

From The Department of Clinical Science and Education,  
Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

# PROGNOSTIC FACTORS FOR WHIPLASH ASSOCIATED DISORDERS

Eric Rydman



**Karolinska  
Institutet**

Stockholm 2020

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Published by Karolinska Institutet.  
Printed by Eprint AB  
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ISBN 978-91-7831-728-8

# Prognostic Factors for Whiplash Associated Disorders

THESIS FOR DOCTORAL DEGREE (Ph.D.)

To be publicly defended Friday, 13 March 2020 at 09.00, at Södersjukhuset, Aulan, Stockholm,

By

Eric Rydman

**Principal Supervisor:**

Professor Sari Ponzer,  
Karolinska Institutet  
Department of Clinical Science and  
Education  
Södersjukhuset

**Co-supervisors:**

Carin Ottosson, MD, PhD,  
Karolinska Institutet  
Department of Clinical Science and  
Education  
Södesjukhuset

Associate professor Hans Järnbert-  
Pettersson,  
Karoliska Institutet  
Department of Clinical Science and  
Education  
Södesjukhuset

**Opponent:**

Håkan Jonsson, MD, PhD,  
Uppsala University  
Department of Surgical Sciences  
Division of Orthopedics

**Examination Board:**

Professor Lena Nilsson Wikmar,  
Karolinska Institutet  
Department of Neurobiology, Care  
Sciences and Society

Associate professor Bengt Sandén,  
Uppsala University  
Department of Surgical Sciences  
Division of Orthopaedics

Professor Andre Stark,  
Karolinska Institutet  
Department of Clinical Sciences,  
Danderyd Hospital



*To Helena, Charlie and Claudia*



# ABSTRACT

Disability and chronic pain secondary to low-speed vehicle collisions has been a known condition since the nineteenth century. Today, whiplash-associated disorders (WAD) are the most common personal injuries reported to insurance companies after motor vehicle accidents (MVAs). The prognosis has great variations, spanning from discomfort for a few days to lifelong disability and severe reduction in quality of life. A few well-accepted prognostic factors exist, including high level of pain immediately after the accident, post-traumatic stress and anxiety, and previous history of pain conditions. However, there is no accepted universal pathomechanism and there is a need for additional surveys regarding common characteristics of individuals with poor recovery potential after a whiplash injury.

The overall objective of this thesis was to investigate possible risk factors for non-recovery after whiplash trauma. Specifically, we aimed to identify potential associations between non-recovery and involvement of insurance companies, genetic markers, cervical radiological degeneration, and sagittal alignment. Additionally, we aimed to investigate the effect of an educational video-intervention on the recovery rate.

The participants in this thesis are derived from four cohorts. The first cohort comprised individuals aged 18–65 years seeking care at an emergency department (Studies I and III). The second cohort comprised individuals aged 18–65 years reporting neck pain to insurance companies after an MVA (Studies I and II). The third and fourth cohorts consisted of individuals aged 16–65 years, also recruited

from an emergency department after whiplash trauma (Studies IV, V, VI, and VII).

In all seven studies of this thesis, inclusion was made by the study team. Information in baseline questionnaires were filled in with regard to demographics and physical and mental health. The patients were followed up with regard to a patient-reported outcome measure (PROM), defined as reported non-recovery or recovery. Secondary outcome measures were level of pain and distress and the Whiplash Disability Questionnaire (WDQ).

For Study V, we performed a randomization to either the intervention with the educational video or to a standard information sheet.

In the studies included in this thesis, financial compensation from insurance companies, facet joint degeneration, sagittal alignment variables (low thoracic inlet angle (TIA) and Neck Tilt), high level of pain and distress were associated with non-recovery. Further, expectation of poor recovery was a risk factor. No prognostic or therapeutic value was demonstrated for genetic markers (represented by COMT gene haplotypes), the educational video, disc degeneration, or cervical sagittal curvature.

This thesis contributes to the general knowledge on those groups of individuals that are at risk of poor prognosis after whiplash trauma. It raises a few new questions regarding prognostic factors. The findings of radiologic profiles being associated with non-recovery must be re-examined in the future, tentatively emphasizing the association between facet joint degeneration and continuous pain.





## SUMMARY IN SWEDISH

Whiplashskador är de vanligaste personskadorna efter trafikolyckor. Ungefär hälften av dem som får en whiplashskada anser sig vara återställda efter ett halvår men många får bestående men. Det finns en stor mängd forskning kring vilka faktorer som kan förutsäga prognosen för den whiplashskadade men det finns inte någon helt samstämmig bild.

Den här avhandlingen handlar om vilka faktorer som kan påverka det långsiktiga resultatet efter en whiplashskada.

Genom enkätstudier, genanalyser och undersökningar med skiktröntgen (datortomografi) har vi kartlagt hur de individer som vi undersökt mår i anslutning till olyckan och följt upp dem i minst 6 månader. Vi har även undersökt den individuella kroppshållningen, genom vinkelförhållanden mellan kotor i halsryggen samt graden av artros i halsryggslederna. Dessa undersökningar har vi därefter jämfört med utfallet efter skadan.

I de studier som ingår i avhandlingen har vi vid uppföljningarna sett att de individer som fått ekonomisk ersättning från försäkringsbolag i lägre grad anser sig vara återställda efter olyckan jämfört med de som inte fått ersättning.

Genomsnittligt ansåg sig 56% inte vara återställda vid uppföljning efter 2 till 4 år.

Individer som vid skadetillfället hade en viss grad av artros i halsryggslederna hade sämre prognos än de som inte hade någon grad av artros. Dessa resultat motsäger tidigare forskning där man anser att artros inte är av betydelse för prognosen efter whiplashvåld mot nacken. Till skillnad mot tidigare forskning har vi använt oss av en ny bedömningsmall vid analys av graden av artros. Denna mall presenteras i avhandlingen.

Vi har också sett att vissa vinklar mellan kotorna, som har med ryggradens form att göra, hade betydelse för prognosen. Förenklat kan man säga att de som hade en kort och bred nacke hade bättre utfall än de med lång och smal nacke.

Vidare har vi sett att gener som är viktiga för kroppens smärthantering, inte tycks vara av betydelse för prognosen efter en whiplashskada. Inte heller skador på halsryggens diskar, eller halsryggens kurvatur var faktorer som påverkade prognosen.

Sammanfattningsvis bidrar den här avhandlingen till förståelsen för vilka faktorer som påverkar prognosen efter en nackskada. Vi hoppas att forskarsamhället i framtiden kan dra nytta av de resultat vi presenterar i avhandlingen och att de i förlängningen kan leda till en mer effektiv behandling för individer med whiplashskador

# LIST OF SCIENTIFIC PAPERS

- I. Predicting nonrecovery among whiplash patients in the emergency room and in an insurance company setting.**  
Eric Rydman, Sari Ponzer, Carin Ottosson and Hans Järnbert-Pettersson  
European Spine Journal 2017 Apr;26(4):1254-1261
- II. Long-term follow-up of whiplash injuries reported to insurance companies: a cohort study on patient-reported outcomes and impact of financial compensation.**  
Eric Rydman, Sari Ponzer, Rosa Brisson, Carin Ottosson and Hans Järnbert-Pettersson  
European Spine Journal 2018 Jun;27(6):1255-1261
- III. COMT genotype and non-recovery after a whiplash injury in a Northern European population.**  
Eric Rydman, Erica Comasco, Hans Pettersson, Lars Orelund, Sari Ponzer and Carin Ottosson  
BMC Musculoskeletal Disorders 2017 Dec 1;18(1):507
- IV. Quantifying cervical spondylosis: reliability testing of a coherent CT-based scoring system.**  
Eric Rydman, Sara Bankler, Sari Ponzer and Hans Järnbert-Pettersson  
BMC Medical Imaging 2019 May 30;19(1):45
- V. Intervention with an educational video after a whiplash trauma—a randomised controlled clinical trial.**  
Eric Rydman, Carin Ottosson, Sari Ponzer, Anna Dahl, Ted Eneqvist, Hans Järnbert-Pettersson and Piotr Kasina  
Scandinavian Journal of Pain. 2019 Nov 20. Pii (Epub ahead of print)
- VI. Association between cervical degeneration and self-perceived non-recovery after whiplash injury.**  
Eric Rydman, Piotr Kasina, Sari Ponzer and Hans Järnbert-Pettersson  
The Spine Journal 2019 Dec;19(12):1986-1994
- VII. The significance of cervical sagittal alignment for non-recovery after whiplash injury.**  
Eric Rydman Peter Elkan, Ted Eneqvist, Per Ekman and Hans Järnbert-Pettersson  
2020 (Manuscript, resubmitted to The Spine Journal January 2020)



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# LIST OF ABBREVIATIONS

PROM	Patient Reported Outcome Measure
MVA	Motor Vehicle Accident
WAD	Whiplash Associated Disorders
FSS	Functional Somatic Syndrome
CCJ	Craniocervical Junction
NRS	Numeric Rating Scale
VAS	Visual Analogue Scale
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
COMT	catechol- <i>O</i> -methyltransferase
RCT	Randomized Controlled Trial
ER	Emergency Room
CPR	Clinical Decision Rule
SF-36	Short Form (36)
AP	Anterior-posterior
ICC	Intraclass Correlation Coefficient
WDQ	Whiplash Disability Questionnaire
NRS	Numeric Rating Scale
ITT	Intention to Treat
PP	Per Protocol
IC	Insurance Company
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic
FSS	Functional Somatic Syndrome
CI	Confidence Interval
LPS	Low Pain Sensitivity
APS	Average Pain Sensitivity
HPS	High Pain Sensitivity
HAD	Hospital Anxiety and Depression
PTSD	Post-traumatic Stress Disorder
SD	Standard Deviation
TIA	Thoracic Inlet Angle



# PROLOGUE

So many stories. Stories of despair, of suffering and of pain. About the day when it all began. The day that they will never forget. The day that would come to change their lives. A traffic accident. Not necessarily a dramatic accident with sirens, helicopters, and cars in flames, but often a quiet bump in the traffic jam on the way home from work. They would eventually come to miss that work so profoundly. The work that they would no longer be able to go back to because of the pain, and all the other perplexing symptoms that would manifest themselves as ghosts. Or shadows. The symptoms that no one would recognize. No one would be able relate to them or grasp the suffering. Many would try, but no one would really understand. The tears would become only their own.

I have often encountered these stories in my profession, often from disillusioned souls who have already realized that I, as a doctor, have nothing new to offer. I have seen the hopelessness in their eyes as they have left my clinic in despair. I could not do anything for you either. I did not understand. I saw nothing on your X-rays. I could not manage to put the puzzle together.

I have often felt confused and frustrated about this group of patients. Frustrated, puzzled, and curious. What is it that I do not see? What is the origin? How can a fully functioning human being become so disabled, so misunderstood, and so hopeless from an injury I don't even understand?

This curiosity was the beginning of this project. I wanted to get a more detailed picture of the individuals that I did not comprehend. I do not know how much wiser we have become from this and how much this work has contributed, but still, I have tried. It was my responsibility to this group of deprived patients. Being torn between hope and despair. The ones nobody understands. The ones fighting Goliath.





# BACKGROUND

## Introduction

The term “whiplash injury” was first used by Dr Harold Crowe in 1928 [1]. The term was intended to describe a new kind of spine injury that was seen in motor vehicle accidents (MVAs), as automobile transportation became more common. Interestingly, similar injuries had been reported approximately 100 years earlier, after the global introduction of the railways. The term “railway spine” was introduced in the nineteenth century. Contemporary physicians associated the symptoms secondary to train-related neck trauma with neurotic personalities and the condition was immediately controversial [2]. Ever since, the medical community has been puzzled over the fact that certain patients present major clinical symptoms and disability, even after minor accidents

In 1995, a group of researchers in the field formed the “Quebec Task Force” and established the definition of whiplash injuries as “an acceleration-deceleration mechanism of energy transferred to the neck which may result from rear end or side impact, predominantly in motor vehicle collisions, but also from diving accidents, and from other mishaps” [3]. The task force also introduced the term “whiplash-associated disorders” (WAD), describing the various clinical manifestations that can be parallel to neck pain after a whiplash injury. Further, they constructed a grading-system for the initial clinical findings (Table 1).

According to the initial terminology, no consideration was given to the time frame and both acute and long-term disability was included. WAD is often used synonymously with “Late Whiplash Syndrome” [4], describing the symptomatology among those group of patients that were not following the expected recovery pattern.

However, the terminology is often bewildering and there is an ongoing debate regarding classification and nomenclature [5].

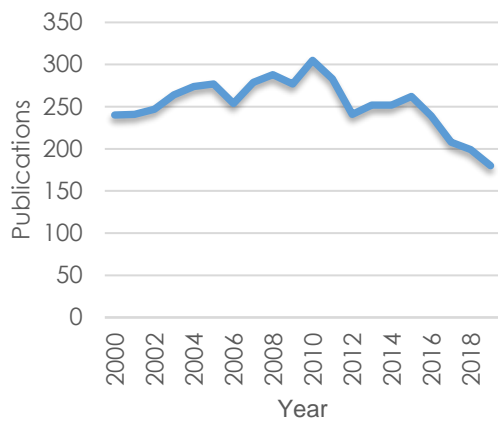
Whiplash injuries represent the most common disability after low-energy motor vehicle accidents (MVA) [6, 7].

In Sweden, it is estimated that 20 000–30 000 persons are affected annually [5, 8] and 150 persons receive permanent disability pension [8].

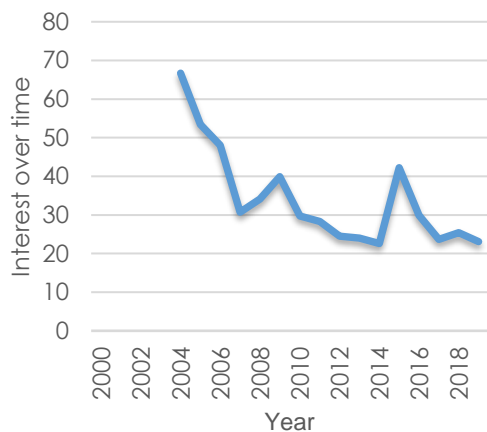
The number of whiplash injuries reported to insurance companies in Sweden has remained unchanged in previous decades [9]. However, the number of published articles with the search term “whiplash injury” and the number of searches on Google appear to be reduced, with the exception of 2015 (the year after the award-winning blockbuster “Whiplash”) (Figure 1 and 2). The interpretation of this skewness could be that the public interest is lower but individual suffering remains.

**Table 1.** Grading of whiplash-associated disorders (WAD) according to Spitzer et. al (3).

Grade	Classification
1	Complaint of neck pain, stiffness or tenderness only. No physical signs.
2	Neck complaint and musculoskeletal signs. Musculoskeletal signs include decreased range of movement and point tenderness.
3	Neck complaint and neurological signs. Neurological signs include decreased or absent tendon reflexes, weakness and sensory deficits.
4	Neck complaint and fracture or dislocation.



**Figure 1.** Publications found using the search term “whiplash injury” on PubMed annually.



**Figure 2.** Interest over time. Numbers collected from the web application Google Trends©.

Although the typical crash pattern among WAD patients is a rear-end collision, no association between prognosis and crash direction, type, or crash impact has been shown (5). Moreover, the symptomatology is not unique for injuries following an MVA but reported after diving accidents, fall trauma, and head banging in a rock music context (6) and other traumatic events. The injury can lead to a broad variety of symptoms in addition to neck pain, which are together referred to as WAD. Since, to date, there are no convincing structural injuries or biological mechanisms that can convincingly explain WAD [10]. Hereby, it

is often described as a functional somatic syndrome (FSS) [11]

It is essential to note that the diversity in the severity of symptoms among individuals is clustered as chronic WAD. Although neck pain is the main impairment, numerous patients describe a broad variety of symptoms derived from the index MVA [12]. These symptoms often overlap other inclusions of FSS, such as fibromyalgia and tension-type headache [13] and include lumbar and thoracic back pain, muscular dysfunction, headache visual symptoms, and myofascial pain [14]. Further, cognitive symptoms—such as fatigue, concentration, and memory deficits—are also widely reported [15].

In general, neck pain has possibly been like a shadow for humans since we became bipedal, some million years ago. This secondarily to the suboptimal load transfer to the discs and joints of the spine when in an erect position [16]. The complex anatomic constitution and demands on weight bearing are suggested to be factors contributing to the high prevalence of neck pain [16]. Globally, unspecific neck pain is the fourth most common disability [17] and affects approximately 5% [18] of the global population. The 12-month prevalence of neck pain to any degree in the general population is reported to be 30%–50% [19]. Moreover, 20%–30% of patients with chronic neck pain report a traumatic onset to the pain [20, 21].

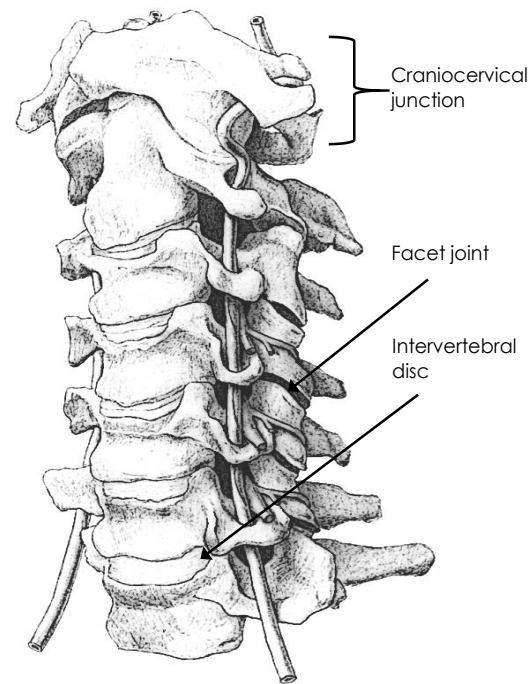
The aetiology of unspecific neck pain is often unknown. However, it has been shown that a history of MVA doubles the risk for developing chronic neck pain [22]. Although WAD patients share characteristics with patients with non-specific neck pain, there are believed to be a few differences. WAD patients often demonstrate a higher level of disability and pain [20] and problems in cognitive functions such as memory loss and dizziness [20].

## Anatomy

The cervical spine has certain unique features, as it is the link between the head and the rest of the body. It has high demands on both motion to allow for the neck's flexibility and the head's range of motion and stability to secure the passage for vital structures, such as the carotid artery and medulla. Further, the cervical spine needs to handle a heavy load, particularly when dealing with sudden forces such as rapid acceleration and deceleration. The cervical spine consists of seven vertebrae. The first two, C1 and C2, have specialized characteristics and are given unique names: atlas and axis, respectively. C1 and C2 form a set of articulations that provide rotational mobility for the skull. C1 serves as a washer that the skull rests upon and articulates in a pivot joint with C2.

Together with the base of the skull they form the craniocervical junction (CCJ), which—apart from the articulations—also consists of several ligaments that are specialized in stabilizing the spine during rotation movements. C3–C7 have more in common anatomy with the rest of the spinal column, with vertebral bodies, pedicles, laminae, and facet joints. The cervical vertebrae are connected through intervertebral discs, uncovertebral and facet-(zygapophyseal) joints, and capsules.

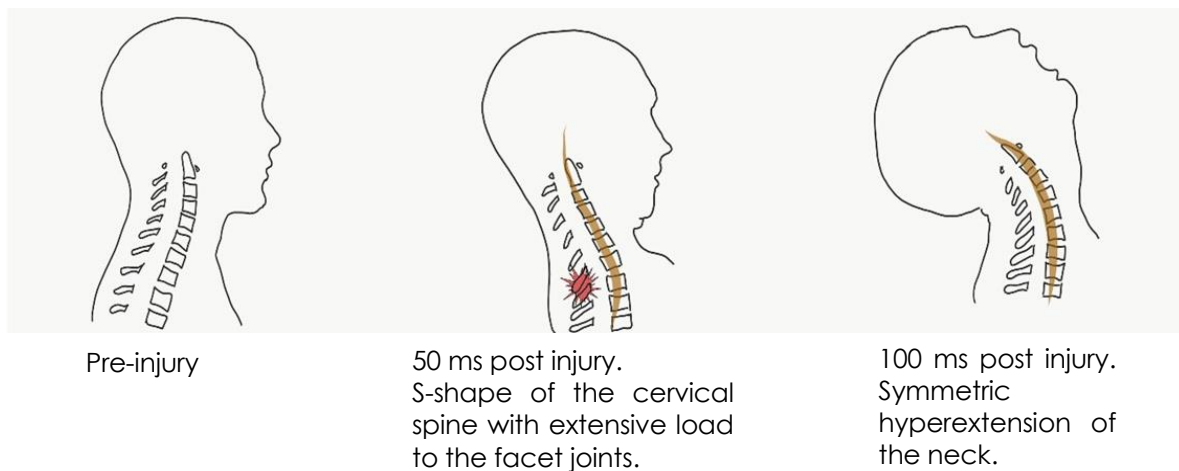
Neck pain can theoretically be originating from various anatomical structures with nociceptive neurons, including muscular fascia, vertebral endplates, and ligaments [23]. However, the facet joints, the intervertebral discs, or a combination of these two segmental structures represent the dominant pain generator in clinical studies [24, 25]. Moreover, in previous decades, the CCJ-complex has been a focus of interest, and instability in this complex has been suggested to be a possible pain source for patients with WAD [26].



**Figure 3:** Anatomical model of the cervical spine.

## The pathophysiology of whiplash

In a typical rear end car crash, according to Isaac Newton's first law of motion [27], the force of motion from the colliding vehicle is transferred to the upper spine and the head of the occupant of the hit vehicle at the time of the crash results in an acceleration-deceleration force on the cervical spine [6]. Traditionally, the pathomechanics of whiplash trauma is believed to be a hyperextension-hyperflexion motion, whereas the posterior tissues are at risk of injury because of the tension load at the hyperflexion where the cervical spine forms a C-shape. However, biomechanical studies indicate that when the occupant's vehicle is hit from behind, the forces at play extend the thoracic spine. These forces result in an axial load on the cervical spine [28] and forces the neck to form an S-shape where the lower cervical spine becomes hyperextended, while the upper cervical spine is flexed. As the force proceeds, the entire cervical spine becomes hyperextended [29, 30]. In addition, there is a supposed element of



**Figure 4.** Sagittal shape of the cervical spine at different time stages of the impact.

rotational force in the whiplash mechanism [31]. It is presumptively rare that the occupant is sitting completely parallel to the impact force.

This biomechanical model leads to extensive compressive loads on the posterior structures of the lower cervical spine, such as the posterior aspects of the intravertebral discs and facet joints, and a distractive traction load to the upper anterior structures [32]. Post-mortem studies emphasize the high frequency of injuries to the facet joints after lethal MVAs [33].

Further, the chronic pain manifestations of WAD are believed to be associated with central sensitization [34] or altered central pain modulation [35]. The mechanisms for these conditions are not fully understood but are believed to be a result of interaction between psychological, neurological, and immunological factors [36]. In analogy with other groups of patients with chronic pain, patients with WAD often exhibit a low pain threshold [37].

### Non-recovery

The definition of non-recovery is highly subjective [38]. There is a major variation in reported frequencies of non-recovery rates

after whiplash trauma—ranging between 4% and 95% [39, 40]. The perception of regression of symptoms is contextualized from the personal experiences and traits of the individual as well as his/her expectations [41]. Nevertheless, the physical aspects (pain and impairments) exhibit the strongest association with the perception of not recovering after a musculoskeletal injury like WAD [42]. In addition, the experience of pain is multifactorial and includes sensory, affective, and central valuation systems [43]. Therefore, it is difficult to interpret the individual's level of pain in terms of aetiology.

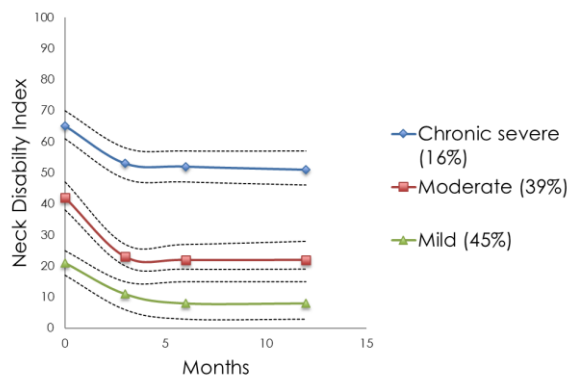
Numerous outcome measures are presented in different longitudinal studies of WAD and the definition of non-recovery is heterogenous and often arbitrary [44]. The most frequent definitions are believed to be absence of self-reported pain or various cut-offs on pain measures (NRS or VAS) [44]. Further, cut-offs on disability scores such as the Neck Disability Index (NDI) or Whiplash Disability Questionnaire (WDQ) are also frequently used as indicators of non-recovery [45].

Notably, the binary self-reported experience of non-recovery, which is frequently used as an outcome measure in this thesis, has obvious advantage of receiving the answer of interest. Self-reported non-recovery has also been

recommended as an outcome measure for global non-recovery [46]. However, it has the drawback of not quantifying the grade of symptoms and identifying individuals with severe symptomatology from a larger group of individuals with milder symptoms.

Individuals recovering after whiplash injury tend to do so the first three months [47]. After this the modulation of recovery-rate is reported to be low [44].

The recovery patterns is suggested to follow one of three specific trajectories, based on neck disability [48].



**Figure 5.** Recovery trajectories in relation to the predicted Neck Disability Index (NDI). Dotted lines represent 95% Confidence Intervals. NDI = Neck Disability Index. Reprinted with permission from Sterling et al. Copyright ©2010 Wolters Kluwer Health, Inc.

### Prognostic factors

A prognostic factor is a variable that predicts the outcome, regardless of its commonness. The reasons why certain individuals with WAD become chronic are considered to be multifactorial [10, 49, 50]. There have been at least 11 systematic review articles evaluating prognostic factors for poor recovery after whiplash injuries [6, 44, 51-60]. These reviews draw, to a certain extent, contradicting conclusions. One of the reasons for this is the difference in categorization, for example, “high age” could be defined as older than 46, than 65, or than 80. This, of course, affects the results. Another issue is the variety in outcome

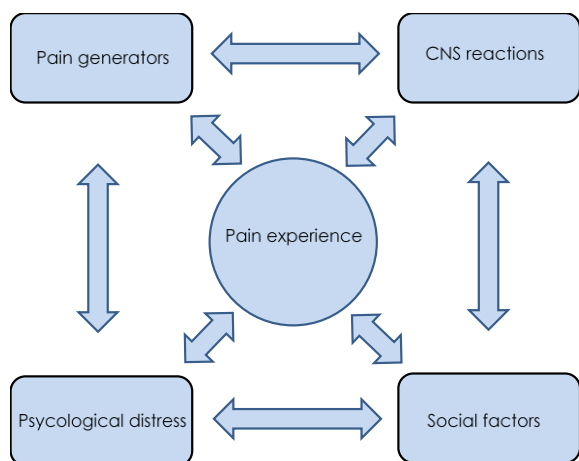
measures, as discussed in the previous chapter. The most undisputed high-risk factors are level of post-injury pain and neck disability, post-injury stress symptoms, catastrophizing, and legal factors [53].

### Initial level of pain

The most robust risk factor of all is high baseline pain intensity—that is, high level of self-reported pain according to VAS or NRS when evaluated at a primary health facility (50, 65). However, the causal relationship has not been fully investigated [61]. Since pain is always a subjective experience that is affected by different degrees by physical, psychological, and social factors (66), it is difficult to analyse what the association between high initial pain level and poor outcome represents. Several reports suggest that individuals with higher pain sensitivity have a higher risk of altered central pain modulation (34) and that patients with a low pain threshold have a worsened prognosis after whiplash trauma [59, 62]. These links have also been associated with the stress response that an MVA can represent [61], particularly for individuals with low serum concentrations of cortisol [63]. Further, it has been suggested that a high initial level of pain could be modified by chronic pain and be an opportunity to depress the chronic component [64].

On the other hand, it is plausible that a high level of initial pain may be a marker for significant biological injury [16]. Since no such injury is evident for most patients in the acute phase, most scientific focus has been on psychological and socioeconomic factors [59].

In addition, a high initial score on the Neck Disability Index (NDI)—for example, a high level of neck disability—is also associated with a poor outcome [65]. Presumably, this association is explained by the high degree of correlation between a high NDI score, low range of motion, and—most importantly—a high level of pain [66].



**Figure 6** Model of the pain experience in relation to:

Pain generators—Anatomical structures, such as facet joints and peripheral nerve injuries.

The central nervous system's (CNS) response to persistent pain, including pain sensitization, mental fatigue, and cognitive dysfunction.

Psychological distress, referring to both psychiatric conditions such as PTSD and natural psychological responses.

Social factors, such as the experienced demands from the surrounding as well as the individual's demands on the surroundings and the individual's own activity and level of participation. Used with permission from Westergren et al. [16] Copyright ©2014 De Gruyter, Inc.

### Preinjury neck pain

In several studies, pre-collision neck pain has been suggested to alter the risk for non-recovery after whiplash injuries [67-69]. Moreover, unspecified pain and co-existing pre-existing pain diagnoses appear to be associated with a poor outcome [62, 65, 70]. Whether this suggested association is linked with general pain vulnerability or biomechanical conditions, such as osteoarthritis or postural factors, has not been investigated thus far.

### Age

There is conflicting evidence regarding whether or not age is to be considered a risk factor for chronic pain after WAD [55]. The cervical spine of the elderly is associated with degenerative manifestations and self-reported disability in general [66]. However, there is no strong evidence for correlation with traumatic onset [21].

### Gender

In several reviews, the female gender has been considered a risk factor for non-recovery [55, 68]. Anatomical characteristics, such as slenderness and more gracile musculature [71], have also been suggested as possible etiologic factors. In average, the female neck is 2.7% shorter than the average male's neck and the former has a 16.6% smaller circumference [72]. Further, it has been reported that women generally are more at risk of transition from acute to chronic pain [73, 74], and it has been proposed that women are more likely to develop central sensitization than men [75]. Nonetheless, the female gender has been considered a controversial prognostic factor in several reviews [53].

### Education level

In several reports, socio-economic factors, like level of education, have also been mentioned as risk factors for non-recovery [68, 76]. Controversially, both high and low educational levels have been suggested as risk factors [6]. Consequently, the evidence is considered to be limited [65].

### **Psychological factors**

The preinjury mental status is believed to be of predictive value for non-recovery [65]. However, the psychological traits of at-risk patients have not been elaborated in the literature [77].

Symptoms of post-traumatic stress, low expectation of recovery, and low coping strategies demonstrate the clearest association with non-recovery [54]; moreover, general mental distress [77], anxiety, and catastrophizing [53] are linked to poor outcomes. The mechanisms for these associations are believed to be complex and the causality is considered difficult to investigate [78].

### **Radiologic findings**

Several anatomical structures visualized through different radiological modalities have been suggested to be at risk of injury and these injuries have been reported to be associated with prolonged/absence of recovery. With MRI becoming more excessive in previous decades, much focus has been placed on imaging soft tissue damage. Injuries of the ligaments of the craniocervical junction have been hypothesized to be one source of pain for WAD patients, but these theories have subsequently been disputed [58]. One study has reported cerebellar tonsillar ectopy (Chiari 1 malformation) being a risk factor but the results from that study have not been reproduced in forms other than case reports [79].

There appears to be an association between morphological muscle changes—like fat tissue infiltration—visualized on MRI and chronic WAD, but the causality has not been proved [80].

Further, the pathology of the intervertebral discs and facet joints has been investigated without previously established evidence for

pre-existing pathology and worsened outcome [51, 65]. However, it has recently been reported that multiple degenerative findings on CT are positively predictive of worsened outcome after whiplash trauma [81].

### **Collision characteristics**

There is no evidence that the type of vehicle collision—such as direction of the collision, occupant's positioning, the presence of airbags and seat belt, awareness of the collision, vehicle type, and head acceleration at the time of impact—are associated with recovery [65]. However, reports of these factors are often self-reported and the possibility of recall bias cannot be excluded [6]. Misclassification of the events of the MVA are likely to occur, not least because of the high frequency of associated PTSD-like symptoms among patients after an MVA [77].

### **Involvement of an insurance company**

Financial compensation as a risk factor for non-recovery is a controversial topic. Cynical voices have questioned WAD as a disorder, claiming that the chronic symptoms are directly or indirectly staged to receive insurance settlements [82, 83]. However, legal involvement has been shown to affect the recovery rate negatively to a certain extent [57]. The causal relationship has not been proven but according to the “compensation hypothesis”, the economic compensation is a risk factor for worse health *per se* [84]. The compensation model—that is, the matter of guilt in the settlement of compensation is reported to be associated with the outcome [74]. Moreover, in areas without medico-legal compensation systems, WAD has been suggested to have a lower prevalence [85].

## Genetic factors

There is an emerging interest in the association between genotypes and various chronic pain conditions [86]. For several FSS, such as chronic widespread pain and fibromyalgia, there is growing evidence for a higher risk for chronic pain for patients with certain genotypes, particularly the COMT-gene [87, 88]. No such evidence exists for WAD. However, in 2011, McLean et al. reported an association between COMT polymorphisms and the outcome after whiplash trauma [89].

## Treatment

Symptomatic pharmacological therapies with analgesic and anti-inflammatory drugs, combined with the advice to stay active, are considered the first-line therapy. However, there is no standardized algorithm for treatment of WAD [90]. For chronic WAD, neck-specific physiotherapy—including muscular strengthening and postural control—appear to have a positive effect [65, 91, 92]. Moreover, general exercise does not appear to improve the outcome [93]. Further, for alternative interventions—such as acupuncture, yoga, and osteopathic treatment—evidence is low in favour of a long-term positive effect [90, 94]. There are also opinions that indicate that doing as little as possible has the best therapeutic effect [95].

One randomised controlled trial (RCT) showed the beneficial effect of segmental fusion in a subgroup of patients with WAD [96]. According to the authors, this subgroup includes those with segmental pain. The identification of this subgroup is controversial, and the reproducibility of the results has been questioned [49].

Further, nerve blocks and/or denervation of the medial branch of the dorsal rami have been

shown to have a therapeutic effect among a subgroup of WAD patients, assuming that these patients are those with pain originating from the facet joints [97, 98]. The medial branches are responsible for the sensory innervation of the facet joints [99] and an adequately administered block inhibits the nociceptive stimuli from the joints. Approximately 30%–70% of the patients report pain relief in blinded RCTs of nerve blocks [97, 100]. However, the grade of evidence for medial branch nerve blocks and/or denervation is considered limited due to the few RCTs conducted [49].

In summary, to date, no highly evident, efficient, and standardized treatment option exists for patient in the acute phase or for patients with chronic WAD [95, 101].



**Figure 7.** Ablation through radiofrequency therapy to the medial branch of the dorsal rami to block the sensory afferent nervous signals from the facet joint. The potential effect is not permanent and is often repeated.



# AIMS

The overall aim of this thesis was to investigate potential prognostic factors for non-recovery after whiplash trauma.

The following were the specific aims for the papers included in this thesis:

## **Study I**

The aim of this study was to validate a clinical prediction model, based on individuals from an emergency department cohort, externally, through a new cohort of individuals from insurance companies.

## **Study II**

The primary aim of this study was to investigate the long-term non-recovery rate after whiplash trauma. The secondary aim was to analyse the association between economical compensation from insurance companies and the outcome.

## **Study III**

The primary aim of this study was to investigate if genetic markers, represented by COMT haplotypes, were associated with the outcome after whiplash trauma. The secondary aim was to investigate possible associations between background variables, haplotypes, and the outcome.

## **Study IV**

The aim of this study was to construct and validate a novel scoring system for assessing degeneration of the intervertebral discs and the facet joints of the cervical spine on CT.

## **Study V**

The aim of this RCT was to investigate the effect of an educational video with patient information regarding WAD compared with usual care.

## **Study VI**

The aim of this study was to investigate the association between cervical radiological degeneration and non-recovery.

## **Study VII**

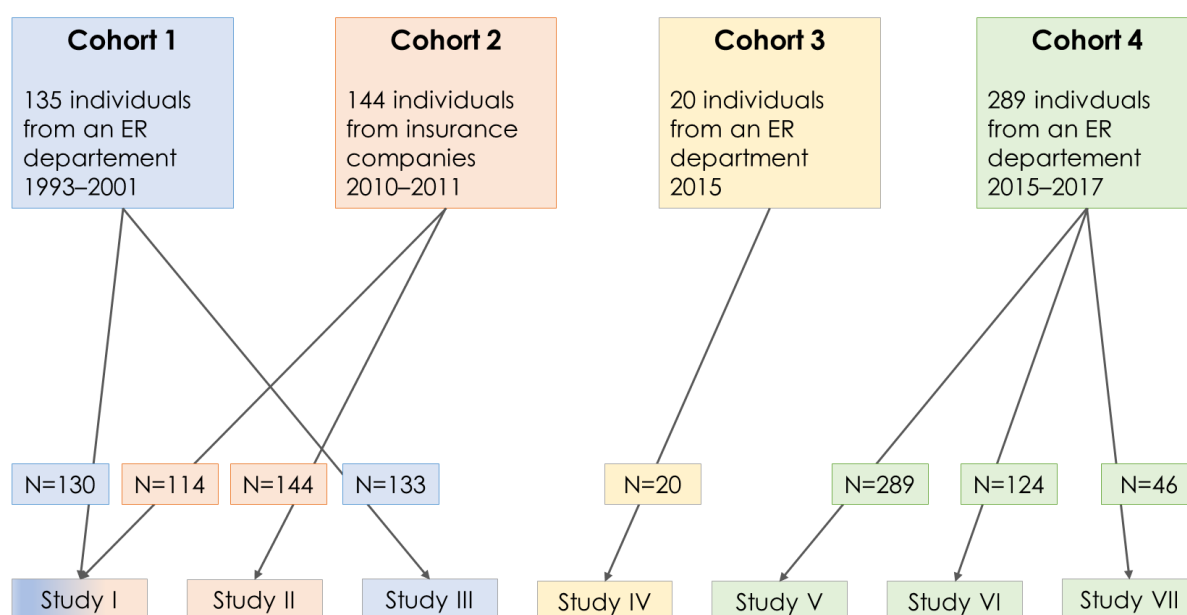
This study has two aims. First, to investigate the inter-rater agreement between two independent raters with regard to sagittal radiological variables of the cervico-thoracic junction on CT. Second, to test the association between these variables and non-recovery after whiplash trauma.



# MATERIALS AND METHODS

Although the overall methodology was to quantitatively investigate possible prognostic factors for non-recovery for individuals with neck pain after a motor vehicle accident through epidemiological hypothetico-deductive models [102], the studies have several

different characteristics and diverge in terms of certain important respects (Table 2). The participants studied in the frame of this thesis originate from four different cohorts (Figure 8).



**Figure 8.** Flow chart of the origins of the participants of the 7 studies in this thesis.

**Table 2.** Overview of the characteristics of the data in the included studies.

	Study I	Study II	Study III	Study IV	Study V	Study VI	Study VII
Research approach	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Study design	Validation study	Cohort study	Cohort study	Validation study	Randomized controlled Trial	Cohort study	Cohort study
Number of participants	130 + 114	144	133	20	289	124	46
Data collection	Questionnaires	Questionnaires	Questionnaires and blood samples	CT scans	Questionnaires	Questionnaires and CT scans	Questionnaires and CT scans
Statistical analysis	Multivariate logistic regression analysis. ROC-curves.	Multivariate logistic regression analysis	Kruskal Wallis, Anova and multivariate logistic regression analysis	Kappa analysis and intra-class correlation	Fisher's exact test	Multivariate logistic regression analysis	Paired sample t-test, POC-curves, Bland Altman plots and multivariate logistic regression analysis

Cohort 1 (135 individuals) is derived from a larger material, which has been the source of several published studies [42, 103-105]. The original RCT [103] consisted of patients with various musculoskeletal injuries secondary to MVA who were admitted to the emergency department. The initial intervention in the RCT was multidisciplinary patient education. Our cohort (Cohort 1) consists of individuals with neck pain as their primary medical complaint after a traffic accident. Moreover, individuals from both arms of the original RCT were consecutively included in Cohort 1.

Studies I and II are based on a cohort of 144 individuals recruited from two major insurance companies in Sweden (Cohort 2). The case workers at the insurance company were instructed to report all new consecutive claimants with neck pain after an MVA. The case workers asked for permission to leave the claimants telephone numbers with the study team. Thereafter, the individuals were contacted by the team. Inclusion and exclusion criteria were checked, and informed consent was sought and provided.

Cohorts 3 and 4 share certain characteristics. In Cohort 3, only the CT-scans of 20 individuals were assessed; however, the individuals in Cohort 4 filled in both baseline and follow-up questionnaires.

## Study I

In this prospective study, a clinical prediction rule (CPR), based on Cohort 1 consisting of 130 individuals from an emergency department, was externally validated through a cohort of 114 individuals from an insurance company (Cohort 2). The original CPR was generated through a binary regression analysis and this logistic model was tested to fit in the new cohort. The following inclusion criteria were followed: age 18–65 years, a maximum of 14 days since the MVA, and good

understanding of the Swedish language. Exclusion criteria were absence of neck pain, previous WAD, and previous non-specific neck pain. Information regarding the factors included in the CPR—that is, level of pain, level of distress, level of education, and employment status—was collected through a telephonic interview. Further, the individual was also questioned whether or not he/she expected to recover from the injury. Demographic baseline data was collected through a web-based questionnaire.

Estimated coefficients for the regression model were derived from Cohort 1 and were used to predict the probability of non-recovery in Cohort 2 by the following equation:

$$\frac{1}{1 + \exp(2.582 - 0.544 \times \text{"<University"} - 0.136 \times \text{"Unemployed"} - 1.684 \times \text{"Pain24-65"} - 2.247 \times \text{"Pain >65"} - 1.165 \times \text{"Distress 5-51"} - 2.143 \times \text{"Distress >51"})}$$

where 2.582 was the estimated intercept.

The individuals were followed up after six months and asked whether or not they had recovered (Yes/No).

## Study II

This study shares its study population with Study I. A total of 144 individuals with neck pain after an MVA were recruited from two major insurance companies in Sweden. Inclusion was made via telephone contact with the study team. Inclusion criteria were age  $\geq$  18 years and reporting neck pain to the study team when interviewed. Exclusion criteria were pre-existing neck pain, poor understanding of the Swedish language, foreign citizenship, other major injuries caused by the MVA, and reporting the accident after over three weeks.

Data was collected through a web-based questionnaire at baseline, after 6 months and after 2–4 years, regarding pain, disability, and psychological factors. The broad follow-up time span was due to a long inclusion period and a shorter long-term follow-up period. At the long-term follow-up, additional questions regarding the insurance process and eventual financial compensation were asked.

### Study III

All participants in this prospective cohort study had obtained a whiplash injury less than 24 hours before admission to the ER. Exclusion criteria were cervical fractures or dislocations, age <15 years, poor understanding of Swedish, or dementia.

A venous blood sample was taken at the inclusion, frozen and stored in a until it was analysed.

The participants filled in a baseline questionnaire regarding demographic, physical, and psychological factors.

The selected single nucleotide polymorphisms (SNPs) in the COMT gene were rs6269, rs4633, rs4818, and rs4680 because of their previously reported association with pain conditions [106]. The SNPs were succulently analysed through PCR analyses and categorized into three different haplotypes in keeping with previous research [89].

The participants were followed up after 12 months with a new questionnaire, including the outcome measures self-perceived non-recovery, SF-36, VAS for pain, and VAS for mental distress.

### Study IV

This is a validation study of a novel scoring system for degenerative changes of the cervical spine on CT scans. The scoring system validated in this study consists of two parts—one for intervertebral discs and one for facet joints.

The portion of the scoring system that addresses cervical disc degeneration is an adaptation from an existing scoring system designed by Walraevens et al. based on lateral radiographs [107]. We chose to use CT scans to determine the grade of degeneration in our scoring because of its superiority over x-ray and MRI in detecting bony manifestations of the degeneration of the cervical spine [108]. The scoring system consists of three variables: height loss of the disc space, anterior osteophytes of the vertebral body, and endplate sclerosis of the adjacent vertebrae. The points for the three variables were added to receive an overall disc degeneration score. Only the spinal segment with the highest degree of disc degeneration was assessed to facilitate the analysis.

The portion of the system that evaluated the facet joints was also based on the work of Walraevens et al. However, in our system, facet hypertrophy was omitted as it has been shown to have a low grade of intra-rater agreement [107] and since it was regarded to be closely linked to facet osteophytes, another variable in the scoring system. The three remaining compounds were osteophytes, irregularity of the joint surface, and narrowing of the joint space. With regard to the discs, only the segment with the highest degree of degeneration was assessed and the points were added to establish an overall facet joint degeneration grade.

**Table 3.** Scoring system for the assessment of disc and facet joint degeneration. AP = anterior/posterior.

Disc degeneration		
Height loss	0 %	0 points
	≤25%	1 point
	>25- ≤50%	2 points
	>50%- ≤ 75%	3 points
	>75 %	4 points
Anterior osteophytes	No osteophytes	0 points
	≤1/8 AP diameter	1 point
	>1/8 - ≤1/4 AP diameter	2 points
	>1/4 AP diameter	3 points
Endplate sclerosis	No sclerosis	0 points
	Detectable	1 point
	Definite	2 points
Overall degree of disc degeneration (1+2+3)	0 points (no degeneration) 1-3 points (mild degeneration) 4-6 points (moderate degeneration)	
Facet joint degeneration		
Joint space narrowing	Normal	0 points
	Narrowed	1 point
Osteophytes	No osteophytes	0 points
	Yes	1 point
Irregularity of articular surface	Normal	0 points
	Irregular	1 point
Overall degree of facet joint degeneration (1+2+3)	0 points (no degeneration) 1 point (mild degeneration) 2 points (moderate degeneration) 3 points (severe degeneration)	

In addition, a total degeneration score was obtained, representing the sum of the disc degeneration score and the facet joint degeneration score.

The study was based on 20 participants aged >18 years, admitted to the emergency department at Södersjukhuset Hospital, Stockholm, Sweden for neck pain after an MVA and requiring medical imaging in the emergency setting according to the Canadian C-spine rules [109].

Three raters—one junior radiologist, one senior, and one senior orthopaedic surgeon subspecialized in spine surgery—analysed and anonymized the CT scans. The assessments were repeated after three months by two of the raters.

The inter-rater agreement was analysed through Kappa analyses for categorical data between multiple observers [110]. The intra-rater agreement was tested using the intraclass correlation coefficient (ICC).

## Study V

In this randomized controlled trial, we investigated the potential therapeutic effect of an educational video for patients after a whiplash trauma. The video consisted of general biodynamical aspects of the trauma; interviews with an orthopaedic surgeon, a physiotherapist, and a psychologist; and neck-specific training advice. The control group received an information pamphlet, traditionally given to patients with neck pain at the emergency department, which is where the study was conducted.

The study had been preceded by a power calculation to estimate the study sample size. This led to an inclusion of 289 participants.

The log from the ER was checked every weekday during the study period for patients admitted to the hospital because of neck pain after an MVA. The eligible participants were contacted within 10 days from the MVA. Inclusion criteria were age 16–65 years and persisting neck pain when contacted by the study team. Exclusion criteria were fractures or injuries requiring in-house care, insufficient understanding of the Swedish language, >2 weeks since the MVA, participation in another study, and not being a Swedish resident.

Enrolment was done, and randomization was ensured at the time of the first contact with the participant. Sequence generation, i.e. the generation of the allocation sequence, was performed by two study nurses who used blocks of 20 envelopes, 10 of which included a note indicating the intervention group and 10

of which indicated the control group. This process was thereafter repeated for every new block of 20 participants.

The same two study nurses ensured allocation concealment by sealing the envelopes and shuffling them thoroughly. The envelopes were numbered continuously. This was implemented by opening the first envelope in order and linking the allotment to the patient.

The participants were asked to fill in a baseline questionnaire that was e-mailed along with a web link to either the information video or the information pamphlet. The baseline questionnaire contained questions regarding demographics, health factors and, whiplash symptoms, including the Whiplash Disability Questionnaire (WDQ).

Six months after the baseline questionnaire, the participants were asked to fill in the follow-up questionnaire. The primary outcome measure was self-perceived recovery, stated with a yes/no reply. Secondary outcome measures were WDQ score and level of pain on a numeric rating scale (NRS). The participants were also asked to reply to questions regarding the intervention. Non-responders, despite two reminders, were contacted by telephone for a short interview regarding the outcome measures and for ensuring that they had participated in the intervention.

Data was analysed according to both per protocol and intention-to-treat principles.



**Figure 9.** Still photos from the educational video showing physiotherapeutic exercises, data-animation, and an interview with an orthopedic surgeon.

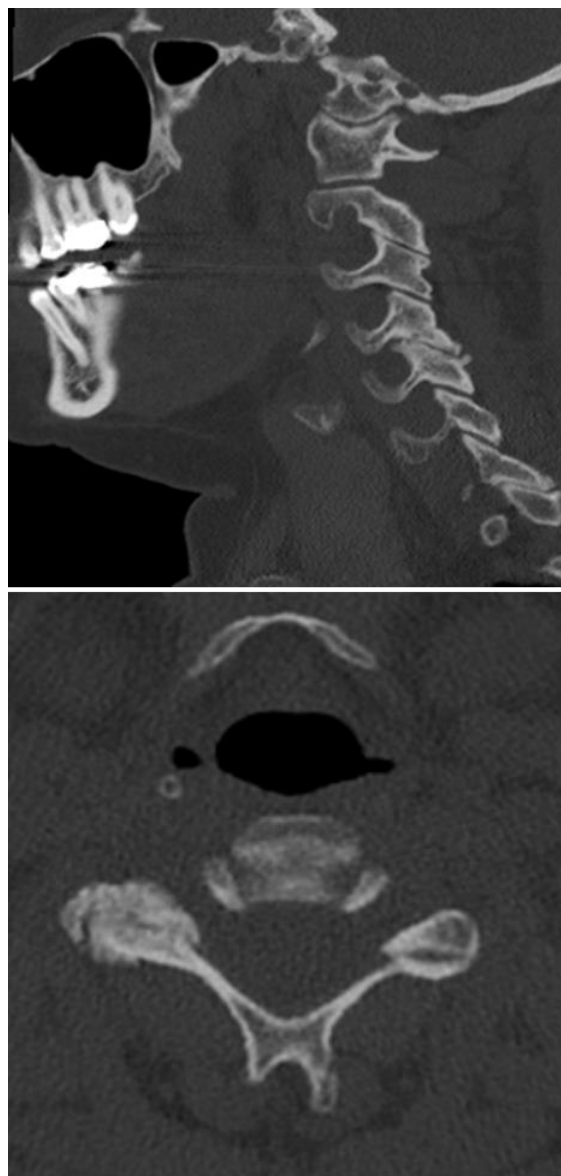
## Study VI

In this cohort study, we investigated the association between pre-existing degenerative changes on CT scans and non-recovery. The participants originate from study 5 (Cohort 4) and were recruited from an emergency department after whiplash trauma. Specific inclusion criteria for this study was existing CT scans that visualized the entire cervical spine. The 124 participants included all the individuals from Study V with valid CT scans and completed baseline questionnaires.

The scans were assessed in terms of degeneration grade according to a validated scoring system (Study 4). The segments with the highest level of facet joint and disc degeneration were assessed and graded on a scale ranging from 0 to 3.

A binary regression analysis was performed to investigate the associations between the variables and the primary outcome measure (self-perceived non-recovery). The variables included in the analysis were facet joint degeneration, disc degeneration, age, gender, education level, sick leave, level of pain, grade of stiffness, level of distress, previous neck pain, and RCT intervention.

The participants were followed up after six months with the primary outcome measure question “Do you feel that you have recovered from the neck injury you reported from the MVA?” (Yes = recovered, no = not recovered). The secondary outcome measure was level of pain according to the NRS.



**Figure 10.** Right lateral and axial view of the cervical spine on CT. Degeneration of the right C4–C5 facet joint. Presence of joint space narrowing, osteophytes and irregularity resulting in 3 points on the degeneration scale.



## Study VII

In this study, we examined 46 patients with neck pain after an MVA using CT scans, and the sagittal alignment variables were assessed by two independent raters. The study population was an extract from Cohort 4, including the participants with a valid CT-scan also demonstrating the tip of manubrium sterni. Patients attending the emergency department of Söderjukhuset Hospital with complaints of neck pain after an MVA were contacted by the study team for eligibility checking and inclusion.

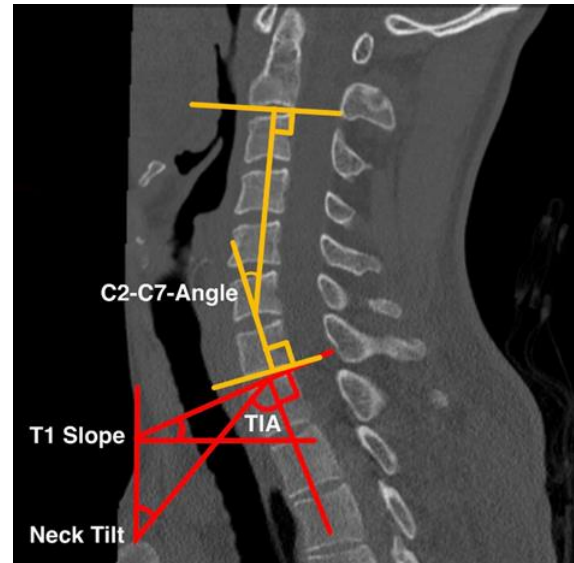
The CT scans were assessed by two independent raters in terms of the sagittal alignment variables—Neck Tilt, T1 Slope, Thoracic Inlet Angle (TIA), and C2–C7 angle (Figure 10). The variables were selected because their proposed importance in the overall sagittal balance and relative independence of body positioning (Neck Tilt and TIA).

The inter-rater agreement was investigated with a paired sample t-test for each of the variables between the raters. Bland-Altman plots for each of the variables were constructed with the mean values for the respective variable on the x-axis and the difference between the two raters on the y-axis.

All radiological variables were dichotomized through ROC curves, where cut-offs for maximum specificity and sensitivity were visually investigated for the risk of non-recovery.

A binary logistic regression was performed to analyse the associations between Neck Tilt and TIA versus non-recovery.

Adjustments were made regarding age, gender, level of pain, level of distress and degeneration grade. A “Thoracic Inlet Triangle” was constructed to illustrate the internal relations between Neck Tilt, TIA, and T1 Slope.



**Figure 11.** The variables assessed on CT scans: C2–C7 angle, Neck Tilt, Thoracic Inlet Angle (TIA), and T1 Slope.



# RESULTS

## Study I

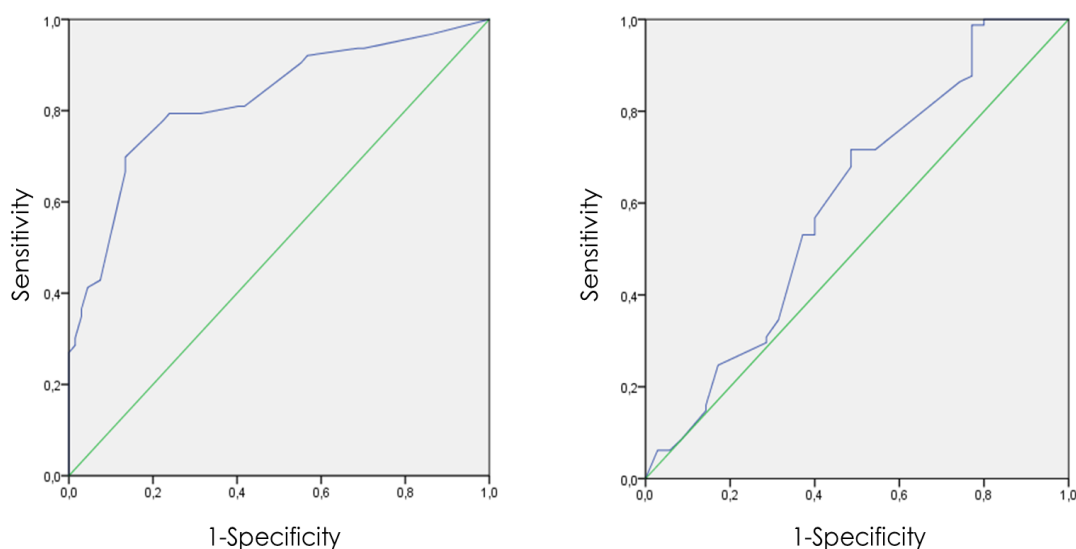
The non-recovery rate was 48.5% in the emergency department cohort (ER) and 70.2% in the insurance company cohort (IC).

Individuals in the IC cohort had a significantly higher mean level of pain, age, and level of distress compared to those in the ER cohort.

The CPR model had low validity when the setting was changed from the ER cohort to the IC cohort. The prediction agreement of non-recovery in the ER cohort was 78% and 62% in the IC cohort. When the cut-off was set to

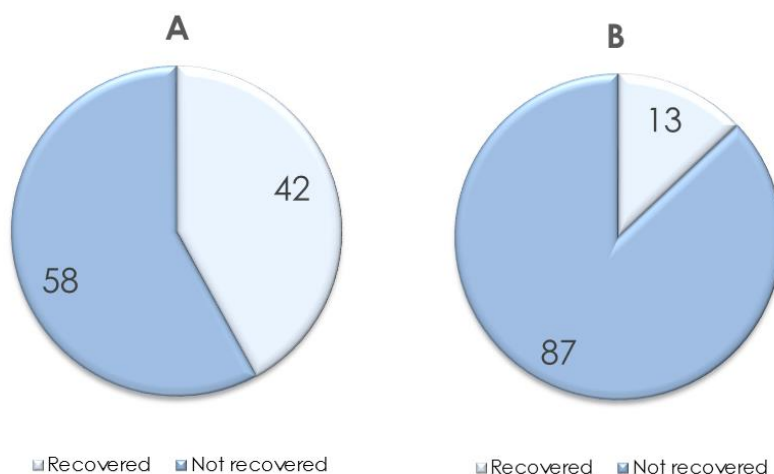
0.56, the sensitivity and specificity for predicting non-recovery were both 78% in the ER cohort. The sensitivity and specificity for predicting non-recovery in the IC cohort was 67% and 50%, respectively. The area under the curve (AUC) was 0.82 (95 % CI 0.75–0.90) for the ER cohort and 0.59 (95% CI 0.47–0.72) for the IC cohort (Figure 12).

There was a difference in the non-recovery rate between individuals expecting themselves to recover and those expecting non-recovery ( $p < 0.05$ ) (Figure 13).



**Figure 12. A** Receiver Operating Characteristic (ROC) curve for the Emergency Department (ER) cohort. The blue lines represent possible combinations of sensitivity and specificity for different cut-off values from the predicted probabilities of non-recovery according to the model. Area under the curve, 0.82 (95 % CI 0.75–0.90).

**B** ROC curve for the Insurance Company (IC) cohort). Area under the curve 0.59 (0.47–0.72).



**Figure 13.** A Non-recovery rate (%) among individuals expecting themselves to recover and B non-recovery rate (%) among individuals expecting themselves not to recover ( $p < 0.05$ ).

## Study II

At six months, 116 individuals (80.6%) had filled in the follow-up questionnaire. All the initially included participants received the final questionnaire after 2–4 years regardless of whether they had answered at the six-month follow-up or not. In addition, 118 (81.9%) of the 144 included participants answered the final follow-up questionnaire at 2–4 years.

After six months, 70% (81/116) of the participants reported non-recovery and after 2–4 years, 56% (66/118) reported recovery.

Further, 73% (27/37) of the financially compensated participants reported non-recovery and 27% (10/37) reported recovery ( $p = 0.016$ ). Among those who did not receive compensation, no difference of the reported recovery rate was found ((51% (42/81) vs. 49% (39/81)).

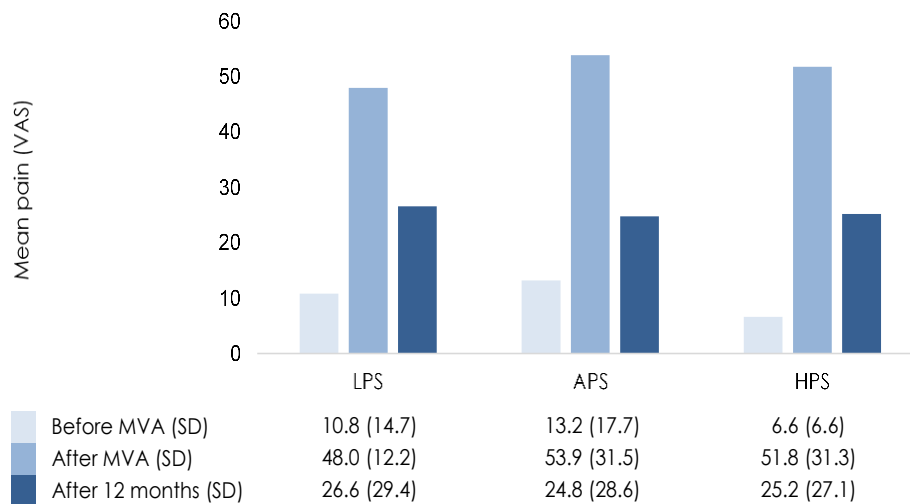
No difference in mean level of pain was seen at baseline, six months, or two-to-four years between the compensated and not compensated groups. The only difference in characteristics between the compensated and

non-compensated participants was the level of mental distress.

When conducting a binary logistic regression analysis, adjusted for possible confounders, the adjusted odds ratio for reporting non-recovery after 2–4 years for the compensated group was 4.3 (95% CI 1.4–13.7).

## Study III

In this study, a total of 128 out of the 133 participants were followed up after 12 months. A majority of the patients (102/133) were constituted with the APS haplotype. There were no significant differences regarding background variables, ethnicity, or symptomatology between the haplotypes. Further, no differences were shown between the distribution of haplotypes and the VAS or SF-36 results before (retrospective rating) and after the accident or at the 12-month follow-up (Figure 14). A high level of initial pain and anxiety were associated with the outcome (Table 4).



**Figure 14.** Association between the different haplotypes and level of pain before the accident, after the accident, and after 12 months of the accident. LPS = low pain sensitivity, APS = average pain sensitivity, HPS = high pain sensitivity, SD = standard deviation

**Table 4.** Association between the predictor variables and self-reported non-recovery at 12 months after the injury. All predictor variables were measured at baseline. Odds ratios (ORs) and 95% confidence intervals are provided.

Predictor variable	Value	Non-recovered/total (%)	Odds ratio (95% CI) Crude	Odds ratio (95% CI) Adjusted <sup>1</sup>
Gender	Male	23/54 (43)	Reference	
	Female	33/74 (45)	1.1 (0.5-2.2)	1.2 (0.5-3.0)
Age	<24	6/13 (46)	Reference	
	25-65	49/110 (44)	0.9 (0.3-3.0)	0.7 (0.2-2.7)
	>66	1/5 (20)	0.3 (0.02-3.4)	0.1 (0.0-1.4)
VAS pain after accident	<24	7/35 (20)	Reference	
	25-65	13/37 (35)	2.2 (0.7-6.3)	2.8 (0.9-8.8)
	>65	36/56 (64)	7.2 (2.7-19.4)	10.4 (3.0-36.6)
Anxiety (HAD)	No	35/93 (38)	Reference	
	Yes	16/22 (73)	4.4 (1.6-12.4)	3.5 (1.1-11.6)
Haplotype	LPS	8/19 (42)	Reference	
	APS	43/98 (44)	1.1 (0.4-2.9)	0.8 (0.2-2.5)
	HPS	5/11 (45)	1.2 (2.3-5.1)	0.9 (0.2-5.6)
Treatment	No	39/91 (43)	Reference	
	Yes	15/32 (47)	1.2 (0.5-2.6)	0.4 (0.1-1.2)

<sup>1</sup> Based on 115 patients in the multivariate regression

## Study IV

Overall, the inter-rater agreement was satisfactory. According to the definition by Landis and Koch [111], all agreements were at least “moderate”, with the exception of facet joint osteophytes and irregularity and endplate sclerosis at the discs, where the agreements were “fair”. The inter-rater agreement analysis for the total joint and disc degeneration grade was categorized as “substantial”.

According to the definitions of Fleiss [112], the inter-rater agreements for the total scores were at least “good”, with the exception of facet joint degeneration for one of the raters and disc degeneration for the other rater, where the level of agreement was categorized as “fair”.

**Table 5.** Inter-rater agreement among the three raters.

Disc degeneration		
	Kappa value	p-value
Height loss	0.47	<0.001
Anterior osteophytes	0.63	0.000
Endplate sclerosis	0.24	0.092
Overall degree of disc degeneration (score 0-9 points)	0.47	<0.001
Facet joint degeneration		
	Kappa value	p-value
Joint space narrowing	0.57	<0.001
Osteophytes	0.31	0.154
Irregularity of articular surface	0.37	0.011
Overall degree of facet joint degeneration (score 0-3 points)	0.54	<0.001
Total degeneration		
	Kappa value	p-value
Total degeneration score (0-12 points)	0.70	<0.001

**Table 6.** Intra-rater agreement between the scoring from assessments by the junior radiologist and the senior orthopaedic surgeon, respectively. ICC: intraclass correlation coefficient, CI: confidence interval.

	Junior radiologist		Senior orthopedic surgeon	
	ICC	95% CI	ICC	95% CI
Disc degeneration	0.68	0.10-0.88	0.60	0.02-0.84
Facet joint degeneration	0.54	-0.28-0.83	0.75	0.36-0.90
Total degeneration	0.82	0.54-0.93	0.73	0.07-0.90

## Study V

The total follow-up rate was 97% (196 of the 203 patients who filled in the baseline questionnaire also replied to the primary outcome measure through either the telephonic interview or follow up questionnaire).

There were no differences between the groups with regard to the baseline data.

No differences in outcome measures were found between the groups (Table 7).

**Table 7.** Comparison between the written information and the educational video and outcome measures at the six-month follow up.

	Written information group (n=93)	Educational video group (n=103)	95% CI for difference between written and educational video group	p-value for difference between the groups
Non-recovery (n <sup>1</sup> )	33.3% (31)	37.9% (39)	-0.2–0.6	0.55 <sup>''</sup>
Level of pain, NRS (mean, n <sup>2</sup> )	2.2 (92)	1.9 (100)	-0.4–1.0	0.35*
Modified WDQ score (mean, n <sup>3</sup> )	21.2 (62)	17.5 (63)	-5.4–12.7	0.42*

<sup>''</sup> Fisher's exact test

\* independent t-test

n<sup>1</sup> number of patients reporting non-recovery

n<sup>2</sup> number of patients followed up NRS

n<sup>3</sup> number of patients followed up with modified WDQ

## Study VI

The total follow-up rate was 97.6% (121/124).

The prevalence of degenerative changes of any type and grade was 66.9% (81/121). The C6–C7 segment was the segment with the highest frequency of facet joint degeneration, and the C5–C6 segment had the highest frequency of disc degeneration.

High age was associated with facet joint degeneration and disc degeneration and the baseline. No other associations, including pain parameters, were shown.

The mean age was 37.0 years (SD = 12.5)

Facet joint degeneration of a moderate degree was associated with non-recovery at six months. No other associations regarding degeneration and the outcome were shown. When investigating the associations between degenerative changes and the level of pain at follow up, it was shown that moderate facet joint degeneration was associated with higher mean level of pain ( $p < 0.05$ ) (Table 9). No other associations were found.

**Table 8.** Demographics and characteristics of the participants. N = 121. NRS = Numeric Rating Scale, RCT = Randomized Clinical Trial.

Variable	Grade	n	%
Facet joint degeneration grade	0 (no degeneration)	54	44.6%
	1 (mild degeneration)	25	20.7%
	2 (moderate degeneration)	25	20.7%
	3 (severe degeneration)	17	14.0%
Disc degeneration grade	0 (no degeneration)	66	54.5%
	1 (mild degeneration)	34	28.1%
	2 (moderate degeneration)	16	13.2%
	3 (severe degeneration)	5	4.1%
Age group (years)	17-29	51	42.1%
	30-45	37	30.6%
	46-60	33	27.3%
Gender	Male	63	52.1%
	Female	58	47.9%
Highest level of education	Not university	69	57.0%
	University	52	43.0%
Sick leave because of index trauma	No	96	79.3%
	Yes	25	20.7%
Level of pain at baseline (NRS)	0-3	41	33.9%
	4-6	51	42.1%
	7-10	29	24.0%
Level of neck stiffness (NRS)	0-2	33	27.3%
	3-6	59	48.8%
	7-10	29	24.0%
Level of mental distress (NRS)	0-3	38	31.4%
	4-6	52	43.0%
	7-10	31	25.6%
Previous neck pain*	No	106	89.8%
	Yes	12	10.2%
RCT intervention	No	53	43.8%
	Yes	68	56.2%

\* missing values = 3

**Table 9.** Binary regression analysis of the associations between non-recovery and degeneration and age, gender, level of education, sick leave, pain, stiffness, distress, previous pain, and RCT intervention. C.I. = Confidence Interval, NRS = Numeric Rating Scale, RCT = Randomized Clinical Trial.

	Value	Count	Non-recovery	p-value	Crude OR	95% C.I.	Adjusted O.R.**	95% C.I.
Facet joint degeneration	0	54	13 (23.6%)	<0.05	Ref		Ref	
	1	25	10 (41.7%)		2.3	0.8-6.4	2.1	0.6-7.3
	2	25	16 (69.6%)		7.4	2.5-21.8	6.7	1.9-24.3
	3	17	7 (38.9%)		2.1	0.7-6.4	1.1	0.2-5.6
Disc degeneration	0	66	21 (32.3%)	0.20	Ref		Ref	
	1	34	18 (52.9%)		2.5	1.0-5.5	1.8	0.5-6.4
	2	16	5 (31.3%)		1.0	0.3-3.1	0.92	0.2-5.8
	3	5	2 (40.0%)		1.4	0.2-9.0	3.04	0.2-46.9

\* missing values n = 3,

\*\* adjusted for all 11 variables in Table 9.



## Study VII

As shown in Table 10, the inter-rater analysis exhibited a satisfying mean level agreement between the two raters. The overall non-recovery rate was 28%. Low Neck Tilt and low TIA were associated with non-recovery at follow-up. For the group with a low Neck Tilt, the non-recovery rate was 50% (95% CI: 36%–78%) and for the group with high Neck Tilt, the non-recovery rate was 8% (95% CI: 3%–25%). Further, the non-recovery rate for the group with low TIA was 50% (95% CI 29%–72%) and for those with high TIA, it was 14% (95% CI 4%–26%).

In addition, low Neck Tilt and low TIA was also associated with higher mean level of pain at follow up (Table 11).

When adjustment was made for age, gender, initial level of pain, distress, and grade of degeneration, associations were found between non-recovery and low Neck Tilt (adjusted OR 9.3, 95% C.I 1.4–61.9) and low TIA (adjusted OR 9.6, 95% C.I 1.5–60.9).

No other associations were demonstrated.

Theoretical models of high-risk and low-risk characteristics of the “Thoracic Inlet Triangle” were constructed to visualize the relationship among the included variables (Figure 14).

**Table 10.** Inter-rater agreement for sagittal alignment variables measured by two raters (n = 46). TIA = Thoracic Inlet Angle, SD = Standard Deviation.

Variable (°)	Mean (SD) rater 1	Mean (SD) rater 2	Mean (SD) rater 1 + 2	Paired difference of Mean between raters	P-value* for difference between raters
Neck Tilt	44.1 (10.0)	44.6 (10.8)	44.4 (10.3)	0.54	0.18
T1 Slope	26.5 (6.1)	26.5 (6.5)	26.5 (6.2)	-0.07	0.83
TIA	70.6 (10.4)	70.8 (11.1)	70.7 (10.7)	-0.15	0.73
T1 Slope + Neck Tilt	70.6 (10.7)	71.2 (11.3)	70.9 (10.9)	-0.61	0.17
C2-C7-Angle	-2.6 (12.2)	-3.3 (12.0)	-2.9 (11.9)	0.72	0.19
T1 Slope-C2-C7 Angle	29.0 (12.2)	29.8 (12.2)	29.4 (12.0)	-0.78	0.21

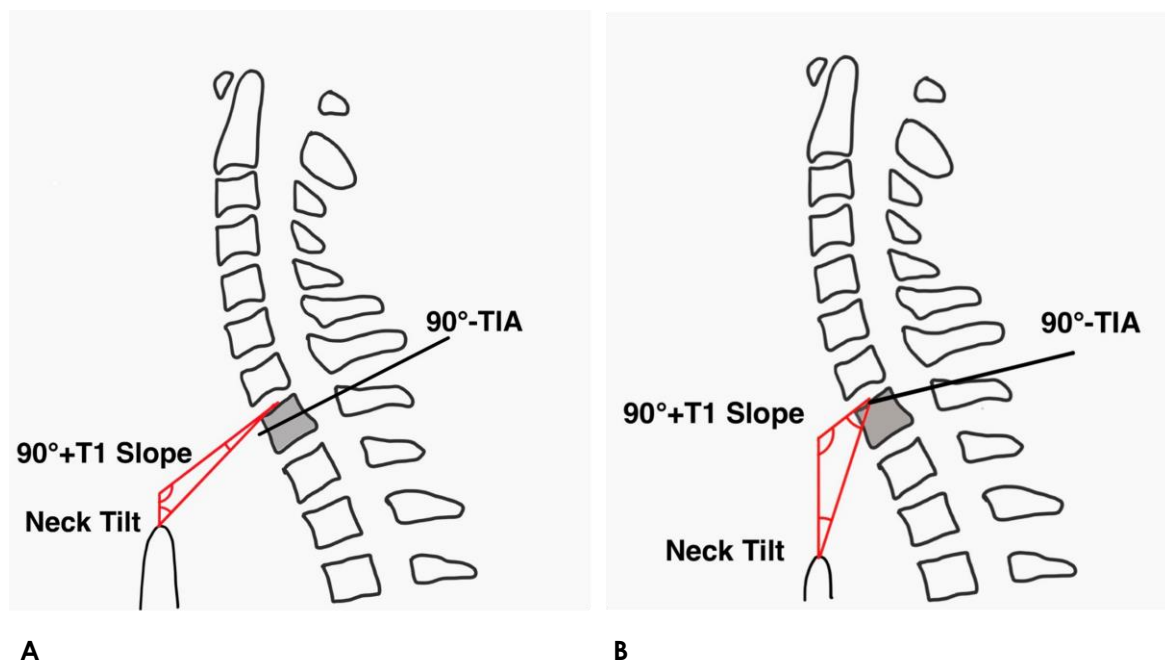
\* Independent samples t-test

**Table 11.** Comparison of non-recovery and pain (NRS) at six months between patients (n = 46) with high and low values of sagittal alignment variables. TIA = Thoracic Inlet Angle, NRS = Numeric Rating Scale, SD = Standard Deviation.

Variable	Degrees	Non-recovered n/N	Non-recovered % (95% CI)	p-value* for comparison of non-recovery	NRS pain mean (SD)	P value** for comparison of NRS
Neck Tilt	<40	11 /22	50 (36–78)	<0.01	3.3 (2.7)	<0.01
	≥40	2/24	8 (3–25)			
TIA	<68	9/18	50 (29–72)	<0.01	2.8 (2.8)	0.04
	≥68	4/28	14 (4–26)			
T1 Slope	<30	7/34	21 (10–32)	0.06	2.0 (2.4)	0.15
	≥30	6/12	50 (39–72)			
C2-C7 Angle	<0	8/28	29 (17–41)	1.00	1.9 (2.3)	0.29
	≥0	5/18	28 (17–39)			
T1 Slope-C2-C7 Angle	<30	3/21	14 (5–36)	0.09	2.0 (2.5)	0.38
	≥30	10/25	40(22–56)			

\*Fisher's exact test

\*\*Independent samples t-test



**Figure 14.** Schematic drawings of the “Thoracic Inlet Triangle” (Neck Tilt + (90°-TIA) + (T1 Slope + 90°) =180°); **A** Low-risk shaped triangle characterized as a high Neck Tilt and TIA (=low ‘90°-TIA’). **B** High-risk shaped triangle characterized-as a low Neck Tilt and TIA (=high ‘90°-TIA’). TIA = thoracic inlet angle.

## DISCUSSION

WAD is indeed a controversial medical condition. Since there are no diagnostic tests, pathognomonic objective findings, or well-accepted treatment options, there are multiple viewpoints regarding this condition. Much attention has been given to the moniker “whiplash culture” [113], which suggests that the cultural context in which the injury occurs is crucial for the prognosis. In other words, in a context where there are no expectations of poor recovery after whiplash trauma, chronicity is rare. This has led to the conclusion among certain groups that whiplash injuries do not exist or that WAD is a fraud diagnosis [114]. Even if expectations of recovery appear to have some prognostic value [115], it is surely not the only explanation for the poor recovery rate seen in numerous reports [116]. On the other hand, strictly physical causes of non-recovery after whiplash trauma are not likely to explain the symptoms for most patients with poor outcome.

The concept of WAD was originally designed to describe an umbrella diagnosis for various medical conditions, with neck pain after an MVA being a common one. There are large variations in the grade of disability and symptomatology between patients who are clustered into this diagnosis. There are few common threads between a patient with major deficit in quality of life, alienation from a social context, and chronic pain and one with only mild neck pain due to an MVA. Such an interpretation of WAD must always be remembered when examining possible risk factors for non-recovery and, by extension, possible interventions and treatment.

Within the frame of this thesis, a few possible pieces have been added to the WAD puzzle.

Study 1 could be considered as an example of the variety in characteristics between different

patient settings. Although the two cohorts both consisted of individuals with acute neck pain after an MVA, there were large differences in symptomatology, mental health status, and outcome. A clinical prediction rule (CPR) constructed for one of the cohorts was not at all transferable to the other. These results are in line with a recently published meta-analysis stating that there is no convincing CPR that has undergone external validation and that can be recommended for clinical use [117]. It could be speculated whether patients admitted to an emergency department must be considered as having a divergent condition compared to individuals reporting a neck trauma to an insurance company.

The poor prognosis of insurance company claimants is illustrated by Study 2. Almost 6 out of 10 claimants considered themselves as not recovered after 2–4 years. Compared to those reporting that they did not receive financial compensation, the financially compensated claimants reported a significantly worse prognosis. Of course, it is impossible to determine if a causal association exists. However, the lack of other differences between the compensated and uncompensated groups, including level of pain, supports the hypothesis that financial compensation is a risk factor for non-recovery.

There is a steadily increasing amount of evidence of association between genetic factors and different medical conditions, including pain conditions [88]. Although the human genome has been sequenced, there is a huge lack of understanding of the mechanisms, interactions, and correlations between genetic expressions and phenotyping. For most complex conditions, like pain experience, single genetic polymorphisms have small effects in explaining these complex mechanisms [118].

The COMT gene is one of the best studied genes with regard to association with pain conditions [118]. Despite this, results are often contradictory and have been explained by heterogeneity in methodology [118].

In Study 3, we implemented a screening regarding SNPs in rs6269, rs4633, rs4818, and rs4680, since these are the polymorphisms with the best evidence of being associated with pain [119]. In our material, no association with the level of pain was detected at three time points (historically, at the baseline and after one year). These results contradict the result from a previous study that employs a similar methodology [89]. Apart from type I and type II errors, the reasons for the different conclusions in these two studies can be speculated. The number of individuals with the haplotype “low pain sensitive” was different between the two materials. There was also a possible difference in the ethical origins of the study participants and this could have led to different genotypes.

The results of this study must be considered as a small piece of information put in to the gigantic hole representing the lack of linkage between genetics and clinical manifestations [120].

For the clinical question of whether there is an association between cervical degeneration and the outcome after whiplash injury, we realized that there was no available scoring system for degenerative changes for assessment on CT. In order to initiate such a study (Study 6), we first constructed such a scoring system. Our classification system is based on one ditto system constructed by Walraevens et al. [107], which is in turn based on the classification by Kellgren [121].

The agreement analyses performed in Study 4 demonstrated a satisfying level of agreement, both between three independent raters and between raters at different points in time. However, classifying cervical degeneration,

particularly facet joint degeneration, is difficult and the intra- and inter-rater agreements are far from perfect. Nevertheless, to date, this coherent scoring system is the only validated system that exists for CT. Until a more robust and user-friendly system is presented, we suggest that our system be the first choice for future studies evaluating degenerative changes of the discs and facet joints of the cervical spine.

In Study 5, the intention was to test if the results from a previous study by Oliveira [122] and Brison [123], where an educational video has been reported to be beneficial for the prognosis after whiplash trauma, were reproducible. In our study, no such beneficial effect was seen. Even if our video was inspired by these two previous videos, they were naturally not identical. It is in the nature of education that the manner in which the information is provided, the timing of the information, and the content is crucial for the perceived intervention [124]. In our study, the focus of the video was on reassurance, in keeping with previous studies [123]. However, we had no control over the patients' interpretations and experiences of the educational video, as little as we did for the previous videos.

The role of patient information for acute whiplash patient has been questioned [125]. There is, to date, no evidence of what information could be beneficial and what information could have possible adverse effects for the prognosis. A patient with a neck injury often seeks information from various sources, including the internet and social media, and the impact from these sources probably biases the effect size of the information intervention given from health care workers [126]. Further, there is an ethical and possible negative effect in providing information about a whiplash injury that is a benign injury with a self-limiting course for

patients not following this optimistic recovery pattern [126].

As patients with neck pain after an MVA have a great heterogeneity with regard to symptoms, expectations, and trajectories in recovery patterns [127], it is probably naïve to believe that a “one size fits all” informational intervention is favourable for everyone [128].

Study 6 questions the common conviction that pre-existing degenerative radiological changes are not associated with the outcome after whiplash trauma [129]. When performing a non-systematic review of the evidence, it was found that previous assessments of degeneration was most frequently arbitrarily performed, and that little regard was given to the facet joints. In our study, the degeneration grade of the discs and the facet joints was graded according to a validated and systemized scoring system (Study 4) on CT. No association was found between disc degeneration and the outcome, which is in agreement with previous studies. However, moderately degenerated facet joints (grade 3/4) were significantly associated with non-recovery and higher pain levels at follow up. These results partially match the suggestion that the facet joints represent the most important pain source for patients with WAD [32].

Since facet joint degeneration in general has not been linked to painful manifestation [130], it is difficult to draw conclusions from our results. One hypothesis could be that the osteoarthritis of the joint is a radiological shadow of segmental instability. Capsular injury of the facet joints has been proposed to be a pain source, and osteoarthritis of these joints or the adjacent joints could hereby be the response to instability [131]. In this thesis, we have not conducted motion analyses, but such investigations could potentially clarify the suggested link between instability, degeneration, and pain. Another hypothesis derived from the association between

degeneration and persistent pain could be that whiplash trauma could function as a trigger for a previously asymptomatic facet joint degeneration. This would be an analogy with an asymptomatic knee osteoarthritis that becomes symptomatic after a modest trauma.

This study has a few important limitations. The cohort was tolerably small ( $n = 121$ ), since the participants consisted of a subgroup from Cohort 4 and the confidence intervals were wide.

It must again be emphasized that the causal relationship between facet joint degeneration and non-recovery cannot be drawn through this study.

In Study 7, we investigated the association between radiological sagittal alignment variables with non-recovery. The main findings were that low Neck Tilt and low TIA were associated with the outcome, in contrast to the T1 Slope and C2–C7 angle. It is a delicate matter to interpret these results. Since the T1 Slope, Neck Tilt, and TIA are correlated with each other, we additionally constructed a “Thoracic Inlet Triangle” in order to make it easier to visualise the internal relationship of the variables. Through this concept, it could be proposed that a long and gracile skeletal structure of the neck has a higher risk for non-recovery than a short and thick one. These results could be considered analogous to anthropometric data, which reveals that neck length and circumference are associated with chronic neck pain [71, 132]. However, these previous reports have been made from assessments on anatomical and topical landmarks rather than radiological ones. Since a gracile neck has less anatomical surface for the load of a collision to be distributed as compared to a thick one, it is likely to assume that this explains these proposed associations. However, they are still to be considered as sporadic reports and none of them have been reproduced.

In our study, the curving of cervical spine—that is, lordosis/kyphosis and T1 Slope—was not obviously linked to the outcome. Even though most of the variables assessed are considered to be more or less constitutional—that is, not affected by body positioning—the gold standard for measuring sagittal balance is radiography in an upright position with standardised methods.

Therefore, the results of the association between Neck Tilt and TIA and the outcome must be looked at as anecdotal observations, not least because of the small sample size and wide confidence intervals. Nevertheless, this study is the first of its kind and the results could hopefully inspire future investigations in this field, tentatively with a larger sample size.

In summary, the findings in this thesis partly verify previous research stating high initial level of pain, expectations of non-recovery and financial compensation by insurance companies being risk factors for worsened prognosis. Contradictory, it suggests facet joint degeneration and to some extent, sagittal alignment variables to be prognostic for non-recovery after whiplash trauma. Again, it should be emphasized that these results need further investigations.

This thesis is intended to further decipher the whiplash enigma. However, as it has been said before, the problem is not finding a solution, the problem is identifying the problem [133]. What are the causes of the initial pain? What hurts? Which mechanisms alter the pain experience and are responsible in the transformation from acute to chronic pain? These questions are far from answered yet. Before we have a clearer image of this, beneficial treatment for this group of patients is not in sight. Maybe it is time to look beyond mean values and prognostic factors at a group level. WAD is not a diagnosis set out of pathological findings. It is a construction made from clustering individuals with somewhat similar clinical findings and having in common

that the symptoms debuted after an MVA. It is highly likely that among this heterogenic group, there are several main causes of the medical condition. Analogies could be made with various other conditions, such as diabetes. High levels of blood sugar can be caused by different pathology. Therefore, more research is needed in the field of WAD, partially consisting of analyses of subgroups with common characteristics.

The link between radiological findings of the spine and painful conditions is an essential field of science that requires further investigation. It is my absolute belief that future studies need to include both large materials and reliable assessments. Currently, both are deficient to a large extent. Considering that in Sweden, and around the world, large health care registers are being produced, there is a great potential in generating a radiological material that is sufficiently large to meet the need for such materials. Already, a vast amount of data can easily be inquired through the registers and hopefully in the future, different registers—including radiographic information—will be able to cooperate to extract even more usable data. Another promising field of development is Artificial Intelligence. In the future, these techniques may potentially facilitate and optimize the assessments of radiographic analysis. This would potentially imply a better understanding of the pain mechanism for various spinal disorders, including WAD.

The quest for answers will continue, so that that the stories do not remain merely stories.

# CONCLUSIONS

The overall conclusion of this thesis is that different cohorts can exhibit different risk-factors for non-recovery after whiplash trauma. Potential anatomical and radiological aspects need further attention before they should be ruled out as associated with non-recovery for certain subgroups with WAD.

Specific conclusions for the papers included in the thesis are:

## **Study I**

Clinical prediction rules (CPR) require external validation. A CPR consisting of four questions with an excellent predictability of identifying patients at risk of non-recovery after a whiplash injury in the emergency department had a low predictability in an insurance company setting. The risk factors for not recovering probably differ among different settings.

## **Study II**

The non-recovery rate for individuals making insurance claims in Sweden is high, particularly among individuals receiving economic compensation even if no causal relationship can be proven based on this study. However, the lack of association between level of pain at the baseline and economic compensation supports the compensation hypothesis—that is, economic compensation is correlated to poor outcome.

## **Study III**

No association between the COMT gene haplotypes and non-recovery or level of pain was found. These results contradict previous

reports. Further studies are needed to determine if COMT haplotypes influence the outcome after whiplash injuries. In addition, high levels of initial pain and anxiety were associated with non-recovery in this study, which is in line with previously published reports.

## **Study IV**

This novel coherent scoring system for degeneration of the intervertebral discs and facet joints of the cervical spine on CT was shown to meet the standards of reliability, both between different raters and by one rater at repeated assessments.

## **Study V**

Intervention with the multiprofessional educational video used in this study had no greater beneficial effect for patients after a whiplash trauma compared to a basic written information sheet.

## **Study VI**

This study suggests that facet joint degeneration is a risk factor for non-recovery after whiplash trauma. Hypothetically, whiplash trauma could function as a trigger for painful manifestation of previously asymptomatic facet joint degeneration.

## **Study VII**

Low Neck Tilt and low TIA were associated with non-recovery after whiplash trauma. In addition, cervical sagittal alignment variables assessed on CT scans demonstrated a high degree of inter-rater reliability.





# ACKNOWLEDGEMENTS

I would have never been able to complete this doctoral thesis without help from others. From the bottom of my heart, I would like to express my gratitude to everyone that has been there along the road. I would like to direct a special thank you to the following people:

**Sari Ponzer**, my supervisor. For your wisdom, your encouragement, your belief, and your competence. My most sincere gratitude to you, Sari. You're a true role model and hero!

**Hans Järnbert Pettersson**. For your endless tolerance and kindness. For all the times you have repeated the same elementary statistics without ever seeming fed up or impatient. Thank you so much!

**Carin Ottosson** for initiating this project and for abiding with me the first years of my research. "The hardest years, the darkest years, the roaring years, the fallen years. These will not be forgotten years!" [134]

**Piotr Kasina** for your loveable personality and all your help with small and big matters in my project. You're all a doctoral student could ever wish for from a roommate!

**Per Ekman** for your endless support and motivation. I know my absence from the clinic has troubled you, but you have always stood up for me.

**Ted Eneqvist**. Your entry to our department has been truly inspiring and motivating! You have become an important part of this project and a dear friend.

**Peter Elkan**. You have qualities that I truly admire. Your patience and thoroughness has been really valuable for my research and you're a clinical example for all spine surgeons.

**Tina Levander** and **Elisabeth Skogman**, our study nurses, for your enormous

contribution in bringing together and following up with the participants in this project. It has always been an honour to have you by my side and keeping all the papers in order. Without you, it all would have been a mess!

To my colleges at VO Bild, especially **Patrik Lindhé** and **Sara Bankler** for contributing with your excellence and input in the field of radiology.

**Erika Comasco**, for your guidance through the jungle of genetics.

**Anna Dahl**, for your excellence in your residence work, laying the ground for Study V. It's a pity you fled to the south!

**Monica Linder** and **Anneli Anderson**, the principle secretaries of our department. You provide so much love and compassion, so much structure, and sense to my workdays. I'm deeply grateful for all the things you do!

**Ulric Willers**, I am deeply grateful for all the support and compassion you showed me while being my boss and for being a huge source of inspiration.

**Lennart Sjöström**, for your mentorship and your academic and clinical tutoring.

**Uffe Hylin** and **Radford Ekholm** for ghostbusting the haunted software I used for this book and for letting me play along!

My former and present roommates, **Christian, Jenny, Usama, Martin, and Jocke**. The small conversations with you guys are, at the end of the day, what makes the difference between a regular working place and a great one. I wish these conversations would be longer and more frequent.

To all my colleges at VO Ort, Södersjukhuset, I love working with you all and have the deepest respect in the tremendous work you do every day.

**Lena Holm** for initiating the RCT and for all the assistance with the contacts with the insurance companies.

To my loveable cousin, **Filip Rydman** for assistance with Google Trends.

All my love to my late father, **Hans**, and mother, **Cecilia**. I know that you are cheerful and proud today. You are my biggest heroes and I am forever grateful for everything you gave me and everything you represented.

My grandmother, **Essan**. I know how much you wanted to live to see this day and I sincerely apologize for taking this long. I hope you enjoy this thesis and don't have too many linguistic remarks!

Finally, to my loving and supportive wife, **Helena**. You're the love of my life and this thesis is an odd kind of love song from me to you.

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## ORIGINAL PAPERS I-VII

### **I**

Predicting nonrecovery among whiplash patients in the emergency room and in an insurance company setting.

### **II**

Long-term follow-up of whiplash injuries reported to insurance companies: a cohort study on patient-reported outcomes and impact of financial compensation.

### **III**

COMT genotype and non-recovery after a whiplash injury in a Northern European population.

### **IV**

Quantifying cervical spondylosis: reliability testing of a coherent CT-based scoring system.

### **V**

Intervention with an educational video after a whiplash trauma - a randomised controlled clinical trial.

### **VI**

Association between cervical degeneration and self-perceived non-recovery after whiplash injury.

### **VII**

The significance of cervical sagittal alignment for non-recovery after whiplash injury. (Manuscript, resubmitted to The Spine Journal January 2020)