuals participating in both HUNT2 and HUNT3 was high (n=33,117). In total, 57.9% of those participating in HUNT2 did also participate in HUNT3. The participation rate in HUNT3 did not differ between those reporting whiplash and those reporting no whiplash in HUNT2 ($p<0.418$). For the Danish Pain Data, participation rate was only 49% (n=740), but only n=55 were lost to follow-up and the response rate for the outcome neck pain was 78.7% and for capability to work 96.9% [83]. These factors allow us to use multiple logistic and linear regression analyses to investigate predictors and to adjust for potential confounders. Still residual confounding cannot be excluded.

Strenghts specific to study one and two

Norway is well-suited for large, medical surveys for several reason [223]. Firstly, Norway has a comprehensive and free health care system, minimizing differences in health care due to socioeconomic situation. Further, individuals born or living in Norway have a national identity number. This number contains information on birth date and sex, is unique to every citizen, and permits linkage between different registries and data files on the same person [223]. In HUNT2 and HUNT3 all questionnaires contained the participants' national identity number [223]. Further, Norway and Nord-Trøndelag have a stable population, where people do not tend to move much, neither within the country nor out of it (net migration out of Nord-Trøndelag 0.3% per year [135]), and a homogenous ethnic population [135, 223].

Using self-reported information in a population-based sample enables investigation of all individuals considering themselves to be sufferers of whiplash. If participants were recruited from GP's or emergency rooms, as in study three, individuals not reporting to these services would not be included, and there would be a risk of only investigating the more severely ill patients or individuals with a tendency for help seeking. Other studies have included participants through insurance companies [30, 54, 128]. Symptom report and recovery after whiplash has been shown to be associated with insurance processes [34, 54, 75, 127]. As HUNT data was collected in no association to insurance or compensations, the risk of systematic differences related to such processes was reduced.

The risk of symptom attribution and amplification of current symptoms was also reduced as the questions on symptoms were asked unrelated to the question on whiplash. The information was collected as part of a general health survey, with neither administrators nor participants being aware of any specific focus or hypothesis.

Strenghts specific to study three

As in Norway, health care in Denmark is free, reducing obvious selection bias due to socioeconomic differences also in study three.

For study three, individuals who visited GP`s or emergency rooms with neck pain after a recent whiplash accidents were invited to participate. This study thus avoids problems related to self-report of the whiplash variable (see below, limitations for study one and two). As the study aimed to investigate individuals in the early phase after whiplash injuries, using data from insurance companies and population-based studies might have been too slow; by the time participants could be included, symptoms might already have become chronic. Further, late inclusion would have to rely on retrospectively collected information about the first days after the accident. Population-based survey data would also not be a good option, as the number of individuals reporting a recent enough injury would be too low. By including directly from the first line health services, patients could be included fast, and participants who could not be examined within ten days of the accident were excluded [40]. Problems related to retrospectively collected data and recall bias were thus minimized. Most previous studies investigating coping have collected information at around 4-6 weeks post-injury [76, 110-112]. Reported coping preferences can therefore in these studies, more than in ours, be the result of living with symptoms, or already having experienced certain coping options as either beneficial or ineffective with regards to whiplash. Further, the chance that the preferences have been affected by health services will be higher in these studies. In whiplash coping has indeed been found to change over time [116], and the one identified study investigating coping within a week of the accident, found no association between coping and outcome [74].

In study three two clinically important outcome measures (neck pain and capability to work), potentially predicted by different factors were investigated. To avoid a sole focus on pain and gain knowledge of how patients function and get on with life, it is important to also assess capability to work.

5.3.2 Limitations

Limitations common for all three studies

Estimates and findings in our studies might have been affected by selection bias[14]. Especially the Danish Pain Data and HUNT3 had lower participation rates than desirable. In HUNT3 non-participants had lower socio-economic status, higher mortality and higher prevalence of several chronic diseases [137]. The prevalence of musculoskeletal pain was, however, higher among participants [137]. In the Danish data used for study three, individuals declining participation (n=200) were more often male, and individuals lost to follow-up (n=55) were more likely to be students or unemployed, and more likely to report pre-collision pain [83]. Our results might thus have been affected by the selection, and the direction is uncertain. A previous study following individuals claiming compensation after whiplash, found only minor differences between individuals participating in the follow-up and those not; for example, the average baseline neck pain was somewhat lower and level of education somewhat higher in participants [127]. In general, individuals that participate in studies are healthier [225], and we might expect that individuals with very severe chronic whiplash, of for instance WAD4, do not participate. As these cases seem substantially different from lower WAD grades, they are often excluded from research on chronic whiplash [29, 40]. Selection bias might indeed have affected the results in this thesis, but studies suggest that the risk of biased results is larger for prevalence estimates of exposures and outcomes than for exposure-outcome associations [226].

In all three studies, the potential predictors investigated were self-reported, as was most demographic information. Our results might thus be affected by bias related to response styles [227]. It has for instance been suggested that some individuals might be inclined to exaggerate, overestimate or use high numerical values in rating tasks [228]. In study one and two, if such high rating lead to increased risk of reporting base-line health complaints as well as whiplash at follow-up, the association between

[14] Selection bias: Distortions resulting from procedures used to select subjects, and from factors influencing study participation (224. Rothman, K.J. and S.L. Greenland, T. L., *Modern Epidemiology, Chapter 9*, in *Modern Epidemiology*. 2008, Lippincot WIlliams & Wilkins: Philadelphia. p. 134.)

predictors and outcome could have been overestimated. Also on study three, high rating behavior could have led to increased tendency to report need of health services and passive coping strategy as well as neck pain and disability. At present, there is little knowledge regarding these issues. However, in an epidemiological study of musculoskeletal disorders, high or low rating behavior has been investigated and no support for such theories found [229].

In addition to the sources of systematic misclassification as discussed above, the studies in this thesis could also have been affected by non-systematic misclassification or nondifferentiality[15] [231]. Nondifferenciality can potentially lead to a loss of power [232] and in cases of independent nondiffertial misclassification of a binary exposure variable, results will be biased towards the null value [230]. In all studies, some of the variables, for instance working capability, accident severity and self-rated health were dichotomized, leading to reduction of variation and loss of power.

Limitations specific to study one and two

The majority of the information used in the articles in this thesis is self-reported. For study one and two, also the grouping variable, chronic whiplash, is self-reported. The lack of medical confirmation and WAD-classification is a draw-back to the studies. Still, as mentioned above, doctors tending to patients after whiplash accidents base the diagnosis on history (the accident), clinical examination and patients self-reported information [41, 42], and the WAD-classification is not always a good predictor of outcome [31, 35].

In HUNT, participants were asked whether they had experienced a whiplash accident - not if they were currently suffering from chronic whiplash. As most individuals recover rapidly after whiplash injuries [38, 233, 234], and as neck pain is the most common symptom seen in chronic whiplash [30, 50, 52] the chronic whiplash group was closer defined by limiting inclusion to individuals reporting a whiplash accident

[15] Nondifferentiality: Nondifferential exposure misclassification occurs when the proportion misclassified on exposure does not depend on the stats of subject with respect to other variables in study, including outcome (230. Rothman, K.J. and S.L. Greenland, T. L., *Modern Epidemiology, Chapter 9*, in *Modern Epidemiology*. 2008, Lippincot WIlliams & Wilkins: Philadelphia. p. 138-139.)

more than twelve months ago and reporting neck pain. Therefore, individuals reporting a whiplash accident (more than 12 months ago) and neck pain were included in the chronic whiplash group, even if the neck pain was caused by something else. Also, in study two, individuals reporting whiplash but no neck pain were set as recovered even if they did not consider themselves as recovered.

Previous research has used similar methods for defining chronic whiplash [66, 67]. Though the lack of medical confirmation is a limitation, it seems that self-reported whiplash has clinical relevance; self-reported whiplash is associated with increased symptom load [66, 67], as well as increased chances of subsequent disability pension awards, even in the absence of neck pain [235]. Also, at least for more recent cases, incidence of injuries based on self-reported data is similar to that from official sources of reporting [236].

In HUNT2 the prevalence of whiplash is around 2.8% [45] to 2.9% [237]. When investigating the reported number of cases within the last 2 years (in the same data), the yearly incidence was calculated to be 0.13%. If the proportion of drivers at risk of whiplash trauma is equal in all age groups, and the period of active driving is set to be 60 years, this would give an expected prevalence in HUNT2 of 7.8% [45]. The discrepancy between expected and observed prevalence suggests underreport of whiplash in HUNT2. This might be related to recall bias: Individuals who experience a whiplash accident and recover fast, might forget the incidence and not think of reporting it when asked years later. Individuals who develop chronic symptoms, might be more likely to remember the accident (resulting in differential misclassification[16]). This theory has been supported in another Norwegian population-based study showing decreasing number of self-reported whiplash injuries with increasing time since the accident [67]. As time passed, the strength of association between a reported injury and somatic symptoms also increased [67]. This suggests that an association between symptom load and whiplash might be found to be higher in our studies than it would be, if all individuals having experienced a whiplash injury reported it.

[16] Differential misclassification here due to recall bias: where exposure is recalled and reported differently among cases and non-cases (230. Ibid.)

In HUNT2 and HUNT3 no information on physical factors involved in the whiplash accident (e.g. speed difference, direction of impact or the use of headrest) is provided. As discussed in the introduction, the prognostic value of collision related factors is not yet clear, but in general most collision related factors seem to be of limited importance [19, 32]. Investigating these factors as predictors, and being able to adjust other associations for these potential confounders would have been interesting, but was not possible in study one and two.

In study two, recovery versus non-recovery from chronic whiplash was investigated. Results from such research can be difficult to compare. Rates of recovery will be highly dependent on cut-offs and measures used to define recovery, and in the literature, many different measures are used [41, 53]. The prognosis after whiplash also varies with study population (e.g. population-based-sample, participants recruited from health services or through insurance companies) [53] and between countries [62].

Limitations specific to study three

The main limitation to study three is the tool used to investigate coping. As described in the methods section, the nine items used are not part of any validated check-list for coping. Items were classified as active or passive based on literature and other inventories, and no factor analyses were run in order to determine whether the classification was justifiable in our sample. Being able to use a validated check-list, or running a factor analyses would have been a valuable addition to the study. However, most validated check-lists for coping are long. As discussed in the method section, the items used in study three were chosen as we wanted to identify simple predictive factors that can be easily noted by health personnel without the use of extensive screening tools.

In study three, information on damage to the car and the speed difference between the cars involved was provided. The analyses investigating the prognostic importance of coping preferences were adjusted for these potential confounders. As most other variables investigated, these physical factors were self-reported, and thus subjective. Though most collision related variables seem unrelated to outcome [19, 32], having

objective measures for the physical factors involved would have been an interesting addition to all of our studies.

In addition to the issues related to selection bias discussed above, there might be selection bias in study three related to participants being recruited from GPs' or emergency units. Individuals that experience rear-end collisions but contact other services or seek no help (due to for instance milder symptoms or different health seeking behaviors) were thus not included. These individuals might differ from study participants with regards to symptom load, coping, and recovery, as well as other factors. Provisional situation at baseline has been compared between participants and matched registry controls, and no statistically significant differences found [70].

As in study one and two, results on recovery/outcome will be highly dependent on the variables or cut-offs used to define recovery.

5.4 Clinical implications

Knowledge and understanding of the factors determining outcome in whiplash is the first step in preventing disability. Our findings indicate that a history of poor health as well as preferring health care, sick leave and medications after the injury is associated with poor outcome. By talking to the patient after the injury, and asking about preferences for treatment and coping as well as pre-injury medical history (or consulting medical journals if available), health personell can potentially - easily and early - identify individuals at increased risk of poor recovery. This can facilitate treatment for those who need it more.

However, as the efficacy of treatment after whiplash is still higly debated, one should be careful when recommending a close follow-up or extensive treatment programs for individuals after whiplash. Maybe the key message to patients should still be - as already stated in the QTF [42] - that pain is usually short-lived and in itself not harmful. Based on current knowledge, health personnel should emphasize that most cases of WAD are self-limited, and generally recommend patients to resume normal activity as soon as possible.

5.5 Further research

Age, gender and depression seem to be of less prognostic importance in whiplash than in other chronic pain conditions. Further research is needed to determine how and why whiplash differs from other musculoskeletal conditions. Also, studies investigating and comparing risk factors for chronic complaints after whiplash accidents between countries would be valuable when aiming to understand the greatly varying incidence of chronic whiplash.

The results of this thesis, as well as previous literature, indicate that pre-injury health and health care use, as well as passive coping preferences are associated with adverse prognosis. In order to determine a specific model of the multifactorial causality of chronic complaints after whiplash, and to investigate potential mediating pathways, further studies are needed.

Treatment of chronic whiplash is not yet efficient, and it is unknown whether targeting risk factors can improve outcomes [76]. It seems that poor mental and somatic health, as well as passive coping preferences are associated with adverse prognosis. But can treatment of other somatic and mental health problems or change of coping contribute to better recovery? Further research is needed to determine whether prognosis improves if patients are advised on helpful coping. Such research should be conducted in randomized controlled trials in no relation to insurance or compensation processes.

5.6 Conclusion

After whiplash accidents some patients develop chronic neck pain and other complaints. Poor pre-injury somatic and mental health as well as a high pre-injury use of health care and medications are associated with development of chronic whiplash. In individuals with whiplash, poor somatic and mental health, and a high use of health care and medications are associated with poor recovery. Preferences for passive coping in the first few days following whiplash are associated with neck pain and reduced capability to work one year later. Health personnel with this in mind can potentially identify individuals at increased risk of an adverse prognosis more efficiently at an

early stage. This can facilitate early treatment for those most in need. However, health care in whiplash is often ineffective and might itself increase the risk of poor recovery. More research on treatment in whiplash is needed; in particular on whether targeting prognostic factors like those identified in this thesis can improve recovery.

Source of data

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