Whiplash Injuries

the effect of early interventions and
the value of smooth pursuit eye movement testing

Ph.D-thesis (summary)

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Preface

This thesis was mainly based on a two-center trial conducted at the Back Research Center, Ringe and Danish Pain Research Center, Århus. The project was made economical feasible by a donation from **Danish Insurance Association**, and was also financially supported by the **Danish Foundation for the Advancement of Chiropractic Research and Postgraduate Education** and the **IMK-foundation**.

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Last but not least, I wish to thank my fiancé **Kjeld** for daily support, huge tolerance and for still being there.

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The manuscripts enclosed in the thesis are not available in the present summary. These reports will be available online after publication.

Report I: A randomized early intervention study comparing the effect of stiff neck collar, "act-as-usual" and active mobilisation on the one year outcome following whiplash injury

Report II: Do smooth pursuit eye movements predict chronic pain and disability following whiplash injuries? A prospective trial with 1-year follow-up

Report III: Smooth Pursuit Eye Movements in Chronic Whiplash-Associated Disorders. A cross-sectional trial

1 Abbreviations

CI = confidence interval

EOG = electro-oculography

IQR = interquartile range

SPEM = smooth pursuit eye movements

SPI = smooth pursuit index

SPNT = smooth pursuit neck torsion (test)

SPNT-diff = outcome of the SPNT-test

WAD = whiplash-associated disorders

2 Summary in Danish

Baggrund. Mén efter piskesmælds-traumer har store personlige og samfundsøkonomiske konsekvenser. Der er behov for mere viden om behandling af akutte piskesmældsrelaterede skader, om mekanismer bag udvikling af kroniske mén, og om risiko faktorer for kronicitet. Test af øjenbevægelser har været anvendt i forsøg på at identificere mekanismer bag kroniske følger af piskesmældstraume, men resultaterne heraf har hidtil været inkonklusive.

Dette arbejde blev foretaget for at bidrage til besvarelsen af følgende videnskabelige spørgsmål:
1. Er der forskel på effekten af tidligt iværksat immobilisering, råd om at "leve som du plejer" og aktiv mobilisering efter piskesmæld målt på smerte og aktivitetsbegrænsning et år efter traumet?

2. Prædikterer tests af øjets følgebevægelser udført tidligt efter piskesmældstraume 1-års prognosen?

3. Kan tests af øjets følgebevægelser adskille patienter med kroniske mén efter et piskesmælds-traume fra raske?

Metode. Data blev indsamlet fra to populationer: 1) én bestående af 753 personer inkluderet inden for 10 dage efter et piskesmældstraume, hvoraf 458 blev inkluderet i et interventionsstudie og 295 i et informationsstudie, og 2) én udgjort af 34 personer med varende mén efter et piskesmældstraume minimum 6 måneder tidligere. Den førstnævnte population blev anvendt ved besvarelsen af alle de tre opstillede spørgsmål, mens den anden population alene indgik i besvarelsen af spørgsmål 3.

Spørgsmål 1: Deltagerne blev randomiseret til én af tre interventioner: 1) Semi-rigid halskrave efterfulgt af et aktivt mobiliseringsprogram, 2) råd om at "leve som man plejer", eller 3) et aktivt mobiliseringsforløb (Mekanisk diagnostik og terapi). Effekten af behandling blev evalueret efter 3, 6 og 12 måneder målt på nakkesmerter, hovedpine, nakkerelaterede begrænsninger og arbejdsevne.

Spørgsmål 2: Deltagerne i interventionsstudiet og en undergruppe fra informationsstudiet fik foretaget tests af deres øjenbevægelser inden for 2 uger efter piskesmældstraumet. Testene bestod i tre optagelser: én foretaget mens projektdeltageren sad i neutral position og to optaget med henholdsvis højre og venstre rotation i nakken. Det blev undersøgt om resultater af sådanne tests prædikterede graden af piskesmældsrelaterede gener et år senere. Status efter et år blev målt på de samme parametre som anvendt i spørgsmål 1.

Spørgsmål 3: Testene af øjenbevægelser blev gentaget i den samme population ved 1-års undersøgelsen, og test-resultater blev sammenlignet mellem dem der stadigt havde mén efter traumet, og dem der ikke havde. Tilsvarende blev den anden patient-gruppe med langvarige mén efter et piskesmældstraume sammenlignet med en rask kontrolgruppe, der ikke havde været udsat for nakke- eller hovedtraume.

Resultater. Der var ingen forskel på effekten af de tre interventioner. Testen af øjenbevægelser kunne ikke forudsige udvikling af varige mén efter piskesmældstraume, og kunne, trods en association mellem varige nakkesmerter og ændrede følgebevægelser, ikke anvendes til at skelne mellem personer med kroniske mén efter piskesmæld og raske.

Konklusioner. Der er ingen overordnet forskel mellem effekten af principielt forskellige interventioner iværksat tidligt efter et piskesmældstraume. Det er uvist om dette skal tolkes som generel mangel på behandlingseffekt. Testen for øjenbevægelser viste sig ikke anvendelig som prognostisk eller diagnostisk test.

3 Summary in English

Background. A large number of people suffer from whiplash-associated disorders (WAD), which is also an enormous economic burden to society. There is a need to learn more regarding the treatment of acute WAD, mechanisms responsible for the development of chronic WAD, and predictors of chronicity. Tests of eye movements have been used in an attempt to identify mechanisms involved in chronic WAD, but results on this topic have so far been inconclusive.

This work was performed to contribute to answering the following research questions:
1. Is there any difference of the effect of immobilisation, advice to 'act-as-usual', and active mobilisation initiated early after a whiplash injury on pain and disability one year later?

2. Does smooth pursuit eye movement testing early after a whiplash injury predict 1-year outcome?

3. Is smooth pursuit eye movement testing useful as a diagnostic tool separating patients with chronic WAD from healthy individuals?

Methods. Data were collected in two study populations: 1) one consisting of 753 patients enrolled within 10 days after a whiplash injury, whereof 458 were enrolled in an intervention trial and 295 in an information study, and 2) one consisting of a sample of 34 persons reporting WAD of at least 6 months duration. The first study sample was used to investigate all three research topics, whereas the second study sample was only dedicated question 3.

Research question 1: Participants were randomly allocated to one of three intervention regimes: Semi-rigid neck collar for 2 weeks followed by active mobilisation, advice to "act-as-usual", and active mobilisation (Mechanical Diagnosis and Therapy). Outcome was measured after 3, 6 and 12 months in terms of neck pain, headache, neck disability and working capability.
Research question 2: Participants in the randomised intervention trial and a sub-sample from the information study went through a test of smooth pursuit eye movements within 2 weeks after the injury. The test consisted in three eye-movement recordings. One obtained in a neutral seated position and two while participants were seated with right rotation and left rotation of the cervical spine. The results of these smooth pursuit tests were correlated with the same 1-year outcome measures as for question 1.
Research question 3: The smooth pursuit tests were repeated in the same cohort at 1-year follow-up. Results were compared between participants who had recovered after the whiplash injury and those who had not. Similarly, results of such smooth pursuit eye movement tests were compared between the other group of patients with chronic WAD and a group of healthy subjects who had not been exposed to a neck or head injury.

Results. There were no differences between the effects of the three intervention groups. Smooth pursuit testing could not predict the one-year outcome, and, in spite of an association between lasting neck-pain and altered eye movements, it could not be used to separate patients with chronic WAD from healthy subjects.

Conclusions. There is no overall difference in the effect of principally different interventions used in acute WAD. Whether this should be interpreted as a general absence of therapeutic effect is not sufficiently elucidated. The test for eye movements was not useful as a prognostic or a test diagnostic.

4 Introduction

4.1 Rationale for this study

During the past decades the extent of the "whiplash-problem" has reached a hitherto unknown level. This is in terms of the number of patients seeking care for whiplash-related health problems, and expressed in expenses to health care, insurance and disability pensions[1].

Health problems related to whiplash injuries can be disabling and are, obviously, a great burden to patients. Often these patients feel lost in the health care system, since it is not known what help they should optimally be offered. In spite of numerous trials conducted in this area, there are no conclusive results telling us what the risk of non-recovery following a whiplash trauma is, what mechanisms are responsible for the development of the chronic condition, or which intervention, if any, should be recommended after a whiplash injury. The trials included in this thesis were conducted to contribute to our knowledge in some of these areas.

4.2 Definitions related to whiplash

The term "whiplash" refers to a whips' movement back-forth-back. "Whiplash" is often used both to describe the mechanism of a trauma and symptoms or complaints related to such trauma, which gives rise to some confusion. In this report the following terms are used:

Whiplash movement pattern: A fast movement accelerating the head and cervical spine back and forth, caused by an energy transfer to the neck rather than by contact to the head or neck.

Whiplash trauma: A whiplash movement pattern of a substantially large force to cause a tissue injury. In the present report there was no attempt to define what magnitude of force/velocity is considered necessary to cause a trauma.

Whiplash injury: Denotes an injury responsible for symptoms initiated in relation to a whiplash trauma. This merely describes that symptoms are present, not that a specific or objectively verified injury is identified.

Whiplash-associated disorders (WAD) [2]: Symptoms and/or disability debuted in relation to a whiplash trauma. WAD is consequently not a patho-anatomical or morphological diagnosis but denotes a clinical condition that is initiated from a whiplash trauma.

The above listed definitions are in consistency with those of the Quebec Task Force on Whiplash-Associated Disorders [2] that agreed on the following definition: *"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 may lead to a variety of clinical manifestations (Whiplash-Associated Disorders)".* The Quebec Task Force suggested a grading of WAD, which has been widely used for classification of WAD. The classification can be seen in Table 1. No clear distinction is in practice possible between grades 1 and 2 since "decreased range of motion" and "point tenderness" was not specifically defined. Normally, persons classified with grade 0 or 4 are not diagnosed as having WAD. Moreover a classification within each grade in relation to duration was suggested (<4 days, 4 – 21 days, 22 – 45 days, 46 – 180 days, and > 6 months). Duration of 6 months or longer was defined as chronic WAD.

4.3 Priorities/delimitations of the topic

This thesis, which is part of a larger project in this area, is focused upon some clinical aspects of WAD, namely the effect of early intervention and the value of a test of eye movements. Consequently, a number of topics within the field of whiplash will not be dealt with, such as:

- the details of biomechanics of the injury mechanism
- whiplash injuries from other mishaps than car collisions
- the "natural course" of symptoms after whiplash trauma

In particular, the eye movement testing was solely aimed at verifying previous results of altered eye movement patterns in patients with WAD, and was not an attempt to do an oto-neurological evaluation of these patients. Therefore there were no other potentially relevant oculomotor and vestibular tests included in this project.

In addition to the above mentioned topics, there are a number of potential prognostic factors, which were registered in our prospective trial, but will not be reported in this thesis.

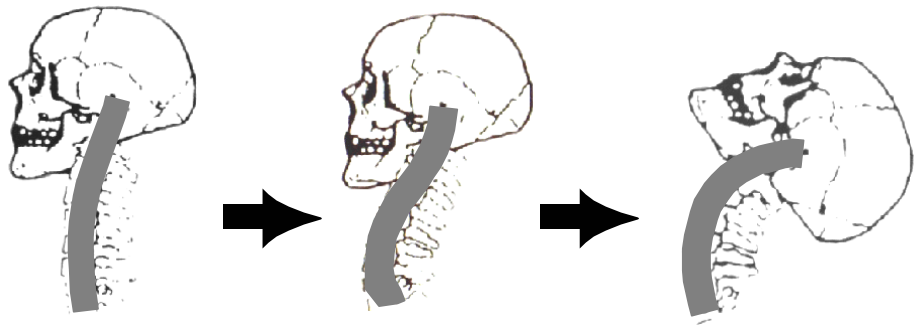
4.4 Biomechanics of the whiplash event

The "classical" whiplash movement pattern, which has been most extensively investigated, is the extension-flexion pattern generated in a person seated in a car which is hit from behind. Good consensus exists regarding this basic movement pattern[3]: When hit from behind, first the back is brought upwards and forwards which compresses the cervical spine. As the neck and trunk are pushed forward by the seat, a relative backwards translation of the head creates extension in the lower cervical spine and coexisting flexion of the upper spine. This brings the entire cervical spine into an s-shape [4-6] (Fig.1). The overall extension has been observed to be within physiological limits [5], whereas this was not the case at the intervertebral levels C6-7 and C7-T1. In this part of the spine, the segmental rotation takes place around another axis than usually [4;7]. This altered extension pattern has been accused of being an important mechanism for whiplash injuries [3;8]. The biomechanics of frontal and side-on impacts have been investigated to a much lesser extend, and mainly with focus on muscle reaction [9-11].

Outside an experimental setting, motions in several planes often occur during a car collision and there is generally no clinically distinction between WAD caused by different collision directions. Symptoms, similar to those caused by a rear-end collision, are reported also after other types of collisions[12-15].

Theoretically, people diagnosed with WAD experience symptoms ascribed to a well-defined trauma. However, persons who report symptoms from the neck, head, shoulder region and/or upper back following car collisions are classified as having WAD, without any proof that they experienced a whiplash movement pattern during the collision. Hence, in reality when using the diagnosis WAD or including research participants who are supposed to be whiplash injured, it is uncertain whether a true whiplash movement pattern was always present. It is unquestionably a problem to classify patients on the basis of their symptoms and a mechanism of trauma for which there is no guaranty that they were exposed to. However, presently it is a fact that clinical decisions often are made on the basis of this information.

Figure 1. The whiplash movement pattern



The drawings illustrate the position of the cervical spine during the extension-phase of a whiplash movement pattern. In the second drawing, the s-shape of the spine is illustrated. (Illustration modified from Grauer et al.[5])

4.5 Symptoms in WAD

The most frequent complaints both in early and in chronic WAD are neck pain, neck stiffness and headache [2;16-23]. The neck pain is generally ascribed to soft tissue injury but also the facet joints seem to be a relevant pain source [24-27]. In addition to neck pain and headache, pain in the shoulders [14;21;28;29], the upper back [30;31] and the arms [14;17;18] are rather frequently reported.

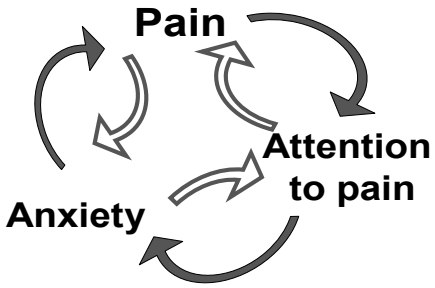
Also other symptoms which are less obviously related to the mechanism of trauma can be present in WAD. These are complaints such as dizziness [14;16-18;28;32-36], visual disturbances[37;38], and problems with concentration and memory [21;37;39-41]. A central mechanism may explain these symptoms, but since pain is the chief complaint in WAD, and suggested also to be an important cause of the cognitive complaints in WAD [42-44] general aspects of pain will be discussed in further details.

4.6 Pain

According to The International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Acute pain is triggered by stimuli of nociceptors [45]. Besides the immediate pain from mechanical strain in whiplash injuries, the acute pain is most likely due to inflammation[46;47]. Inflammatory mediators cause sensitization of nociceptors and consequently an increased nociceptive input to the spinal cord [48]. This increased bombardment with nociceptic input can lead to a central sensitization with hyperalgesia extending beyond the site of injury, referred pain, and allodynia [48;49]. Under normal conditions, these modulations will resolve after inflammation but sustained central excitability can be induced by the nociceptive afferent stimuli [48;50]. Signs of generalized central hyper-excitability and spinal cord hypersensitivity have been observed to be present in chronic WAD [51-54], and presence of this phenomenon within one month of a whiplash injury was observed to be associated with poor recovery [55;56]. This indicates that handling of the acute pain might be of importance for prevention of chronic WAD.

In the handling of patients with pain it should be realised that pain perception is a result of a complicated interaction between sensory input, cognition and emotion. Models of pain perception include factors such as culture, gender, age, experience with pain, anxiety, depression, and handling of pain/ coping [57;58;59]. Attention to pain seems to be a central feature in pain perception, and increased attention to pain has been shown to increase the experienced pain intensity[60;61]. The attention towards pain is influenced by for instance affect and coping strategies, and some factors related to pain intensity might, thus, alter pain perception due to alterations of attention [60]. This leaves a complex and potentially self-perpetuating interplay between different components of pain perception (Fig.2).

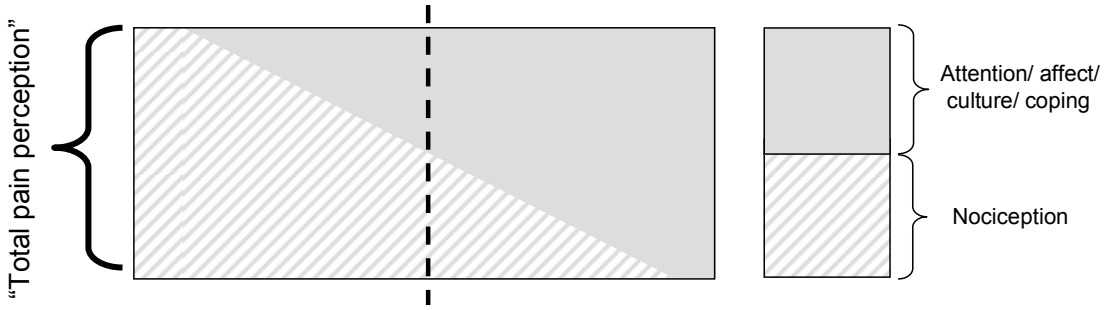
Figure 2. A schematic illustration of a possible interplay between pain, attention to pain and anxiety



Avoidance behaviour related to fear of pain has also been recognised as an important factor in development and maintenance of chronic musculoskeletal pain and related disability [59;62;63]. Avoidance behaviour is a natural adaptive reaction to acute pain, but it is considered a maladaptive response if it persists after tissue has healed [61;63]. Also excessive ignorance of pain leading to a suppressive behaviour and overload has been proposed as a mechanism behind the development of chronic pain [61].

Fig. 3 is a simplistic illustration of the components of pain perception. In theory all pain experiences, can be placed somewhere in this model.

Figure 3. Components of pain perception



In the left side of the rectangle, pain is only due to the sensory input, as in a pinprick. In the right side the pain perception is not caused by any nociceptic input. All pain experiences can in theory be placed along the rectangle - the dotted line indicates a situation where pain perception is equally due to physical damage and psychological factors.
Illustration modified from[162]

5 Background: Intervention and prognosis

5.1 Rationale for treatment in acute whiplash injury

Treatments offered in acute whiplash injuries are aimed at reliving acute symptoms, and, even more important, at preventing that symptoms persist as a chronic condition. Mechanisms behind chronic WAD are not clear. However, at least two aspects seem necessary to take into consideration: 1) tissue damage must heal and inflammation resolve, and 2) negative expectations and anxiety of symptoms should be avoided.

Both immobilisation and mobilisation have been used to enhance soft tissue healing, and to reduce pain. In relation to soft tissue injuries in other body areas than the neck, mobilisation has been generally recommended rather than immobilisation [64;65]. In case of fibre ruptures, short term immobilisation is recommended to accelerate formation of scar tissue [66-68]. Since an excessive focus on tissue damage might enhance anxiety, advising patients to "act as usual" has become a common strategy in an attempt to reduce unsuitable pain behaviour.

5.2 Previous trials regarding early interventions after whiplash injuries

In the latest published systematic, critical review of conservative treatment for WAD, fifteen randomised clinical trials or controlled clinical trials were identified [69]. From these, twelve papers concerned acute intervention [70-81] and one was classified as dealing with an acute-subacute population [82]. That review covered all but one paper [83] regarding acute intervention that was identified in another review, which did not solely look at conservative treatment [84]. In addition one trial was identified from Medline [85] and one trial presented at "Whiplash associated disorders - a world congress", Canada in 1999 was available from a PhD-thesis but has not been formally published [86]. Characteristics and results of trials published in English on acute intervention in WAD are summarised in Table 2.

The fourteen reviewed trials, generally tested interventions that addressed a neck injury and did not focus upon handling of pain or potential anxiety. Advice to "act as usual" was observed to have a somewhat better effect than sick listing and soft collar [73]. An "act-as-usual" regime has so far not been compared to any active treatment regimes. In three trials, different mobilisation programs were found to have better effect than use of a soft neck collar [70;85;87]. Soft collar was not observed to have any effect in itself [75], and also exercises aimed at improving kinaesthetic control had no additional effect compared to a 'basic' treatment [81].

Methylprednisolon[83] and pulsed electromagnetic therapy [74] were both observed to have a positive effect compared to placebo-interventions, and ultra-reiz current was reported to have superior effect to a treatment program without this aspect[72]. All of these trials involved small study samples and should be interpreted with caution.

In three parallel-group studies differences were found regarding frequencies of total recovery that seemed clinically relevant [77;79;86]. In one trial, it was observed that about twice as many who had been in an active mobilisation regime were pain-free after 6 months, compared to those who had received an information leaflet [79]. In the second of these trials, it was observed that persistent symptoms at 2-years follow-up were about half as frequent after a single instruction in mobilising exercises and posture correction as after miscellaneous physiotherapeutic modalities and repetitive movements[77]. In the third parallel-group trial, patients who had worn a semi-rigid neck collar for four weeks and had

active mobilisation afterwards, were about three times as likely to be pain-free after one year than those who received active mobilisation alone [86].

Outcome measures in previous studies varied considerably, but group comparisons were most frequently reported as comparison of average pain intensity [73;74;76;77;79;80;86], comparisons of the prevalence of certain symptoms [70;77], or comparisons of the proportion of groups recovered [73;79;83;86]. Recovery was defined either as no pain [79;86], low pain [79], or having returned to work [73;83;86]. Most of the observed effects on average pain were too small to be of clinical relevance [73;74;80]. In acute WAD it is the primary aim of treatment to avoid persistent symptoms, and the effect of early intervention is probably most clearly interpretable by comparing the proportions of participants who are recovered rather than comparing mean symptom intensity. Since a large proportion of participants are expected to recover spontaneously the average symptom intensity describes effects of intervention less well, and comparisons of mean values could hide important differences if the study sample includes subgroups with different outcome profiles.

There are a number of shortcomings in most of the methods of the trials referred to. First, many trials were performed with small sample sizes resulting in only few participants with persistent symptoms at follow-up and little basis for a group comparison. Other methodological problems were that concealed randomisation procedures were not described except in one trial [79], that in three trials there was no blinding [70;80;81], and that in six, blinding was not described [75;77-79;85;86]. In some of the trials there was a risk that the large number of participants lost to follow-up could introduce bias [81;86;87], and in one trial about 30 % of those randomised did not attend treatment, and no information was provided about what intervention non-attendants were randomised to [77].

It is therefore difficult to draw conclusions based on previous trials. Generally, it seemed that active approaches (light exercises, mobilisation, advice to "act-as-usual") had a positive effect on outcome compared to rest (advice to rest, soft collar, sick listing), but observation of a positive effect of a semi-rigid collar worn 4 weeks before active mobilisation compared to active mobilisation alone was an interesting exception to this.

5.3 Previous trials regarding prognosis following whiplash injuries

Prospective trials published in English, identified through the two latest published systematic reviews on prognostic factors following whiplash events [69;88] and newer papers identified through Medline, are summarised in Table 3. Trials regarding oculomotor function as prognostic variables are summarised in Table 4 and are dealt with in chapter 6.3.

The risks for non-recovery observed in the above trials varied considerably. One year or more post injury, the literature showed that between 0 and 15 % had not returned to work [14;89-92], and between 12 % and 44 % had some degree of diminished working ability[17;29;35;93;92]. Severe symptoms of a duration of 6 months or more were reported by 9 – 44 % [14;31;91;94-96], whereas some degree of persistent symptoms were reported in from 34 %[17] to 79 % [97]. Studies conducted in Lithuania [98] and Greece [28] differed from other trials since essentially no persistent symptoms after whiplash injuries were reported.

These diverging results could, among other factors, be due to different recruitment procedures, study samples not being equally severely affected at baseline, different outcome measures and cultural differences. Only considering samples recruited at emergency units does not result in a narrower spectrum of estimated recovery rates. In

one trial, only 2 out of 180 in an emergency unit-population, all reporting initial neck pain, had persistent complaints [28], whereas about 60 % [99] and 79 % [97] reported persistent pain in other populations from emergency units. These differences could be ascribed to culture, and the exceptionally good prognosis observed in Lithuania and Greece has been interpreted as a consequence of these populations not expecting to have long-lasting symptoms [100;101]. However, it should be noted that in the population from Lithuania, only 30 % reported initial neck pain and it is questionable whether it is reasonable to regard a sample with this low frequency of initial neck pain as a sample of whiplash injured individuals. Furthermore, there might be another tradition for reporting of personal information in these countries, which may result in under-reporting of symptoms. There were also large variations between trials that included only participants with initial neck pain [23;28;90;96;102]. Also cultural factors do not explain all differences. Even trials within the same countries reported quit diverging rates of non-recovery. In Sweden the reported rates of non-recovery (" any residual symptoms") ranged from 58 % - 79 % [14;97] in cohorts recruited from emergency units, while frequencies of sick listing were comparable between other Swedish cohorts [14;91]. Different recovery rates do not seem to be explained by a single factor. To be able to compare results, equal inclusion criteria should be used which consider not only type of accident but also initial symptoms. Moreover outcome should be assessed by standard tools.

Partly due to the above mentioned variations in methods, the picture is also somewhat unclear concerning prognostic factors. Crash-related factors [12;14;15;17;20;23;35;89;90;92;103-109], initial symptoms and physical signs [18;21;23;29-31;35;90;92;95;104;105;110], psychological factors [21;22;30;90;94-97;110], and influence of litigation [18;23;29;90;105;111]were evaluated. Crash-related factors were generally not found to be of prognostic value. Intensity of initial pain has quite consistently been associated with outcome [18;21;23;29-31;35;90;92;95;104;105;110], and also clinical signs such as cervical mobility and radiating pain were in most observations found to be associated with outcome [23;29;31;92;110]. Results regarding psychiatric symptoms and personality traits were diverging, but it seemed that psychological stress, including post traumatic stress, was of some importance [22;30;95;96].

Litigation was found to have a negative effect on prognosis in two of six trials addressing this topic. In one trial both the involvement of a lawyer and a tort insurance system contrary to a no-fault system were significantly correlated to poor outcome [18]. It should be noted that the outcome in this study was time to claim closure, and, even though this was observed to correlate with symptom intensity [112], there is a risk that it failed to describe the true state of recovery. According to the other study [113], having claimed for compensation after 3 months was associated with persistent pain after 1 year. It was unclear whether this analysis was adjusted for initial pain intensity, and claiming compensation could therefore be a proxy for more physical distress.

It is difficult to draw conclusions regarding the relative importance of all of these potential risk factors since many trials failed to take interactions between variables into account [17;23;30;91;103;104;108;111]. Also, the relative explanatory value of prognostic factors could not be evaluated, since information of the potentially important prognostic factors has not been evaluated in multivariate models. By now, there is good evidence that high initial pain intensity is correlated to poor outcome, whereas results on other prognostic factors are less conclusive. The reported pain intensity might be the best overall reflection of crash impact, tissue damage, attention to pain, handling of pain and

psychological stress reaction. Thus, it does not leave any information about mechanisms behind chronic WAD and cannot guide the direction of secondary prevention.

6 Background: Eye movement testing

6.1 Eye movements and equilibrium

Since patients with WAD frequently report dizziness/vertigo [14;16;17;17;18;28;32-36;36;114;115], it is reasonable to consider an oto-neurological approach to these patients. Both oculomotor and vestibular tests have been investigated in WAD [116]. Especially a test of smooth pursuit eye movements (SPEM) has achieved some attention as a potential diagnostic test since abnormal findings were observed to be very specific to WAD [33;117;118]. Based on these previous findings, we included the so called "smooth pursuit neck torsion test" in our clinical trials, and the following paragraphs regarding oculomotor tests will therefore mainly focus on SPEM.

6.1.1 Basic eye movement physiology

Eye movements consist of two main types: Smooth pursuits and saccadic eye movements [119]. Smooth pursuit eye movements (SPEM) track slowly moving objects in the visual field. The purpose of smooth pursuits is to stabilize moving objects on the retina [120]. It takes a moving object to perform SPEM, since they cannot be carried out voluntary without a moving stimulus [121]. SPEM can be maintained up till velocities of 40 - 60 degrees/sec with constant velocities [121;122]. Using sinusoidal stimuli the limit of smooth pursuit has been shown to be 1.2 Hz with a maximum velocity of 75 degrees/sec [123].

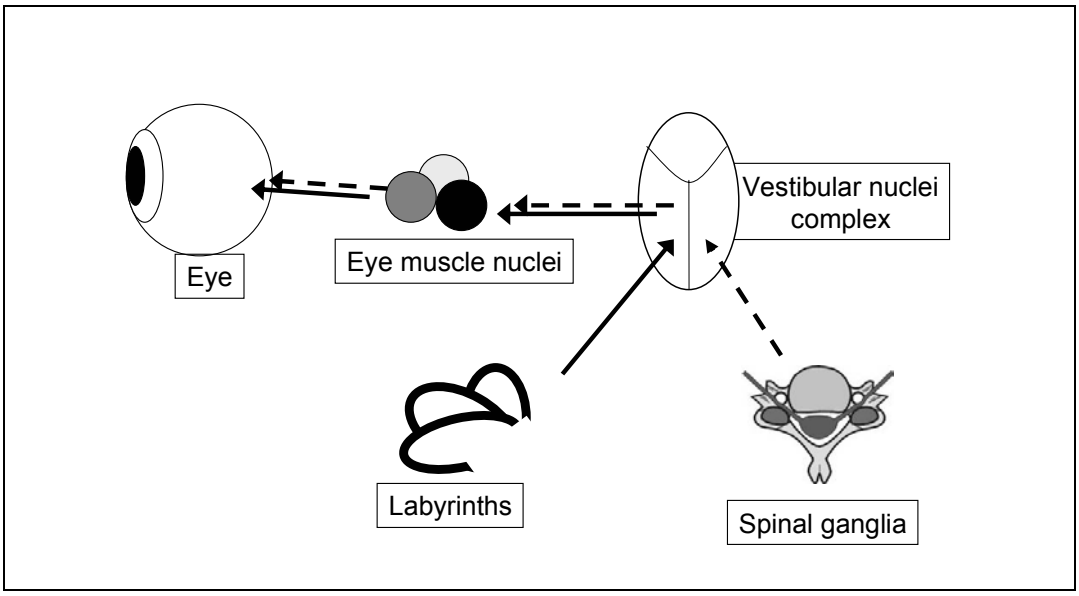
Saccades shift rapidly the gaze from one object to another. They can be voluntary activated when moving the eyes fast to a fixing point or reflex mediated in order to keep an object in focus [119]. The purpose of saccades is to move the eyes as quickly as possible, so that the point of interest will be centred on the fovea. Saccades and smooth pursuits work together to follow an object and keep it in focus.

By means of the vestibular ocular reflex an image can be kept on the retina also while the head is moving. Via the vestibular ocular reflex the eyes are moved on the basis of information from the inner ear. When the head is moved, signals arising in the labyrinths are transferred via the vestibular nuclei to the eye muscle nuclei (Fig.4). These input result in an activation of eye-muscles that make a "counter-rotation" of the eyeballs compared to the movement of the head. This is the reflex that makes it possible to read while shaking the head. In addition to input from vision and from the inner ear, input from cervical proprioceptors contributes to eye coordination (Fig.4). The cervico-ocular reflex provides information about neck position but is under normal conditions overridden by the vestibular ocular reflex [124].

6.1.2 Equilibrium

The systems involved in eye coordination are closely related to those involved in posture and equilibrium. Equilibrium is maintained via signals from the inner ear, from vision, and from proprioception and sensation (e.g. pressure on foot soles). These signals are integrated in the vestibular nuclei, cerebellum and the parapontine reticular formation [124;125]. As long as signals of different origin are in accordance with each other they are interpreted on a subconscious level, but if they do not seem to "agree", this will lead to dizziness or even to motion sickness [124;126;127].

Figure 4. Schematic illustration of the main pathways involved in the vestibulo-ocular reflex (uninterrupted arrows) and cervico-ocular reflex (broken arrows)



6.2 SPEM measuring in WAD

6.2.1 Recording of eye movements

Electro-oculography (EOG) was used for recording of eye movements in all previous trials identified concerning SPEM in patients with WAD, in which the method for recording was reported [33;117;118;128-133]. EOG is based on the fact that an electrical dipole exists from a positive potential of the cornea and a negative potential in the retina. This dipole is along the line of sight and thus moving with the movements of the eyeball [134]. The main advantages of EOG are that it is easy to perform, there is no discomfort to the patient, and that it is a relatively cheap method. Disadvantages with the method are that it is sensitive to changes in illumination since the corneo-retinal potential changes with light, and to electrical and electromyographic noise, e.g. blink artefacts [134]. For research purpose other methods could be considered superior to EOG [134]. Due to a higher signal-to-noise ratio, infrared reflection oculography and search coil technique have been recommended. Search coil technique requires a clinician who is trained in mounting a silicone device on the eye, and the technique can irritate the cornea. Furthermore it is a costly procedure. Infrared reflection oculography is less expensive than the search coil technique but requires exact positioning of the recording device on the head, which is time consuming and could be distressing to patients with pain [134]. EOG-recordings were used in reports II and III to match previous trials, and because this was considered the most appropriate method if the test should have any potential for implementation in clinical practice.

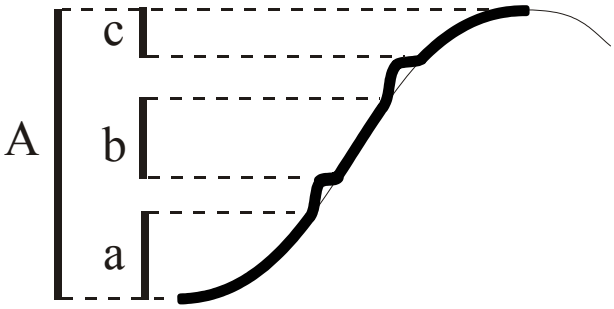
6.2.2 Outcome measures used in SPEM testing of patients with WAD

The ability to perform smooth pursuit eye movements is most often quantified as a velocity gain, which is defined as the proportion between the velocity of the eyes and the velocity of the target (i.e. velocity gain = eye velocity / target velocity). In previous investigations

of SPEM in WAD, two different methods for analysis of the EOG-recordings were described.

In one method, the proportion of a SPEM tracking which was not interrupted by corrective saccades was determined [33;117;118;135] (Fig.5). However, although the method was based upon recognition of saccades in the eye movement recording, it was not precisely defined how saccades were identified. The result obtained by this method was reported as a velocity gain, but was not calculated as a gain in the traditional sense[33;117;118;135]. This method was described for analysis of SPEM that followed a sinusoidal velocity-pattern, and was the principle used for SPEM analyses in our reports II and III. Contrary to previous studies, it was conducted in a purely computerized manner in our trials.

Figure 5. Analysis of a sinusoidal eye movement recording



$$\mathbf{SPI} = \frac{\mathbf{a + b + c}}{\mathbf{A}}$$

The thin sine-shaped line illustrates the target's track during roughly one half period (= one track from the left to the right). The bold, line mirrors the eye movement. During the intervals a, b and c the eyes follow the target smoothly, but two times they miss the track, making a saccade. The outcome of this analysis was in previous trials referred to as a 'velocity gain', and is in our trials named the 'smooth pursuit index' (SPI):

The other method, referred to in previous trials, was developed for a system using a constant target velocity. The SPEM performance was quantified by determining what proportion of the total tracking the eye velocity was close to the target velocity (+/- 4°/sec) [136]. This parameter was named a velocity distribution, but papers concerning WAD referred to this method and reported results as velocity gains [128;130;132]. The principle of both these methods was to determine what proportion of the tracking, uninterrupted SPEM were performed. Values obtained by the two methods are, nevertheless, not directly comparable because different stimuli were used, and since different criteria were established for the definition of what was considered interruptions in SPEM.

The recordings of eye movements are transformed into the desired outcome measure either by means of a computer program or by visual interpretation. Since EOG is rather sensible to noise, it is necessary to identify and handle parts of the recordings which are interrupted by noise. The most apparent source of disturbances is blinking.

6.2.3 The Smooth Pursuit Neck Torsion Test

Principally, two ways of testing SPEM have been applied in patients with WAD: A "standard" tracking test in which subjects are seated in a neutral position, and a "Smooth Pursuit Neck Torsion (SPNT) Test". In the SPNT test, smooth pursuits are investigated

both in the neutral seated position and while the subject is positioned with the cervical spine in rotation. The outcome of the SPNT test, called 'SPNT-diff', is the difference between the test result obtained in the neutral position and the mean of results obtained in respectively left and right cervical rotation. Tracking ability reduced in the rotated positions compared to in the neutral position has been suggested to be a consequence of altered input from cervical proprioceptors [117;127;135].

6.2.4 Theories about aetiology of altered oculomotor function in WAD

Abnormal patterns of eye movements can indicate pathology either of the orbital apparatus, which moves the eyes in the orbits, or of the mechanisms, which organise and control eye movements. This includes the vestibular apparatus, the brainstem and the cerebrum. Moreover, it has been demonstrated that patients with tension-type headache [135] and rheumatoid arthritis patients with dislocation of the upper cervical spine [137] have an abnormal pattern of smooth pursuit eye movements. The authors suggested that erroneous input from tension in neck muscles [135] or from tissue derangement [137] create a cervical input which is in disagreement with other parts of the sensory picture, which might lead to disturbance of the oculomotor function. Injury to the brainstem is another possible explanation for this phenomenon in patients with dislocation of the upper cervical spine [137].

Both brainstem injury and disturbance of the γ-muscle spindle input have been proposed as explanations for oculomotor disturbances in WAD [117;118;128;131;132], but none of these theories has been confirmed. The theory involving γ-muscle spindles suggests that inflammatory substances in the deep neck muscles lead to hyper-excitability of nerve endings and increased sensory input to the central nervous system. This results in a mismatch between sensory inputs which effects oculomotor control and can result in dizziness. It was hypothesised that because diverging sensory information will lead to a reflex adjustment, disturbed input from the cervical spine will lead to reflex activation of neck muscles and hence increased muscular tension in the neck. This could explain one mechanism for sustained neck pain in chronic WAD [124;127].

6.3 Previous trials regarding oculomotor testing after whiplash injuries

Table 4 summarises trials regarding tests of eye movements in WAD with special emphasize on results for smooth pursuit eye movements. Smooth pursuit tracking was the most frequently investigated test of oculomotor function in WAD together with tests of saccade velocity and latency. Eleven papers were identified in which tracking tests of SPEM in WAD were included [33;34;117;118;128;130-133;138;139].

Results of smooth pursuit testing were most often reported as velocity gains, but in some instances it was not defined how the gain was calculated [34;117;131;133], and in other cases, the methodological descriptions revealed that the traditional definition of a velocity gain probably was not used. In three trials reporting results in terms of velocity gains [128;130;132] the method developed by Bergenius [136] was referred to. As noted above, this method, however, did not result in velocity gains as outcome, but used velocity distribution instead [136]. It is therefore unclear how gains in the three above mentioned trials were calculated.

The main part of trials was conducted in a cross-sectional design including patients with chronic symptoms [33;34;117;118;130;132;138;139]. In three prospective trials, oculomotor function was investigated within one week to three months after the injury [38;128;131]. In one of these, abnormalities of the optokinetic reflex found maximum one week after injury resolved within three months and no evaluation of prognostic value of the test

was performed [38]. Conflicting observations regarding the predictive value of oculomotor testing were found in two prospective trials both using a tracking test and a test of saccades [128;131]. No conclusions can be drawn regarding prognostic value since the trials were both small and methods were not thoroughly described.

In all but one [133] of the identified cross-sectional trials, findings of abnormal smooth pursuits were reported in patients with WAD. Those defining a limit for a pathologic test result did this as a result diverging more than 2 standard deviations [33;128;130], or more than 3 standard deviations [117] from a control group's mean value, or as a result exceeding the 97.5 percentile of results of healthy controls [118]. Therefore by definition, some of the participants in the control group also had pathological results. The ability of the test to distinguish between groups was presented in two trials [33;118] and could be calculated from presented data in one [128]. In these trials, high specificities and relatively high sensitivities were found of oculomotor testing in patients who had sustained a whiplash trauma 8 months to 16 years previously as compared to healthy subjects.

In many trials it was not defined how the raw signal was transformed into the outcome measure. In three trials in which the "smooth pursuit neck torsion test" was investigated, it was described that interpretation of signals were performed visually [33;118;140]. The interpretation was performed by a blinded investigator, but there seems to be a risk of bias if patients blink, grimace or move due to pain or discomfort. Such activity will be detected as increased noise in the recording. It is surprising that none of the identified previous trials commented on the handling of blinks. Blinking cannot be avoided and will in some way disturb the signal of the EOG-recording.

In short, nothing final can be concluded regarding the usefulness of oculomotor testing in persons who have been exposed to a whiplash injury. Very little evidence exists from prospective trials, and results from cross-sectional trials are difficult to interpret and to compare due to diverging and insufficiently described methods.

7 Objectives

The principal aim of this thesis was to contribute to the understanding of WAD by generating knowledge about prognosis and treatment after whiplash injuries. Our specific objectives were to obtain answers to the following research questions:

1: Is there any difference of the effect of immobilisation, advice to 'act-as-usual', and active mobilisation initiated early after a whiplash injury on pain and disability one year later?

(This question is dealt with in **report I**)

2: Does smooth pursuit eye movement testing early after a whiplash injury predict 1-year outcome?

(This question is dealt with in **report II**)

3: Is smooth pursuit eye movement testing useful as a diagnostic test separating patients with chronic WAD from healthy individuals?

(This question is dealt with in **reports II and III**)

8 Methods

8.1 Study Populations.

This report deals with information collected in three populations: One prospectively followed population included for our main trial, one cross-sectionally investigated patient population, and one healthy control group.

8.1.1 The prospectively followed population

Participants were recruited for a two-center trial at the Danish Pain Research Center, Aarhus University Hospital and at the Back Research Center, Ringe, from emergency units and general practitioners in four Danish counties.

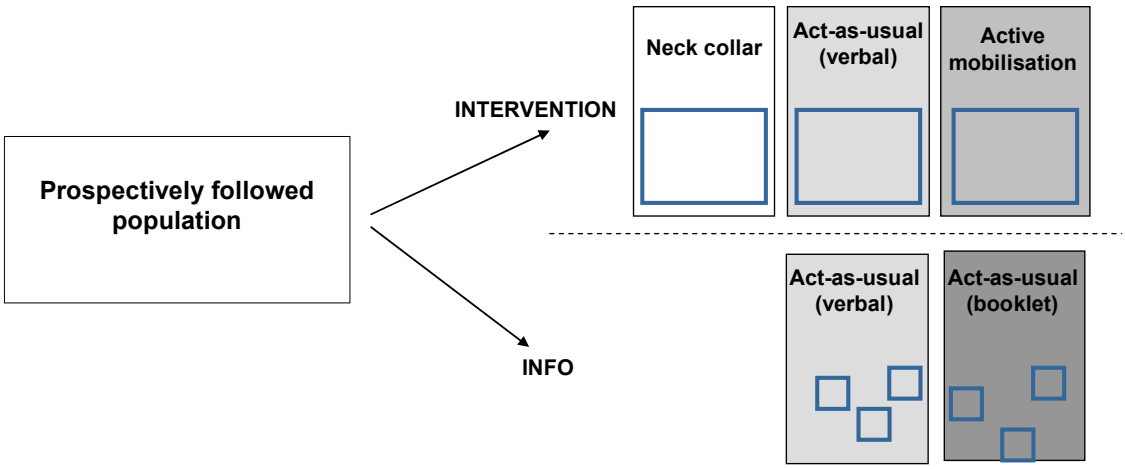
To be considered for inclusion, subjects should be involved in a car collision which caused symptoms within three days and it should be possible to perform the inclusion procedures within 10 days of the accident. The accident should have caused no other injuries than those considered related to a whiplash trauma and there should have been no contact trauma to the head. Moreover, participants should be generally healthy prior to the accident and should not have had any considerable neck pain prior to the accident.

Those included were allocated into two sub-populations: One with more substantial initial symptoms and an expected increased risk of developing persistent symptoms (n = 458), and one with minor complaints (n = 295). Those with the most severe complaints formed a study sample for a randomised interventional trial, whereas participants with less severe complaints were enrolled in an information trial (not to be reported in this thesis) (Fig.6). The allocation to these two sub-project were performed on the basis of a score summing pain intensity (highest score on neck pain, headache, radiating arm pain), cervical range of motion, number of non-painful complaints and gender. Due to this procedure, participants with an initial pain score of more than 4 or total cervical range of motion below 260 degrees were always allocated to the intervention trial, whereas less intensive pain or a larger range of motion could result in allocation to the intervention trial in combination with other factors (Table 5). Participants with more substantial symptoms were allocated to the intervention trial because we did not consider very mild symptoms to be an indication for treatment, and to accomplish a larger frequency of persistent symptoms than was expected in an unselected population. As brought up in section 5.2, it is difficult to demonstrate differences between treatment effects if a substantial proportion of participants recover spontaneously, leaving too few chronic cases for group comparison.

Participants in the information trial were randomised to verbal or written information. This randomisation was mainly to accomplish that the two groups receiving verbal advice to act as usual both were both enrolled under the same conditions and, thus, could be merged in a later work regarding prognostic factors.

Participants included in the intervention trial and a sub-sample from the information-trial composed the sample for the prognostic investigation of eye movements (Fig.6). The flow of the prospectively followed population is illustrated in Fig.7.

Figure 6. Participants in the prospectively followed population

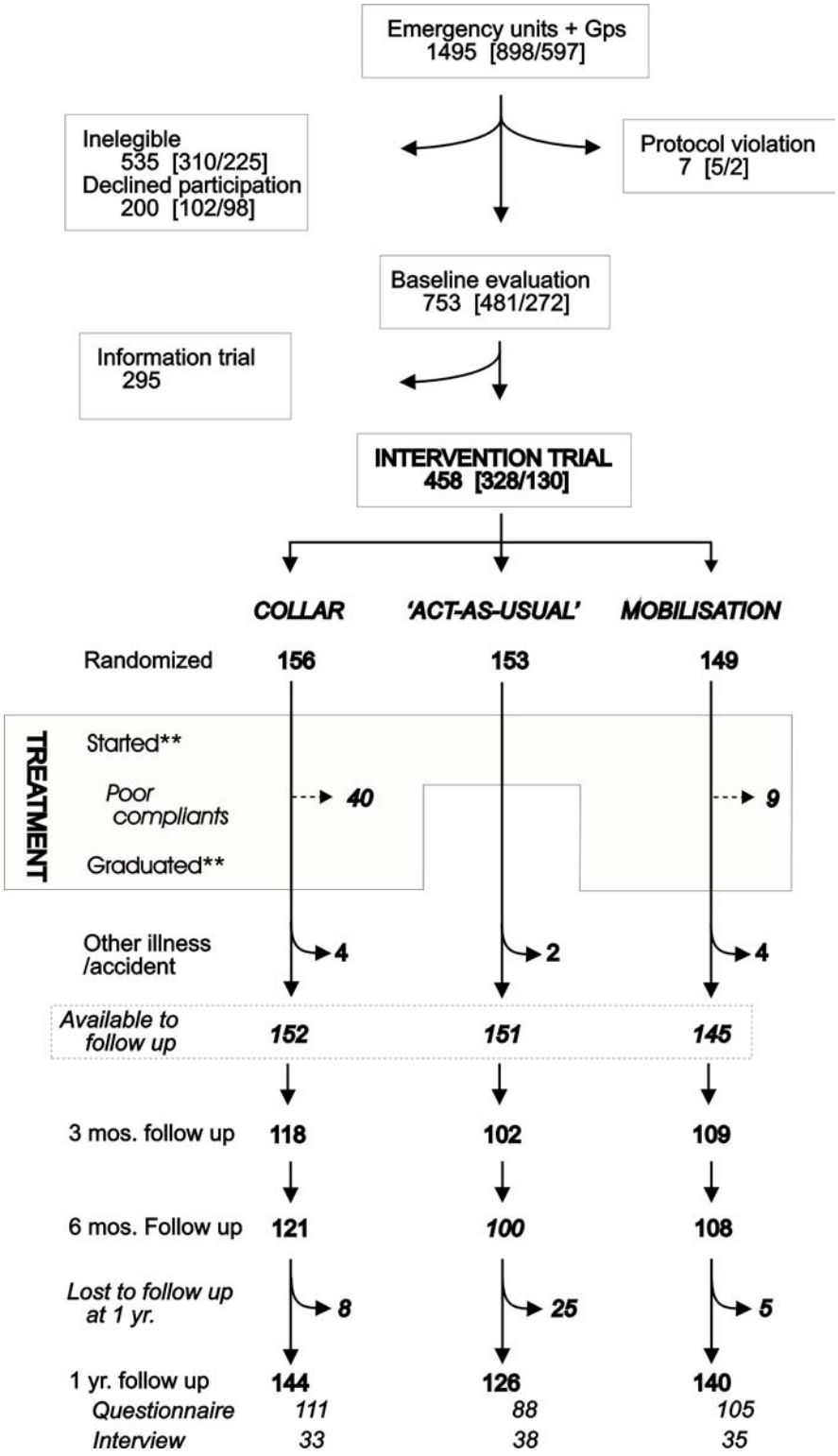


Participants in the prospectively followed population were allocated into two sub-projects according to symptoms.
Participants in the intervention trial and a sub-sample drawn from the information-trial who were enrolled at the Back Research Center composed the sample for the eye movement investigation (illustrated with blue boxes).

8.1.2 The cross-sectionally investigated population

The cross-sectionally investigated population (n= 34) was part of a cohort included for another trial at the Back Research Center (otherwise unrelated to this report) after having responded to advertisements in local newspapers or being referred from their general practitioner. To be included, participants should have been involved in a car collision a minimum of 6 months previously and should have experienced pain or other health complaints ever since. They could not participate if they suffered from other illness or if they had had any head injury either in relation to the car collision or at any other time.

Figure 7. Flow of participants in the intervention trial



The broken arrows illustrate that poor compliant participants were not excluded from the analyses.

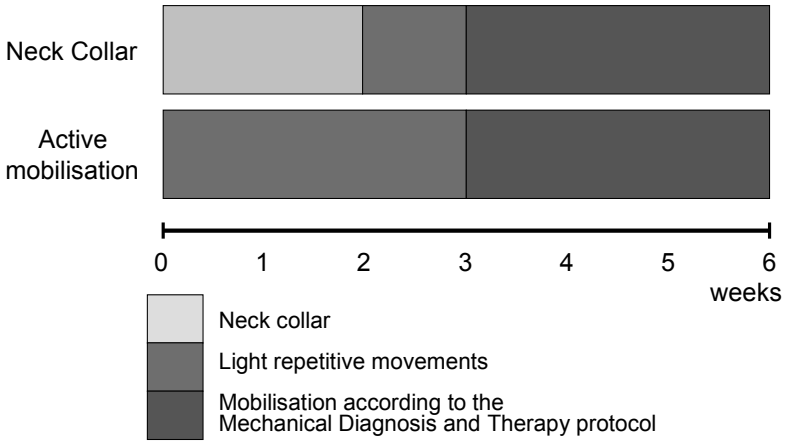
8.1.3 The control group
Healthy volunteers, who were not familiar with eye movement testing, were included in a control group (n = 60). They had no history of a significant head or neck trauma, had never been in coma, and had not been on sick leave because of neck trouble within the last year. Also, they had no neck pain on the day of the examination.

8.2 Study Procedures
8.2.1 Research Question 1 (see report I for more details)
Is there any difference of the effect of immobilisation, advice to 'act-as-usual', and active mobilisation initiated early after a whiplash injury on pain and disability one year later?

8.2.1.1 Inclusion procedures
All participants in the prospectively followed population were visited in their home by a project nurse. At this visit, baseline questionnaires regarding general health, crash related complaints and sociodemographic factors were filled in. Furthermore, the nurse measured cervical range of motion. Using this collected information, the project nurse filled in the allocation-scheme to determine whether participants were allocated to the intervention- or the information project. The randomisation procedure was performed by computerised minimisation independently within the two sub-projects. Participants in the intervention project met for a clinical examination at the research center, as did a randomly drawn sub-sample from the information project.

8.2.1.2 Interventions
Those with the most severe complaints were randomly allocated into one of three intervention groups: 1) Semi-rigid neck collar worn for two weeks followed by an active mobilisation programme for a maximum duration of four weeks, 2) advice to "act-as-usual" and information about the rationale for being active despite some pain, or 3) an active mobilisation programme for a maximum of six weeks after the principles of Mechanical Diagnosis and Therapy ®. The last four weeks in interventions 1) and 3) were parallel (Fig.8). All participants had information about use of ice and analgesics and general information about WAD.

Figure 8. Time schedule for the neck collar- and the active mobilisation intervention



Compliance to treatment was evaluated in the collar- and the active mobilisation groups. It was graded as *good, average* and *poor*. Good compliance to the collar required wearing it for more than 10 days and afterwards attending the program at the physiotherapist's as planned. In the active mobilisation group, good compliance required that all appointments with the physiotherapist were kept and home exercises were performed adequately. Good compliance did not necessarily imply that the treatment program was followed for 6 weeks if symptoms had resolved. However, the collar should under all circumstances be worn for the two weeks prescribed.

8.2.1.3 Follow-up

Questionnaires regarding accident-related symptoms and their consequences were sent to the participants 3, 6 and 12 months after the car collision. They also had an additional clinical examination after 3 and 12 months.

8.2.1.4 Outcome measures

The main outcome measures were neck pain, headache, neck disability and working ability at the 1-year follow-up. Neck pain and headache intensities were measured on 11-point box-scales (0 = no pain, 10 = worst possible pain). The box-scales were chosen since such rating scales with a definite number of pain levels are practical to use, and have been shown to be as sensitive to changes in clinical pain as visual analog scales [141;142].

Neck disability was measured by means of the Copenhagen Neck Functional Disability Scale (CNFDS) (0 - 30, 0 = no neck disability, 30 = extremely disabled due to neck trouble)[143]. This scale was developed in Danish and was shown to reflect both patients' and doctors' assessment of functional status [143], but it has not been validated in a population of patients with WAD. No standard procedure to handle missing answers in the neck disability scale was described and we chose to do a worst case replacement of missing items when a maximum of 2/15 items were unanswered. This meant that the neck disability outcome could be included from 100 participants in addition to those who completed all items of the scale.

Working ability was assessed by means of a calendar that was filled in by participants at time of the 1-year follow-up. Participants were asked to mark all days since the accident when they had been sick listed, had been working reduced hours or had altered job-functions due to WAD. Only information from the last month preceding 1-year follow-up was included in the present analyses.

The change in pain scores from baseline to 1-year follow-up, use of medication, SF-36, and number of non-painful complaints were evaluated as a secondary outcome measures.

8.2.1.5 Statistical Methods

The outcome variables neck pain, headache and disability were analysed both as continuous outcomes and dichotomised into "minimal" and "considerable". Pain scores from 0-3 and disability scores from 0-6 were defined as "minimal". Dichotomisation of outcome variables enabled us to compare the frequency of participants in the interventions groups who had considerable long-lasting complaints. Working ability was dichotomised into "unaltered work capability" and "altered work capability". Altered wok capability was defined as having any sick listing or days with reduced working hours in the last month preceding the 1-year follow-up.

As secondary outcome, the proportion of participants with improvement/ worsening of pain from baseline to the 1-year follow-up were compared between groups. Improvement after one year was defined as a minimum of 3-points reduction on the box-scale and worsening as a minimum of 3-points increase of pain as compared to the values at baseline. Linear and logistic regressions were used for group comparisons. These analyses were adjusted for baseline variables which have earlier been observed to have an influence on outcome. Intention-to-treat analyses were performed.

8.2.2 Research Question 2 (see report II for more details)

Does smooth pursuit eye movement testing early after a whiplash injury predict the 1-year outcome?

8.2.2.1 Study Procedure

The population investigated for this part of the trial is illustrated with red boxes in Fig. 6. Recordings of smooth pursuit eye movements were performed at baseline and 3 and 12 months after the injury, in addition to the procedures described for the interventional trial (*8.2.1*).

8.2.2.2 Eye movement recording

SPEM testing was performed by means of EOG. Surface electrodes were mounted lateral to the outer corner of the eyes for registration of horizontal eye movements. During each registration a dot moved horizontally from side to side following a sinusoidal velocity-pattern.

Three registrations, each lasting 60 seconds, were performed: One in a neutral seated position, one with right rotation of the cervical spine, and one with left cervical. The rotated positions were obtained by rotating the torso while the head was still facing forward. Rotation was taken as far as possible without causing pain. The recordings were performed in a random order. These three recordings constitute the SPNT-test.

8.2.2.3 Analysis of eye movement recordings

Besides placement of the electrodes, all parts of obtaining and analysing the signals from the eye movement were computerised. First, fractions of the registrations, which were not accepted for analysis due to predefined parameters (see report III), were removed. In the remaining recording, saccades were identified as parts where the eyes moved at twice the velocity of the target or faster for at lest 20 milliseconds. After identification of saccades, the outcome, named the “smooth pursuit index” (SPI), was calculated as described in section 6.2.2 (Fig.5). The SPI has a value between 0 and 1 (0 = no smooth pursuits performed, 1 = perfect smooth pursuit tracking).

8.2.2.4 Outcome measures

Neck pain intensity, headache intensity, neck disability and working ability at the 1-year follow-up, defined as in the interventional trial (8.2.1.4), were outcome measures.

8.2.2.5 Statistical methods

Those who had an examination of eye movements at baseline and delivered the 1-year follow-up data were considered complete cases. For participants who had a baseline eye movement recording but were lost for the 1-year follow-up, the last observation (3 or 6 months data) was carried forward and used in the analysis.

Two predictor variables were investigated: The SPI obtained in the neutral seated position and the SPNT-diff. SPNT-diff was defined as the difference between SPI obtained in the neutral seated position and the mean of SPI values obtained in the rotated positions:

$$\text{SPNT - diff} = \text{SPI}_{\text{neutral}} \quad \frac{(\text{SPI}_{\text{right rotation}} + \text{SPI}_{\text{left rotation}})}{2}$$

The analysis of the predictive value of these variables was planned in three steps: First, it was determined whether an association existed between SPI respectively SPNT-diff and each of the four outcome measures by linear and logistic regression. Second, if a significant association was discovered, the cut-point of SPI/SPNT-diff that led to the most optimal discrimination between recovered and non-recovered was established. This was by means of receiver operating characteristic (ROC) curves using the dichotomous end-point variables, with priority of a high specificity[144]. Third, if an adequate distinction was made between recovered and non-recovered the positive and negative predictive values of SPI and SPNT-diff were calculated for the determined cut-point.

8.2.3 Research Question 3 (see reports II and III for more details)

Is smooth pursuit eye movement testing useful as a diagnostic test separating patients with chronic WAD from healthy individuals?

8.2.3.1 Study Procedures

8.2.3.1.1 Chronic patients versus healthy controls in the cross-sectionally investigated population

Patients with chronic WAD and healthy controls had smooth pursuit eye movements recorded as described for research question 2 (8.2.2.2 and 8.2.2.3) twice on the same day, with an approximately 15 minutes break between the two test sessions. In addition to the recordings in the neutral seated position and in the rotated positions, a recording was performed while the cervical spine was in extension.

8.2.3.1.2 Recovered versus non-recovered participants in the prospectively followed population

The participants in the prospectively followed population had smooth pursuit eye movements recorded at the 1-year follow-up examination in the same manner as at baseline. This population was divided into recovered and non-recovered participants according to the four previously described outcome measures using the cut-offs described in section 8.2.1.5 (pain >3, disability >5, and altered work ability in the last month preceding the 1-year follow-up).

8.2.3.2 Statistical methods

8.2.3.2.1 Chronic patients versus healthy controls in the cross-sectionally investigated population

In addition to answering question 3, data from the cross-sectionally investigated population was used in the evaluation of the reproducibility of SPEM-recordings. The reproducibility was evaluated by means of limit of agreement [145], which denotes how much two recordings from the same person should be expected to differ.

Group comparison of SPI-values from the neutral seated position was performed in a regression analysis using values obtained in both test sessions. The

investigation of SPI-values obtained in other neck positions was planned in three steps: First, the association between neck position and SPI was evaluated in a linear regression analysis performed for each study group separately. Second, if an association between SPI and neck positions was discovered, it was investigated by means of ROC curves if an operational cut-point of SPNT-diff could be established. Third, in case the SPNT-diff could discriminate between patients and controls, the cut-point was used in a calculation of the sensitivity and specificity.

Four post hoc analyses were performed as a consequence of the information obtained in the main analyses. In these, SPI results were evaluated in relation to 1) time passed since the accident, 2) self-reported severity of neck pain and headache, and 3) self-reported dizziness. The fourth analysis dealt with the parameters for the saccade definition, and recordings from the WAD and the control group were re-analysed using different minimum velocities to define saccades.

8.2.3.2.2 Recovered versus non-recovered participants in the prospectively followed population

The analyses of smooth pursuit recording as a diagnostic test followed the same procedure as described in 8.2.2.5 with the one exception that the included recordings of eye movements were performed at the same time as the outcomes were measured. The steps of the analysis were: Looking for an association between SPI/ SPNT-diff and the outcome measures, determining discriminating power by means of ROC, and using the established cut-point to calculate the sensitivity, specificity and predictive values.

9 Summary of results

9.1 Research Question 1 (see report I for more details)

Is there any difference of the effect of immobilisation, advice to 'act-as-usual', and active mobilisation initiated early after a whiplash injury on pain and disability one year later?

From a total population of 458 participants (see flow-chart Fig. 7), 271 participants were included at the Back Research Center and 187 at the Danish Pain Research Center. The median number of days from the car collision to inclusion was 4 (IQR: 3-7). Baseline characteristics were similarly at the two centers and in the three intervention groups. In the "act-as-usual group", 16 % were lost for follow-up as compared to 5 % in the collar group and 3 % in the active mobilisation group. Those lost to follow had baseline variables similar to others (Table 6).

Poor compliance to the intervention was more frequent in the neck collar group than in the active mobilisation group (26 % versus 6 % of participants). Other treatment modalities received in addition to the intervention in the project was reported by 46 %, 52 %, and 43 % in the collar, "act-as-usual" and active mobilisation groups, respectively, at the 3-months follow-up. Considering compliance for the "act-as-usual" group is not meaningful. However, at least there were not significantly more participants in that group, than in the others, who sought additional care.

An improvement in neck pain and headache was observed during the follow-up period, with the greatest improvement observed between baseline and 3-months follow-up. Participants in the active mobilisation group tended to have better outcome on pain and working ability, but no significant group differences were observed on neck pain, headache or neck disability at any follow-up time, or on the secondary outcome measures at the 1-year follow-up.

Poor compliant participants in the collar group had generally better outcome than others (Fig.9), whereas participants who sought other treatment than offered in the project had generally poor outcome (Fig.10). Overall, 25 % (95 % CI: 21-29 %) of participants reported lowered working ability in the 12th month after the injury, while 14 % reported fulltime sick-listing during that month. Working ability was observed to be slightly more affected in the collar group compared to the other interventions, but, also, frequencies of altered working ability did not differ significantly between groups.

Figure 9. Neck pain intensity in the neck collar group at baseline, 3 months and 1-year follow-up in relation to compliance to treatment

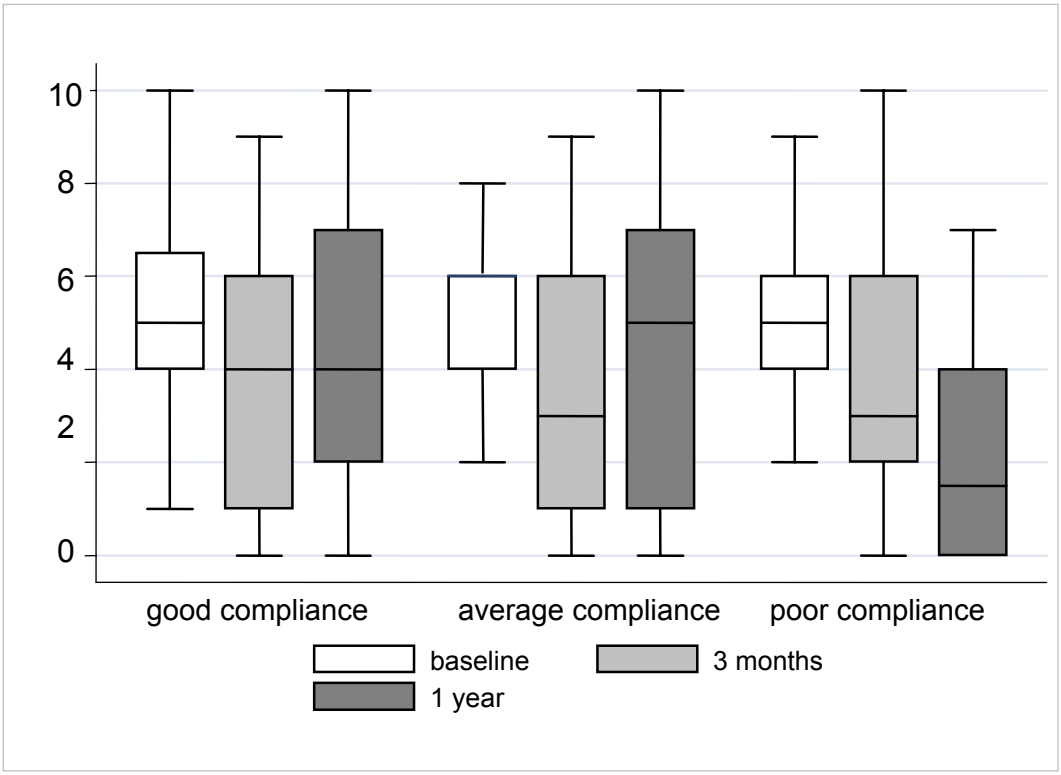
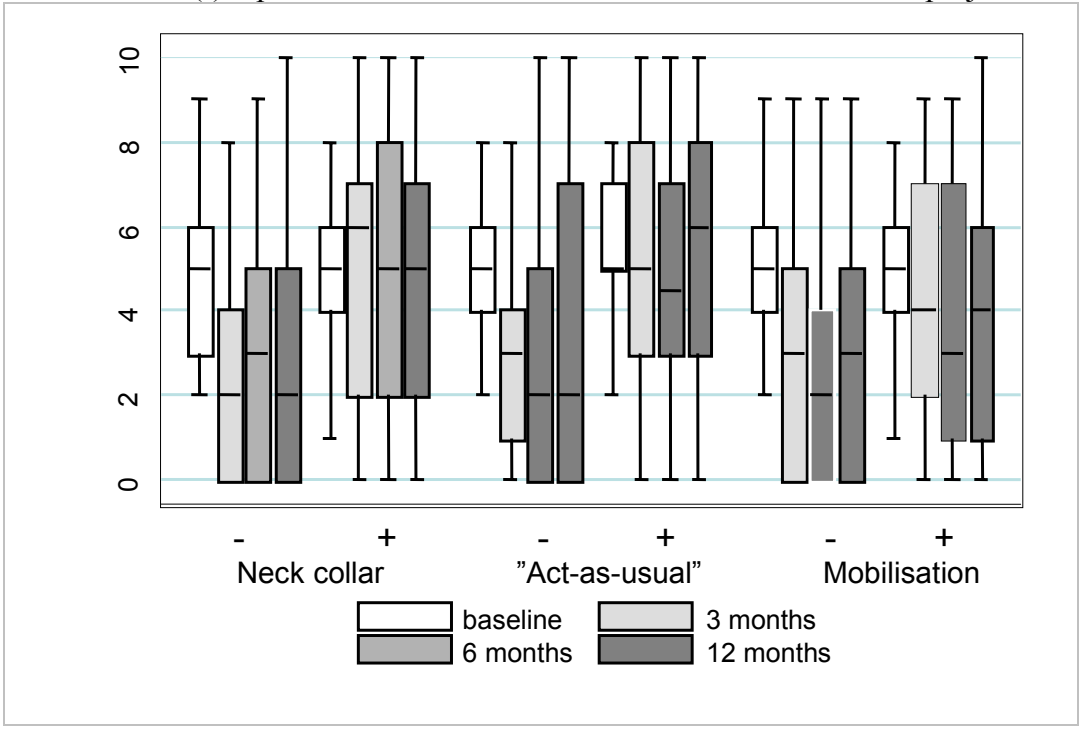


Figure 10. Neck pain intensity in participants who reported additional treatment (+) and in those who did not (-) report treatment in addition to the interventions in the project



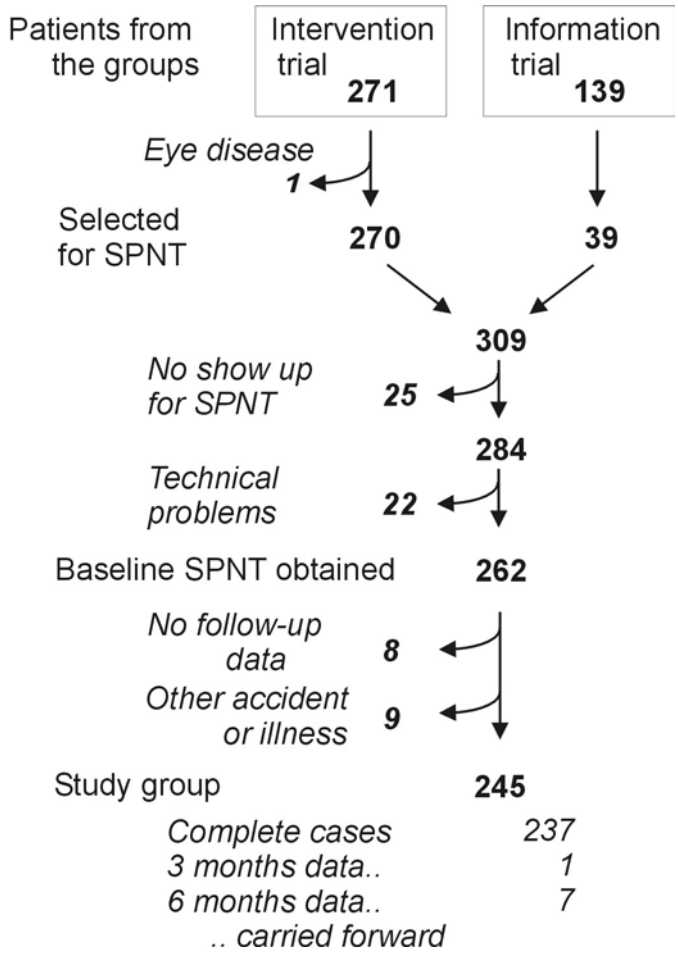
9.2 Research Question 2 (see report II for more details)

Does smooth pursuit eye movement testing early after a whiplash injury predict the 1-year outcome?

The flow of participants is illustrated in Fig. 11. Data from 245 participants were included in the analyses. Characteristics of the investigated population and those excluded or lost for follow-up were comparable in the study group and those lost or excluded.

SPI-values were about similar in different neck positions. No significant associations were observed between the SPI obtained in the neutral position or SPNT-diff at baseline and the outcome variables. Therefore the subsequent steps in the planned analysis were not performed.

Figure 11. Flow of participants included for SPEM testing in the prospectively followed population



In the flow-chart, "SPNT" represents both eye movement testing in the neutral seated position and performance of the SPNT-test.

9.3 Research Question 3 (see reports II and III for more details)

Is smooth pursuit eye movement testing useful as a diagnostic test separating patients with chronic WAD from healthy individuals?

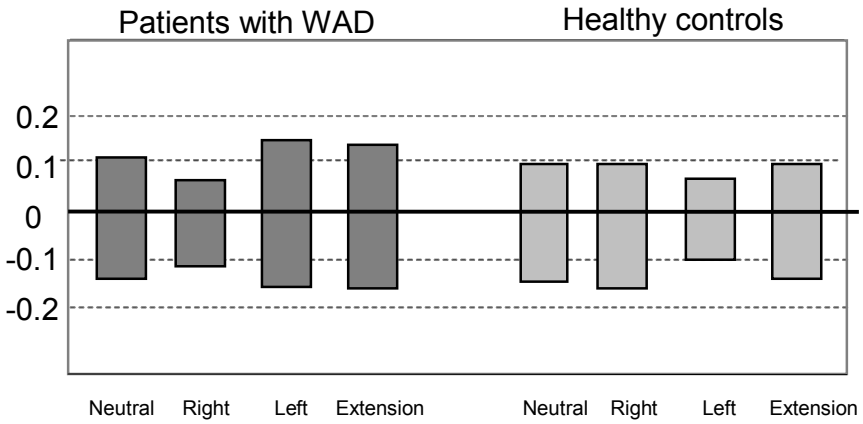
9.3.1 Cross-sectionally investigated population

Thirty-four patients (28 females; 6 males) and 60 controls (33 females; 27 males) were examined. Patients had been exposed to a whiplash trauma a median of 4 years previously (IQR: 30 - 90 months). Their median neck pain on the examination day was 5.5 (IQR: 3-7) and 39 % of the patients were sick listed or had stopped working due to WAD.

The limits of agreement are illustrated in Fig.12. Generally SPI-values differed about 0.1- 0.15 between sessions.

Patients with WAD tended to obtain lower SPI-values than the healthy controls in all neck positions. The difference was not statistical significance, and there was no effect of changing neck positions on the SPI in any of the groups. Therefore no further analyses concerning the diagnostic value of the SPNT-test were performed.

Figure 12. Limits of agreement between SPI-values obtained in two test-sessions



The bars indicate the 95 % limits of agreement in patients with WAD in the cross-sectionally investigated population and in healthy controls in each of four neck positions.
Neutral = neutral seated position, Right = right rotation, Left = left rotation

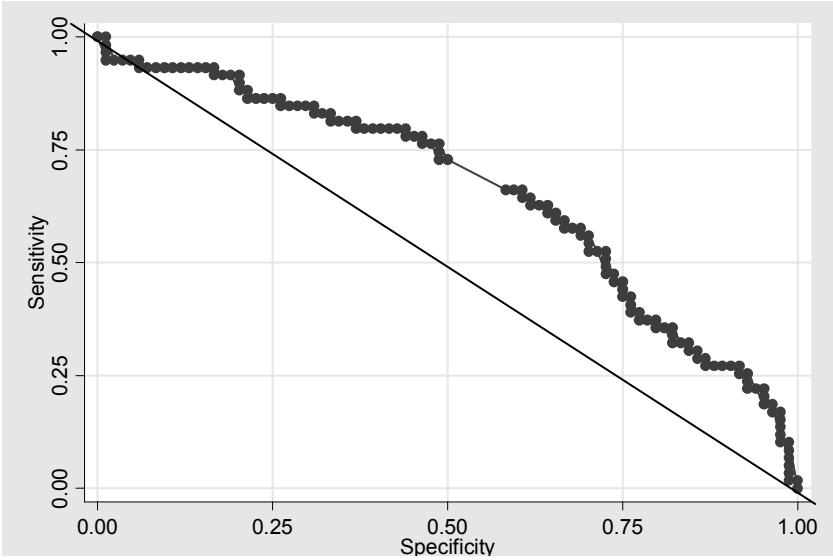
Post hoc analyses revealed no relevant association between SPI-values and time passed since the accident (Table 7), and we did not observe any difference in smooth pursuit performance between patients with severe pain or dizziness and others (Table 8). The saccade definitions tested post hoc did not reveal a definition which improved the diagnostic value of the test (Table 9).

9.3.2 Prospectively followed population

At the 1-year follow-up, 42 % (95 % CI: 35 – 49 %) of the 245 participants reported considerable neck pain, 42 % (95 % CI: 35 – 49 %) considerable headache, and 40 % (95 % CI: 32 – 49 %) considerable neck disability. From this population, 20 % (95 % CI: 15 – 26 %) reported reduced working ability.

There was a statistically significant association between SPNT-diff and neck pain at the 1-year follow-up (coefficient 7.8 p = 0.04). No other significant associations were observed between SPI-values or SPNT-diff and any of the outcome measures. A ROC-analysis revealed that the ability of SPNT-diff to discriminate between mild and considerable neck pain was rather poor (area under the curve = 0.66 (95 % CI: 0.56 - 0.75)) (Fig.13). Therefore we only determined the sensitivity that corresponded to specificities observed in previous trials [33;118;128] to be able to compare results.

Figure 13. Receiver operating characteristic curve



Receiver operating characteristic (ROC) curve for cut-points of SPNT-diff obtained at the 1-year follow-up examination in relation to neck pain (mild versus considerable). The curve shows sensitivities and specificities for possible cut-points of SPNT-diff (each indicated with a dot). No reasonable distinguishing between participants with mild and considerable neck pain could be obtained. The most optimal cut-point, giving equal weights to sensitivity and specificity, would result in a sensitivity of around 60 % and a specificity around 70 %.

10 Discussion

10.1 Intervention Trial

In our study, prescription of very different interventions directed towards neck pain and dysfunction did not have different effects on the general recovery. This lack of positive results requires further reflection. Could it mean that acute WAD is not a treatable condition? Or were the interventions based on an inappropriate rationale? Or does it mean that all interventions were effective, but at equal levels? We did not include an untreated control group, and intervention effects cannot be compared to a situation with no handling of persons with acute WAD. An untreated group was not part of the design because we expected that most people would seek some kind of help anyway. It was therefore considered more relevant to compare the effect of some feasible interventions.

For the continued discussion it was assumed that the similarity of results between groups denoted absence of therapeutic effect above that of the natural course.

10.1.1 Population

The trial was conducted with a sufficient number of participants to be able to demonstrate possible group differences. The population was recruited from emergency units and general practitioners within 10 days of an accident. In this way the study sample consisted of persons who had sought care after a whiplash trauma and, of these, we included those with the most substantial complaints. We considered this a relevant population in relation to early intervention. The score used for allocating participants to either the intervention- or the information trial was derived from seemingly important prognostic factors. Looking back, it would have been preferable to base this allocation only on symptom intensity. Fortunately, the allocation was determined by neck symptoms in the majority of participants. We were not able to judge whether any significant selection took place before referral of potential participants to the trial. However, we were in daily contact with all involved emergency units and believe that referral was generally unselected. Moreover, the inclusion procedures were carried out at a visit in the homes of potential participants, which we believe increased recruitment of newly injured participants to a great extent. About 13 % of referred persons refused to participate. This seemed to be due to either unwillingness to receive the investigated treatments or mild symptoms that was expected by the person to resolve spontaneously. Some also refused to participate because of the travelling distance to the research center.

It is obviously a problem to recruit a study population on the basis of a mechanism of trauma rather than on a specific diagnosis. Even though we selected those with more substantial complaints, it is possible that within the population different subgroups existed which responded differently to treatment and hence blurred a potential treatment effect.

10.1.2 Interventions

The three intervention regimes carried out in this trial were chosen on the basis of previous studies indicating that each of them had positive effects [73;79;86]. We also based our rationale for treatment on the concept that either soft tissue healing should be addressed or fear-avoidance behaviours should be reduced through information.

Even if our treatment modalities were appropriate they might not have adequate duration or intensity. The median number of consultations with the

physiotherapists was quite low, but similar to the number of consultations in a previous trial [79], in which relevant effect of mobilisation based on Mechanical Diagnosis and Therapy ® was observed. That previous trial observed that initiating active mobilisation within 96 hours had better effect than starting treatment 2 weeks after a whiplash injury [79]. However, the numbers of patients with late pain were small. In the present trial only very few participants started intervention less than 4 days after the accident; and we could not conclude on this matter. The collar was prescribed for only two weeks in our trial compared to four weeks in one earlier study [86]. In that earlier study it was not reported to what extent the participants wore the collar as prescribed. Our shorter duration was based on the idea that immobilisation of soft tissue injuries is generally recommended to be short lasting and followed by light mobilisation [66;67].

One physiotherapist was involved at each research center. One of these had a diploma in Mechanical Diagnosis and Therapy ® from the McKenzie Institute International and was considered to be highly competent in this field. She trained the other physiotherapist prior to the trial and via continuous contact during the project period. The active mobilisation part in both the collar group and the active mobilisation group were performed by the same physiotherapists. This was a weakness, if the therapists preferred one treatment programme to the other, but could on the other hand strengthen the trial since personal differences between clinicians was not an item.

A rather substantial number of participants did not wear the collar as prescribed and poor compliance to interventions was more frequent in the collar group than in the active mobilisation group. One shortcoming of the criteria for grading of compliance was that it did not necessarily involve the same kind of effort to obtain *good* compliance to active mobilisation as to the neck collar. The collar should be worn for more than 10 days irrespective of symptoms, whereas there was no demand of a minimum number of consultations or days doing mobilisation-exercises if participants in the active mobilisation group recovered in short time. It should be noted that those with poor compliance to the collar recovered well compared to other participants, and most likely poor compliance reflected that those who felt least distressed from symptoms did not want to wear a collar. Therefore poor compliance in the collar group did not seem to affect results. Poor compliance in the active mobilisation group was too seldom to affect the results significantly.

It has been observed that patients' own expectancies to an intervention are associated with outcome [146]. It might be a shortcoming that we did not ask about expectancies since we randomised to very dissimilar interventions. We chose not to do that, because we did not wish to introduce doubt about the foregoing information stating that the three interventions were believed to be equally relevant. Focusing on expectations might diminish treatment effect when persons are randomised to a treatment they in the first hand had "decided" was no good.

10.1.3 Contamination

Choice of other treatments in addition to those prescribed in the trial was frequent. Almost half of participants reported having received additional treatment, and our results should probably rather be interpreted as the effect of *prescription* of the tested interventions than of the specific effect of the interventions. This may be seen as a weakness but, nevertheless, reflects the real life situation. The number of patients seeking other treatments was about similar in the three intervention groups. There was a concurrence between receiving extra treatment and a poor outcome. This indicated that those not

responding to the intervention they had in the project sought other care, and that they did not experience substantial effect of other treatments either.

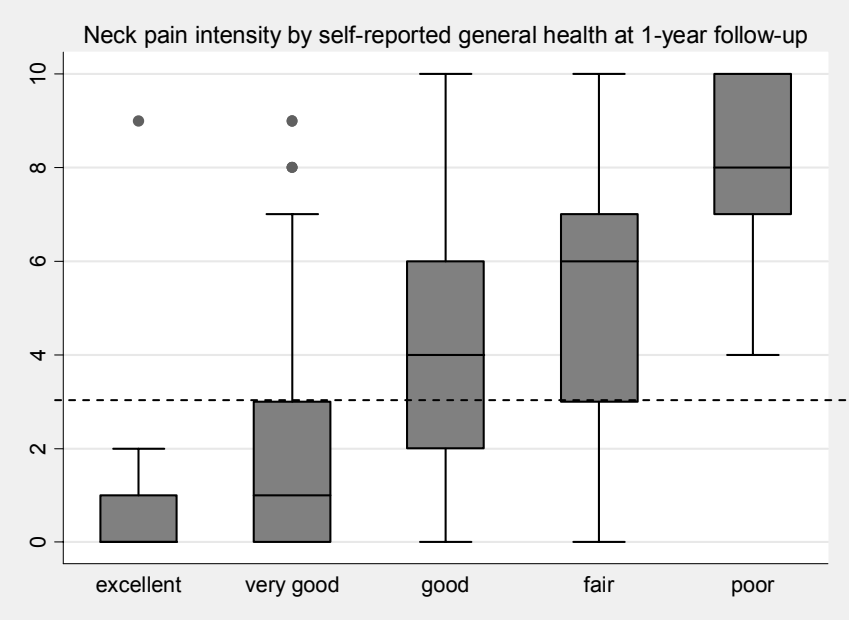
10.1.4 Loss to follow-up

Most participants were lost to follow-up in the "act-as-usual" group. This might reflect that these participants had not recovered and were unsatisfied with the handling of their symptoms in the project, but could also merely reflect that they did not feel they "owed" us as much as the others. Those lost to follow-up were similar to the responders both concerning socio-demographic factors and in relation to baseline symptoms.

10.1.5 Outcome measures

Neck pain, headache, neck disability and working ability were used as primary outcome measures to cover aspects of pain, daily function and handicap. It could be argued that these outcome measures were not sensitive enough since neck pain and headache are not the only possible lasting complaints following whiplash injury. However, neck pain and headache were the most frequent complaints in the cohort both at baseline and at the 1-year follow-up, and the chosen outcome measures were observed to correlate well with measures of self-reported general health and quality of life (Fig.14).

Figure 14. Neck pain intensity at the 1-year follow-up in relation to self-reported general health



Neck pain intensity at the 1-year follow-up in relation to self-reported general health (SF-36 "In general would you say your health is: excellent/ very good/ good/ fair/ poor"). The broken line indicates the chosen cut-point between mild and considerable neck pain. An about similar relation was observed for headache and neck disability. Dots denote outlier values.

Working ability was not measured by a validated method, and could be influenced by recall-bias since the calendar with information about sick listing and reduced working

hours was filled in retrospectively. We chose to evaluate these data as binary outcome variables (affected / unaffected working ability), since it to a large extent showed to be the nature of the variable: In general, either participants worked as before the accident in the 12th month after their accident, or they were sick listed or on reduced working hours every day. Data from the neck disability scale was only fully available from 173 out of 304 participants returning their questionnaire. This was mainly caused by single missing answers in the scale, which there was no formal way to deal with. Missing answers were replaced with worst case scores if no more than 2/15 answers were missing. In this way disability scores from 100 additional participants could be included. We considered such handling of data to be less problematic than excluding data from a large number of participants.

Another problem with these outcome measures was that they are not specific to symptoms of WAD. Hence, part of the reported symptoms would be expected also in a background population unexposed to neck trauma. This blurs the picture of the course of symptoms related to WAD, but is expected to be equally problematic in all intervention groups.

10.2 Eye movement testing

Smooth pursuit eye movement testing did not show to be of any predictive value after whiplash injuries and was not observed to be a useful diagnostic test in chronic WAD. Decreased smooth pursuit performance when measured in the rotated neck positions was associated with persistent neck pain, but findings regarding eye movements in chronic WAD were inconsistent. Diverging findings regarding smooth pursuit eye movements reported in this thesis could be a consequence of smooth pursuit testing being irrelevant in WAD. If a whiplash trauma is not able to affect control of smooth pursuit eye movements, it is of course nonsense to test smooth pursuits in these patients. However, some previous trials pointed towards altered eye movements in patients with WAD and there is also some evidence that other cervical disorders may affect smooth pursuits [135;137;147], which was our rationale for concentrating on this test. Some aspects of our method deserve further reflection, as described below.

10.2.1 Eye movement recording and analysis

The principles of EOG-recordings are well-established and the system we used was able to sample relevant information. The method used for analysing the recordings was completely computerised. With this method, the software recognised the parts of a recording that were acceptable for analysis, identified saccades and calculated the corresponding SPI and SPNT-diff. Hence, the process was not prone to bias in the way visual interpretations might be. According to our test protocol, no other interruption of smooth pursuits than corrective saccades did lower the SPI. This was a strength of the system since lack of motivation or different types of noise did not result in a low SPI-score. However, there was a risk that useful information was excluded due to this rather strict analysis. *If* disturbances such as total loss of the track or increased blinking activity can be triggered by altered eye coordination, we probably overlooked some smooth pursuit abnormalities.

Even when saccades are believed to be systematically and objectively identified they are not necessarily optimally defined, and changing the velocity-limit that defines a saccade can change the SPI considerably. With the system used, an infinite number of saccade definitions can in principle be chosen. We tested nine different velocity-limits for the saccade definition in our cross-sectionally investigated population

without finding one that lead to a better distinction between patients and controls. We therefore conclude that other saccade definitions, within reasonable frames, would not change conclusions.

In the prospectively followed population, results of the SPNT-test obtained at the 1-year examination were significantly associated to neck pain at the 1-year follow-up, whereas no association was observed between SPEM and symptoms at baseline. A possible explanation for this might be that due to acute pain, the positions with cervical rotation did not differ adequately from the neutral position, and hence did not affect proprioception. Another possibility is that cervical proprioceptors are not primarily affected by the acute trauma but rather by lasting abnormal muscle tension. Furthermore, even if damage to proprioceptors which effect SPEM exists in acute WAD, it is likely that the acute pain often is due other to pain sources also.

Reproducibility of test results was another critical factor in smooth pursuit testing. The limits of agreement [145] between two test sessions showed that generally two recordings should be expected to differ about 0.1 – 0.15. This inconsistency of test results limits the conclusive value of the test in relation to individual patients.

10.2.2 Populations

The sample size in the cross-sectionally investigated patient population was smaller than intended because some patients who volunteered did not show up. Also the inclusion of a chronic patient population by means of advertising causes a number of problems. First, participants were included due to their reporting of having health complaints which were related to an accident up till 8 years previously. In such a population it is more uncertain whether other accidents or diseases may influence health status than in a prospectively followed population. Further, recruitment by advertising might select a certain population. It is a fact that the cross-sectionally investigated WAD population was rather heterogeneous both regarding symptom intensity and duration of WAD. We looked into possible consequences of variation in time since accident, severity of pain and presence of dizziness without identifying a pattern. However, these post hoc analyses were performed in small sub-groups and may not have revealed some important factors.

The prospectively followed cohort was discussed in relation to the intervention trial (section 10.1.1). In relation to smooth pursuit testing, it should also be considered if different sub-populations exist in WAD. As in any other comparative trial it might be that results of a potential subgroup with affected oculomotor coordination disappear in the general results. Also, it could be relevant to compare results of those with persistent symptoms to persons without any neck pain rather than to those with neck pain ≤ 3. In both populations included for eye movement testing, it was a potential problem that medication was not stopped in a suitable period prior to the test. The fact that we did not observe different SPI results in the neutral seated position in those reporting use of medication compared to those who did not appears reassuring, however, it is possible that the effect of different medications may go in different directions [121], thus masking a difference.

10.2.3 Comparison with previous results

Our results cannot be directly compared to those of previous trials, since different assessments of SPEM were used, and in a number of earlier publications the performed methods were not adequately described [32;34;125;128;130;132;133]. Regarding the SPNT-test, one research group using visual interpretation of recordings found this test capable of

distinguishing between chronic WAD patients and healthy controls [33;118]. In one trial they reported a specificity of about 90 % and a sensitivity of around 70 % [118]. Another research team, using computerised analysis, however, did not observe the SPNT-test to differ between healthy controls and a group of 26 patients with chronic WAD [139]. In contrast, smooth pursuits were observed to be altered in these patients when obtained in the neutral seated position.

Diverging result could be a consequence of different methods or dissimilar study populations. We observed that a larger part of the tracings in our trials were excluded due to blinks and other disturbances in patients with WAD than in healthy subjects. It therefore seems problematic that the authors of previous trials did not describe any handling of noise. Doing visual interpretations, as was performed in some previous trials [33;117;118;140], there seems to be a risk of bias if extensive blinking reveals information of patient status, counteracting the blinding of the clinician. We believe that the computerized method we used was superior to visual interpretation, since it is as sensitive to velocity-changes, it is obviously objective and we find it important that our method can be reproduced, contrary to the previous trials in this field. Moreover, compared to other applied methods it was a strength that direct recordings of blinks was introduced.

Concerning study samples, it might be crucial if symptom intensity, duration of symptoms or the prevalence of dizziness in patients were not comparable. In some trials a larger part of participants were dizzy [33;117;118] or the participants were referred to the department either for an otoneurological examination [33] or because of severity of symptoms [130]. It seems that the observations of altered eye movements were more common in populations with more severe symptoms than our. Moreover, these previously investigated populations had a longer duration of symptoms than our prospectively followed cohort [33;117;118;130;138]. If chronicity and severity of symptoms are factors that determine the usefulness of smooth pursuit testing, obviously, it cannot be used as a predictive instrument in unsorted cases of newly injured patients.

10.3 Summary of discussion

It is a general problem of the trials in this report, as it is in other research in the field of WAD that basic knowledge about the aetiology and pathology is sparse. As a consequence, it is not certain if the focus of this research project was relevant.

Our interventional trial had sufficient power to demonstrate relevant group differences, it was randomised, observers were blinded, and data analyses were performed without revealing the identity of project groups. Therefore, despite the uncertainties mentioned in the discussion above, we believe that results are adequately solid to support our conclusions.

Our results of smooth pursuit eye movement testing were diverging. Due to the designs of trials and sample sizes the results from the prospectively followed population should have the greatest impact on conclusions.

11 Conclusions and perspectives

11.1 Main conclusions

None of the interventions immobilisation, advice to "act as usual", or active mobilisation, can be recommended over the others in patients with WAD in the early phase after a whiplash injury. Smooth pursuit eye movements, investigated in a 'standard' test and with the 'smooth pursuit neck torsion' test, is not a useful prognostic sign after whiplash injuries, and it is not a useful diagnostic test in chronic WAD.

11.2 Perspectives

A number of potential prognostic factors still remain to be evaluated in relation to the presented prospectively followed population, and subgroups responding differently to the evaluated interventions will be searched for. In addition, data from magnetic resonance imaging and bone scintigraphy are available and will be analysed. It would be useful to compare the investigated population exposed to a whiplash injury to the general population.

When all data have been analysed and interpreted, their relative importance can be appreciated within the aspects of the bio-psycho-social model. However, even with this broad perspective, it is not sure that we will obtain useful answers about the handling of patients with WAD. I believe that one reason for this is the definition of WAD, and think we should consider whether it is relevant to regard WAD as one single entity. Therefore, in the future we should focus on identifying subgroups within WAD in an attempt to get rid of the "having whiplash"-concept in every case of a car crash. It seems that defining all health complaints related to whiplash traumas as one single condition is equivalent to regarding all fall-accidents as leading to one single disease, no matter if it was a stumble on the pavement or a fall from the first floor. When moving forward, we should therefore search for other options, if we want to obtain more clinically relevant information about this poorly understood group of patient

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Table 1. The Quebec Task Force's classification of WAD

CLASSIFICATION GRADE	CLINICAL PRESENTATION
0	No complaint about neck. No physical signs.
1	Neck complaints of pain, tenderness or stiffness only. No physical signs.
2	Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of motion and point tenderness.
3	Neck complaint AND neurological sign(s). Neurological signs include decreased or absent deep tendon reflexes, weakness and sensory deficits.
4	Neck complaint AND fracture or dislocation.

Table 2. Summary of trials concerning early intervention after whiplash injuries

Author	Design	No. of partici-pants	Interventions	Follow-up	Effect measures	Results Overall prognosis	Effect size Comments
Bonk [70]	RCT Not blinded	102 52 ♂, 45 ♀ 5 in (1) were removed due to non-compliance to therapy	1: Active and passive mobilisation (ad modem Maitland), strength and isometric exercises. Posture advice. 7 sessions during 3 weeks. 2: Collar (type not described) for 3 weeks during day time. No other sessions than at inclusion.	1, 2, 3, 6, 12 weeks	Prevalence of neck pain, neck stiffness, headache, shoulder pain, arm pain.	(1) superior to (2) concerning all symptom prevalence (significance not stated)	Effect sizes at 12 weeks: Neck pain: 2 % (1) vs. 16 % (2) Neck stiffness 0 % (1) vs. 12 % (2) Headache: 0 % (1) vs. 6 % (2) Shoulder: 0 % (1) vs. 6 % (2) Arm pain: 0 % (1) vs. 6 % (2) 5 non-compliant removed from the analyses. Instruments used for self-reported outcomes not described.
Borchgrevink[73]	RCT Single-blinded	201 81 ♂, 120 ♀ 23 lost to follow-up	1: Advice to "act-as-usual". 2: Soft collar (on and off at day + all night) and sick leave 2 weeks. All: self-training, NSAID.	2, 6 weeks 6 months	Pain (neck, headache, shoulder) 6-point NRS Attention (concentration, memory) Buzzing in the ears Pain distribution Pain during daily activities Neck and shoulder mobility Neck pain + headache intensity (VAS 0-100) Intensity of main symptoms Sick leave beyond treatment regime Feeling of global improvement	(1) superior to (2) concerning attention, pain distribution, pain during daily activity, pain intensity (VAS) at 6 months No group-diff: pain NRS, ear buzzing, mobility, sick leave, global improvement Overall symptoms at 6-mo: 17 % severe headache, 13 % severe neck pain 2 % not returned to work 6 % part time sick leave	Effect sizes: Pain distribution 9.2/100 Attention 0.3/5 Pain during activity 0.14/4 VAS neck 4.5/100 VAS headache 11.8/100 No order of priority to 12 outcomes.

Table 2. Summary of trials concerning early intervention after whiplash injuries

Author	Design	No. of partici-pants	Interventions	Follow-up	Effect measures	Results Overall prognosis	Effect size Comments
Crawford [85]	RCT allocation to groups based on casualty record number No blinding described	108 40 ♂, 68 ♀ 12 lost for follow-up – were not included in the 108 described	1: Advice to mobilise freely, advice sheet with self-mobilisation exercise regime. Average 6 days use of collar 2: Soft collar for 3 weeks, afterwards self-mobilisation using advice sheet as in (1). Average 26 days use of collar. Both: Soft collar + NSAID from the emergency department until randomisation (was performed twice per week)	3, 12 weeks 1 year	Activity of daily living (5 activities, 0 -10 points) Pain (VAS 0-10) Cervical range of motion (0-380 degrees) Time to return to work	(1) superior to (2) concerning time to return to work No difference: Activity of daily living, pain, range of motion Frequency of non-recovery not reported	Effect sizes: Time to return to work 34 days (2) vs. 17 days (1) No difference in number of patient requiring physiotherapy in the two groups. A proportion of participants in the mobilisation group used collar due to pain, and a proportion in the collar group wore the collar more than 3 weeks.
Foley-Nolan [74]	RCT Double blind	40 28 ♂, 12 ♀ none lost to follow-up	1: Soft collar with pulsed electromagnetic therapy. 2: Soft collar (no PEMT), dummy generator. Both 12 weeks 8 hours /day All: NSAID, after 4 weeks hot packs, ultrasound, repetitive movements if "unhappy with progress."	2, 4, 12 weeks	Pain (VAS 0-10) Cervical range of motion, CROM (0-6, summed from 4-point NRS in each of 6 directions) Subjective assessment of progress (9-point NRS)	(1) superior to (2) concerning: Pain at 2, 4 weeks, mobility 12 weeks, assessment of progress 4 weeks. No difference: Pain after 12 weeks, mobility 2, 4 weeks, assessment of progress 12 weeks Overall: 6/40 =15% completely well	Effect sizes: Pain 4 weeks 0.7/10 CROM 12 weeks 0.5/6 Progress 4 weeks 85 % vs. 35 % moderate/ much better (at 12 weeks 85 % vs. 60 % NS) 9 in (1) and 12 in (2) had additional treatment after 4 weeks.
Gennis [75]	CCT group assign-ment due to record number Blinding not described	250 100 ♂, 96 ♀ 54 lost to follow-up, equally frequent in (1) and (2)	1: Rest, analgesia + soft cervical collar as tolerated for two weeks. 2: Rest, analgesia Both: No other intervention-contact than at inclusion.	6 weeks	Telephone interview: Pain (4-point NRS) Additional care sought	No significant group differences Overall: 38 % recovered completely after 6 weeks	Collar worn median 14 days for median 6 hours/ day (information from 63 %)

Table 2. Summary of trials concerning early intervention after whiplash injuries

Author	Design	No. of partici-pants	Interventions	Follow-up	Effect measures	Results Overall prognosis	Effect size Comments
Gurumoorthy [86]	RCT Blinding not described	220 75 ♂, 145 ♀ 105 lost to follow-up: 41 % (1) 53 % (2) 49 % (3)	1: Semi-rigid collar 4-weeks followed by active mobilisation programme (2 weeks 3 times a day), thereafter also isometric strengthening exercises. 2: Active mobilisation and isometric strengthening exercises as in (1) including in the first 4 weeks. 3: Subjects were returned to the care of their family doctors.	4, 6 weeks 3, 6, 12 months	Pain (VAS 0-100) Pain drawing Inability to perform activities of daily living (checklist of 20 activities) Time till returned to work at pre-accident level	(1) superior to (2) and (3) concerning pain intensity + area, frequency of no pain after 12 mo	Size effects: 18 % vs. 58 / 60 % pain > 0 after 12 months. 21 % (1) vs. 30 (2) and 37 % (3) did not return to pre-accident working level (NS). PhD-thesis. Not formally published. Unclear how missing values were handled in survival analyses. Subjects in (1) younger and more intensive pain at baseline.
Hendriks#	RCT No blinding described	16 2 drop-outs	1: Ice, home exercises, advise + ultra-reiz current 15 min per session 2: As (1) without ultra-reiz current. All: 5 sessions within 7 days	6 weeks after treatment	Pain (VAS, McGill pain questionnaire) Range of motion	(1) superior to (2) on pain and cervical mobility	
McKinney [77]	RCT No blinding described	247 randomised 170 attended treatment Gender not reported 42 lost to follow-up: 7(1), 17 (2), 18 (3)	1: Rest, advice to mobilise after 10-14 days. (n =33) 2: Physiotherapy 10 hours during 6 weeks. Heat, cold, short wave diathermy, hydrotherapy, traction, active and passive repetitive movements. (n = 71) 3: Advice, one session 30 minutes. Verbal and written instructions on posture correction, use of heat, analgesics and soft collar for short periods. Instruction in mobilising exercises. (n = 77) All: soft collar, analgesics.	2 years	Duration of pain and stiffness (retrospectively reported after 2 years). Intensity of persistent pain (VAS 0-10). Frequency of persistent symptoms.	(3) superior to (1) and (2) concerning frequency of persistent symptoms No difference in time to recovery or severity of persistent pain	No information regarding what group non-attendants were randomised to. No intention-to-treat analysis. Inclusion to (1) stopped because of ethical considerations. A total of 47 participants reported persistent symptoms. Effect size: 23 % (3) vs. 46 % (1) and 44 % (2) reported persistent symptoms.

Table 2. Summary of trials concerning early intervention after whiplash injuries

Author	Design	No. of partici-pants	Interventions	Follow-up	Effect measures	Results Overall prognosis	Effect size Comments
Mealy [76]	RCT Single-blinded	61 37 ♂, 24 ♀ 10 lost to follow-up	1: Applications of ice 24 hours, mobilisation using 'Maitland technique', daily exercise every hour. 2: Soft collar, advice to rest and gradually mobilise after 2 weeks. All: Analgesics as required.	4, 8 weeks	Pain (VAS 0-10) Cervical range of motion	(1) superior to (2) concerning pain intensity and mobility at 8 weeks	Effect sizes at 8 weeks: Pain difference 2.2/10 (No scale for mobility was given provided). No information on duration of treatment or number of sessions.
Pennie & Agamber [78]	RCT Allocation based on casualty number Blinding not described	135 58 ♂, 77 ♀ 7 lost to follow-up or excluded	1: Soft collar (n= 58) or moulded collar of foam (n=16) 2 weeks, afterwards instruction for exercises. After 6 - 8 weeks physiotherapy if not improved. 2: Traction, exercises, advice on neck care and sleeping posture.	5 months	Self-reported improvement (4-point NRS) Cervical mobility Percentage reduction of pain in the neck, arms, back, head (VAS 0-100) Time off work	No significant group differences were observed	Moulded foam collars were not available for the entire trial because of technician's illness.
Pettersson [83]	RCT Double blinded	40 22 ♂, 18 ♀ 1 lost to follow-up	1: Methylprednisolone, 15-minutes bolus + 23-hour infusion. 2: Placebo administered as (1) All: Soft collar 1-2 weeks, exercises, early mobilisation and information.	2, 6 weeks 6 months	Total number of sick days Sick leave after 6 mo	(1) superior to (2) concerning sick leave after 6 mo and total number of sick days 30/40 = 75 % completely recovered after 6 mo. 4/40 = 10 % on sick leave	(1) > (2) regarding symptoms as well, not tested for significance Effect sizes: 0 vs. 4 on sick leave at 6 mo
Rosenfeld [79;148]	RCT Blinding not described	97 29 ♂, 59 ♀ 9 lost to follow-up	1: Active mobilisation (ad modem McKenzie) started within 96 hours. 2: as (1) started after 14 days. 3: Leaflet with advice to rest the neck during the first weeks, and holding advice regarding posture and suitable activities incl. light exercises to be initiated a few weeks after the injury. A soft collar could be used. 4: As (3) after 14 days.	6 months 3 years	Change in pain intensity (VAS 0-100) Proportion of patients reporting pain = 0 Proportion reporting pain < 11. Change in cervical mobility	(1) and (2) superior to (3) and (4) concerning reduction in pain, (1) superior to (2) concerning change in pain, proportion recovered (not tested for significance) No difference on mobility Overall:	More participants in (3) and (4) reported co-interventions. NS Effect size: (1) vs. (3): 31/100 change in pain level (1) vs. (2): 15 /100 (3) vs. (4): 8 /100 No pain at follow-up: 8/21 (1), 5/22 (2), 4/23 (3), 1/22 (4)

Table 2. Summary of trials concerning early intervention after whiplash injuries

(continued)			1+2: Mean number of sessions = 4 3+4: No other intervention-contact than at inclusion.			Pain <11 at 6 mo in 32 %	
Schnabel [80]	RCT Not blinded	200 77 ♂, 123 ♀ 50 lost to follow-up: 36 % (1) 15 % (2)	1: Collar 1 week all time (type of collar not described). No other intervention-contact than at inclusion. 2: Active mobilisation (exercises) 2-5 visits during 1 week. All: NSAID.	6 weeks	Average total pain (VAS 0 –10) Perceived disability (VAS 0 –10) Prevalence of symptoms	(2) superior to (1) concerning prevalence of neck pain, headache, shoulder pain, prevalence of reporting no symptoms, pain intensity, perceived disability. Overall: No symptoms at 6 weeks in 56 %	Effect sizes: Prevalence after 6 weeks: neck pain 45 % vs. 28 % headache 27 % vs. 14 % shoulder pain 34 % vs. 16 % No symptoms 44 % vs. 65 % Difference pain intensity: 0.56/ 10 Difference disability: 0.64/ 10
Söderlund [81]	RCT Not blinded	59 24 ♂ 35 ♀ 13 lost to follow-up	1: Instruction in mobilising exercises, posture advice. 2: As (1) + exercises aiming to improve kinaesthetic sensibility and neck muscle coordination. All exercises were performed at least 3 times a day.	6 weeks 3, 6 months	Pain Disability (0- 70) Self-Efficacy (0- 200) Pain intensity (VAS 0-10) Cervical mobility Cervicocephalic kinaesthetic sense Prevalence of symptomatic subjects at 6 mo based on pain score	No significant group differences	Little difference between treatment regimes

(1), (2), (3): intervention 1, intervention 2, intervention 3
CCT = controlled clinical trial
NS = not significant
NRS = numeric rating scale
mo = month
RCT = randomised clinical trial
VAS = visual analog scale
# Information from Seferiadis [84]

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Berglund, Sweden [149]	Cohort study based on claim reports from insurance company.	1: Drivers involved in rear-end car collisions who reported an injury to the neck coded as AIS 1, n= 232 2: Drivers involved in rear-end car collisions without bodily injuries, n= 204 3: Subjects covered by traffic insurance not exposed to collision, n= 3688 Response rate 77 %	Not described	Risk factors within the exposed group not evaluated.	General health Fatigue Depression Sleep disturbances Headache Neck pain Back pain Stomach-ache - during preceding 3 months All 4-point NRS scales	7 years after WL: Relative risks of symptoms in (1) compared to unexposed: Headache 3.7 Low back pain 1.7 Ill health 3.3 All symptoms except depression and stomach-ache were increased. 23 % report headache, 18 % ill health	Cases defined solely from insurance files.
Borchgrevink, Norway [94]	Prospective clinical trial, recruitment from emergency clinic. 6 months follow-up.	n = 99 (43 % ♂) 11 lost for follow-up	19 % severe headache 26 % severe neck pain Other frequencies of symptoms or intensities not stated	Personality and psychiatric symptoms measured by the Millon Clinical Multiaxial Inventory. No association with outcome.	Recovered/ non-recovered. Non-recovered defined as having constant or daily neck pain or headache that did not exist before the accident	45 % previously asymptomatic had severe symptoms after 6 mo 28 % had daily symptoms after 1 year	Intensity of symptoms or disability due to symptoms not reported
Borchgrevink, Norway[150]	Prospective clinical trial, recruitment from emergency clinic. 2 years follow-up.	n = 52 (MRI n= 51) (42 % ♂)		MRI findings (Categories: No, posture abnormalities, spondylosis, disc abnormalities) Radiographic findings (Categories: No, posture abnormalities, reduced intervertebral space, spondylosis) Factors associated with poor 3 mo prognosis: Spondylosis or disc abnormalities. No relevant association in mulltivariat analyses.	Symptom frequency (4-point NRS)	Frequency of constant discomfort after 2 years: Neck pain 9 % Headache 9 %	Vertebral fracture and signs of nerve compression were exclusion criteria (not stated whether this was found) No registration of symptom severity or disability.

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Brison, Canada [17]	Prospective clinical trial, recruitment from emergency clinic. Data collection from telephone interview. 6 months follow-up.	n = 353, 60 % reporting initial WAD (37 % ♂) 27 lost for follow-up, 19 lost for interview at 6 mo	Frequency of symptoms: Headache 72 % Neck Stiffness 71 % LBP 53 % Upper limb 41 % Dizziness 35 % Sleeping problems 54 % Fatigue 48 %	Self-reported crash characteristics Gender Age Body mass index. Factors associated with increased risk for WAD at 6 mo: Increasing age (age 51-70, RR= 2.1) Accident on highway (RR= 2.8)	WAD definition: Neck and/ or upper back and/ or shoulder pain graded as: severe occasional or consistent or as: moderate regularly or daily	34 – 36 % reporting WAD after 6-24 months At 6 months reported 36 % modified work activity	BMI and some crash related factors tended to be associated to outcome.
Bylund & Björnstig, Sweden [151]	Prospective clinical trial. Hospital setting. 2.5 years follow-up.	Total n = 255 (48 % ♂) Cervical strain n = 141 (43 % ♂)		Gender Cervical strain compared to other diagnosis Factors associated with increased risk of sick leave and pension: Female gender Cervical strain	Sick leave Disability pension	5 % receiving disability pension at follow-up	No significance levels or statistic tests presented. No symptom outcome measures.
Cassidy, Canada [18]	Prospective cohort study based on insurance claims. Followed to claim closure.	n = 7462 (39 % ♂)	Frequency of symptoms: Reduced neck mobility 87 % Headache 84 % Pain upper limbs 42 % Dizziness 45 % 46 % sick listed due to injury	Tort or no-fault insurance system Age Gender Education level Baseline neck pain Painful jaw Pain in arms Broken bones At fault for collision Lawyer retained Initial health care provider Factors associated with prolonged time to closure with: Tort system Female gender Increased age Higher education Higher baseline pain intensity Full-time employment	Days from injury to claim closure.		2064 excluded from analyses because of uncertainty about reason for reopening claim.

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

(continued)				Anxiety before collision Painful jaw Concentration problems Not being at fault Being married Pain in arms Broken bones Lawyer involved			
Drottning, Norway [152]	Prospective clinical trial. Emergency department. 1 year follow-up.	n= 587 (51 % ♂) 120 lost for follow-up	38 % at least 'occasional, moderate' headache	Pre-injury headache Pre-injury neck pain Collision speed (not clear how estimated) Collision direction Initial pain intensity Initial neck stiffness Factors associated with increased risk of chronic headache: pre-injury headache* pre-injury neck pain* rear-end collision* initial neck pain intensity initial headache intensity * unclear if association significant	Diagnosis of chronic cervicogenic headache	3.4 % cervicogenic headache after 1 year	Statistical methods not described. No information provided concerning participants lost to follow-up.
Drottning, Norway [30]	Prospective clinical trial. Emergency department. 4 weeks follow-up.	n= 107 (56 % ♂) 7 lost for follow-up	Neck pain 79 % Headache 55 % Interscapular pain 35 % Mean neck pain intensity 3.7 (SD = 1.7)	Age Gender Symptoms before accident Post traumatic stress (Impact of event scale, 0- 65) Presence of neck pain Neck pain intensity Neck stiffness Headache Interscapular pain. Factors associated with high symptom score: Post traumatic stress (cut-point = 20, RR = 2.7) Neck pain intensity.	High symptom / low symptom group. High symptom defined as: at least moderate daily or strong occasional symptoms (4-point NRS for intensity and frequency of symptoms) or still out of work	42 % in high symptom group after 4 weeks.	

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Gargan & Bannister, England [31;153]	Prospective clinical trial. Emergency department. Blinded interviewer. 2 years follow-up.	n = 50 (48 % ♂) No loss to follow-up.	3 asymptomatic 41 % neck pain 30 % headache 21 % interscapular pain visual disturbances 5% 0 % dizziness	Psychological status by GHQ Neck mobility Factors associated with poor outcome at 2 years: GHQ at 3 months (31 % sensitivity 94 % specificity) Neck mobility at 3 months (sensitivity 44 % specificity 91 %)	Symptoms recorded as *asymptomatic/ nuisance* (no symptoms or mild symptoms not interfering with activity) *intrusive/ disabling* (handicapped work or leisure activities or lost job due to the injury)	32 % intrusive or disabling symptoms after 2 years.	No risk factors identified at baseline.
Greenfield & Ilfeld, USA[# 104]	Prospective clinical trial. Private sector. 6 weeks follow-up.	n = 179 Number lost for follow-up unclear.		Sociodemographic Physical Crash factors Radiological Treatment Factors associated with poor recovery: Interscapular and upper back pain.	Recovery (improvement)		
Harder, Canada [12]	Prospective cohort trial. Recruitment insurance company. Data from claim reports.	n = 2810 (40 % ♂) n= 1551 no other injury besides whiplash. Cohort only including subjects who received compensation. Same cohort as in [110]	Not provided	Gender Age Number of dependents Marital status Employment status Vehicle type Direction of collision Seatbelt use Speed limit Factors associated with prolonged time of compensation: Female gender Age More dependents Not employed fulltime Collision in truck or bus Being passenger Frontal or sidewise collision	Time from injury to last date of compensation	4 % not closed claim after 1 year.	204 cases with recurrence and 1743 without police report data excluded. Small effects of all single predictive factors (RR>0.8 except for collision in truck/ bus)

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Herrström, Sweden [89]	Health care based registration of traffic injuries. Data collection via questionnaires. 1 year follow-up.	n = 158 (46 % ♂) 33 lost for follow-up (21 ♂, 11 ♀)	Not provided	Type of collision Previous headache or neck pain Profession Gender No associations with duration of symptoms.	Duration of symptoms (retrospectively answered) Presence of lasting symptoms after 12 months	After 12 months: 30/125 symptoms more than 6 months 35 % neck complaints 27 % headache 12 % sick leave>4 weeks. 6 % sick leave at 12 months	Higher response rate among women. Severity of symptoms not registered.
Hijioka, Japan [103]	Data obtained from insurance database.	n= 400 (55 % ♂) Not described if follow-up data were available in all cases	Not provided	Gender Age Degree of vehicle damage (6 degrees) Admission/ non-admission to a hospital Factors associated with prolonged treatment duration: Increased age Car damage = 0 (no damage) or 4 (½ of car damaged) Admission to hospital	Duration of treatment (from patients presented at hospital till end of treatment. Not described how treatment or end of treatment was defined)	Not provided	Indication for treatment not described, no description of symptoms.
Hildingsson, Sweden [14]	Prospective clinical trial. Hospital setting. Follow-up 25 (6-43 months) post injury.	n = 93 (43 % ♂) 4 lost for follow-up	Neck pain 88 % Neck stiffness 69 % Headache 54 % Shoulder pain 40 % Arm pain 14 % Dizziness 23 %	Type and force of impact (self-reported) Initial symptoms Radiographic findings (5 standard projections) Previous neck/shoulder pain Height Gender No associations with outcome	Major complaints = inability to return to previous work Recovery = no residual symptoms in the patient's opinion	Follow-up: 42 % recovered 14 % minor discomfort 44 % major complaints 15 % sick leave or pension 29 % neck pain	Participants lost to follow excluded from trial. No registration of symptom intensity

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Hodgson & Grundy, England[# 105]	Insurance population cohort. 10 years follow-up.	n = 93 40 lost for follow-up		Sociodemographic Physical Crash Pre-existing Radiological Treatment Litigation Factors associated with increased risk of persistent symptoms: Rear-end collision	Symptoms Effect on job or hobby		
Karlsborg, Denmark [22]	Prospective trial from 2 emergency care units and 2 neurology departments. 7 months follow-up.	n = 39 (41 % ♂) 5 lost for follow-up	Neck pain 100 % Headache 94 % Decreased cervical mobility 91 % 88 % WAD grade 3	Radiological findings MRI findings Symptom checklist (SCL-90-R) Social changes and stress factors unrelated to injury (interview) Neuropsychological testing Factors associated with poor outcome: Stress unrelated to trauma	Number of complaints	29 % complete recovery Neck pain 47 % Headache 44 % Decreased cervical mobility 32 %	No intensity of symptoms or disability registration.
Kasch, Denmark[20]	Prospective trial from emergency care unit. (Same cohort as referred to below) 3 months	n = 141 (48 % ♂) 123 were examined at least twice and were included in the analyses	Neck pain 85 % Headache 82 % Arm or shoulder pain 53 % Low back pain 32 %	Speed difference between involved vehicles (estimated by participants) Weight of the colliding cars (estimated by participants) Body mass index (BMI) Age Factors associated with increased risk of reduced cervical mobility: Age BMI	Cervical range of motion Neck pain (VAS 0-100) headache (VAS 0 -100)	see below	
Kasch, Denmark[29;99]	Prospective trial from emergency care unit. 1 year follow-up.	n = 141 (48 % ♂) 9 lost for follow-up	Neck pain 85 % Headache 82 % Arm or shoulder pain 53 % Low back pain	Cervical range of motion (CROM) Pain intensity (VAS 0-100) Non-painful (0-15) complaints Neck muscle strength and endurance (workload) Compensation claim Factors associated with increased risk of	Non-recovered = not returned to daily activity or to work Handicapped defined as: Reduced working	8 % not returned to daily activity Additionally 4 % returned to modified job function About 60 % neck pain and 50 %	Initial pain, number of non-painful complaints and workload did not predict handicap as single-factors,

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

(continued)			32 %	handicap in multivariate analysis: Reduced CROM (PPV = 40 %, NPV = 98 %)	capacity, lost job, in job training or received/ applied for disability pension.	headache after 1 year (read from figure)	but could increase accuracy in combination with CROM.
Kyhlbäck, Sweden [154]	Prospective clinical trial. Orthopaedic clinic. 1 year follow-up.	n = 83 (34 % ♂) 15 lost for follow-up	11 grade 1 71 grade2 1 grade 3	Self-efficacy scale (confidence in activity despites pain) Age Gender WAD grade Factors associated with higher persistent pain or pain disability: Lower self-efficacy Higher age Male gender	Pain disability index (0-70) Pain intensity (VAS 0 -100)	10 % pain-free 16 % VAS score <11 at 1-year follow-up	
Mayou & Bryant, England [113]	Prospective clinical trial. Consecutive inclusion from emergency department. 3 year follow-up.	n = 278 (39 % ♂) 21 lost for follow-up after 1 year 84 lost for follow-up after 3 years	not provided	Gender Prior emotional problems Negative emotion Perceived threat Blame Initial emotional distress Claiming compensation at 3 months Factors associated with poor psychological outcome: Initial emotional distress Psychological vulnerability Perceived threat Factors associated with poor physical outcome: Claiming compensation at 3 months	Psychological consequences Physical outcome (pain 6-point rating scale) Social outcome	11 % limited daily activities at 1-year follow-up	Analyses do not seem to include baseline pain intensity.
Mayou & Bryant, England [90]	Prospective clinical trial. Emergency department. 1 year follow-up.	n = 63 (43 % ♂)) Included at a mean of 25 days after injury 6 lost for follow-up	Neck pain 100% Headache 13 % Low back pain 18 % Acute stress disorder 35 %	Age Gender Crash factors Eysenck Personality Inventory Beck Depression Scale Spielberger Anxiety Scale Mental-state interview Medical symptoms Litigation	Neck symptoms Poor social adjustment	37 % neck pain 40 % significant psychological symptoms 15 % difficulties with housework 25 % poor global social outcome All returned to work	Psychiatric and pre-existing psychological factors were associated with mental state at 1 year. Not described if

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

(continued)				Factors associated with persistent neck pain: Neck pain immediately after accident Being female passenger			definition of persistent symptoms was based on standard outcome measures.
Miettinen, Finland [95;155]	Participants included from insurance companies. 3 year follow-up.	n = 312 contacted n = 201 answered 1st questionnaire 19 lost for follow-up after 1-year 57 lost for follow-up after 3 years	WAD grade: 0: 1.5 % (n = 3) 1: 47.5 % 2: 39.4 % 3: 11.1 4: 0.5 % (n = 1)	Condition of health before the accident Pain before accident Depression Psychic stress (GHQ) Subjective opinion of work ability Neck disability Factors associated with increased risk of impaired health: Higher neck disability Higher neck pain Low back pain after injury Depression Psychic stress Not believing to be capable of work after 2 years In multivariate analysis: only neck disability significantly associated	Impairment of health (not defined)	After 1 year: 31 % recovered 8.5 % significantly impaired health After 3 years: About 10 % significantly impaired health 3 % sick leave > 3 month less than 2% sick leave > 6 months	Grading of injury based on medical certificate claim report Insurance companies received notice of 508 traffic accident related neck injuries while a total of 1999 rear-end collisions were registered the same year.
Miles, England[#106]	Prospective clinical trial. Emergency care unit. 2 years follow-up.	n = 73 Number lost for follow-up unclear.		Sociodemographic Crash Radiological Factors associated with persistent symptoms. From [69]: Degenerative changes associated with persistent symptoms and neurological signs	Symptoms Neurological signs		
Minton, England [107]	Prospective clinical trial. Emergency department. 1 year follow-up.	n = 174 (37 % ♂) n = 96 baseline “pure whiplash” n= 134 “pure whiplash” at 1 year		Vehicle damage n = 79 (examination of vehicle by engineers) Gender Type of headrest Distance head to headrest Seating position Height + weight ¨	Overall disability (0-9) based on >20 items regarding activity	Not provided	A number of subjects are in “in and out” of the cohort during the trial. The definition of

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

(continued)				Factors associated with increased risk of disability: Female gender (only significant after 3 months) Increased age in females			disability was not based on standard outcome measures.
Nederhand, the Netherlands [156]	Prospective clinical trial. Emergency department. 6 months follow-up.	n = 100 (31 % ♂) 8 lost for follow-up	Not provided	Prognostic factors not evaluated	Neck disability index recovered (0-4) mild (5-14) moderate (15-24) severe 25-34 disabled >34	47 % recovered, 23 % moderate , 11 % severe or total disabled after 6 months	
Norris & Watt, England [23]	Prospective clinical trial. Emergency department. 6 months follow-up.	n = 61 ("approximately" 50 % ♂) No information of follow-up rate	Neck pain 100 % 27 group 1 24 group 2 10 group 3 (groups almost defined as WAD grades)	Radiographic findings Crash factors (self-reported) Symptom group Litigation Factors associated with poor outcome: Group 3 compared to 1 (only time off work tested for significance)	Time off work Residual neck pain Complete recovery	34 % completely recovered	No data regarding symptom severity or frequencies of disability. Not described if definition of recovery was based on standard outcome measures.
Obelieniene, Lithuania [98]	Prospective trial based on the Traffic Police records. 1 year follow-up.	n = 210 from 277 potential subjects (86 % ♂) 10 lost for follow-up n = 210 age and gender matched controls 17 lost for follow-up	47 % pain shortly after accident Neck pain 10 % Neck pain + headache 18 % Headache 19 %	Not relevant since no cases of chronicity were observed	Neck pain and headache compared to control group	No accident induced neck pan or headache after 20 days post injury The intensity and frequency of pain did not exceed what was reported by the control group	Low frequency of initial pain.

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Olsson, Sweden [97]	Prospective clinical trial from emergency department. 1 year follow-up.	n = 130 (38 % ♂) 7 lost for follow-up	6 grade 1 123 grade 2 1 grade 3	Cognitive, emotional and behavioural aspects of pain measured by West Haven-Multi-dimensional Pain Inventory (MPI) Decreased risk of persistent pain for "adaptive copers" Highest risk for frequent pain in the "dysfunctional" cluster. 6 items of MPI predicted 96 % of non-recovered and 77 % of recovered.	Residual pain which the participant relate to the accident Frequency (5-point NRS) and intensity (VAS 0-10) of pain.	79 % persistent pain. 14 % symptom free 9 persons did not know whether symptoms were related to the accident	Adjusting for age, gender and severity of injury lowered the discriminating ability of MPI Not described if definition of recovery was based on standard outcome measures.
Partheni, Greece [28]	Prospective clinical trial. Emergency department. 6 months follow-up.	n = 180 (48 % ♂) No loss for follow-up.	Neck pain 100 % Headache 48 % Dizziness 14 % Arm pain 11 % Shoulder pain 51 %	Not relevant since persistent symptoms almost non-existing	Prevalence of symptoms	Symptoms resolved within 4 weeks in 91 % 2/180 neck pain at 6 months Persistent symptoms were mild (not defined)	Stated that grade III WAD was excluded, but neurological deficits reported in cohort.
Pearce, England[157]	Prospective trial. Consecutive enrolment of patients referred for medico-legal assessment. No follow-up time provided.	n = 80 29 ♂ examination 8 -52 months after injury No information of subjects lost for follow-up	WAD grade 1+2 Neck pain 100 % Headache 60 %	No analyses of predictive factors	Headache duration	15 % constant headache after 3 weeks	Only described one contact with participants, a minimum of 8 months after injury.
Pennie & Agamber, England [78]	Prospective clinical trial. Emergenxy department. 5 months follow-up.	n = 151 ? ♂ 7 lost for follow-up		Litigation (compensation claimed in 81 %) No significant difference on recovery between claimants and non-claimant.		14 % symptoms at follow-up	Inadequate description of outcome.

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Pettersson, Sweden [91]	Prospective clinical trial. Hospital setting. 2 years follow-up.	n = 40 (55 % ♂) 1 lost to follow. Control group n = 80 age and gender matched.	Physical symptoms not provided.	Temperament and Character Inventory No association with recovery	3 groups: 1: Recovered 2: Mild intermittent symptoms 3: Severe daily pain and still on sick leave.	26/ 39 = 67 % grp 1 8/ 39 grp 2 5/ 39 = 13 % grp 3	No described if definition of recovery was based on standard outcome measures.
Radanov [93] Sturzenegger [15], Switzerland	Prospective clinical trial. Recruitment from primary care (a) and an insurance company (b). 2 years follow-up.	n = 137 (a) (42 % ♂) 20 lost for follow-up. n= 16 (b) (75 % ♂)	Neck pain 92 % Headache 57 % Fatigue 56 % Shoulder pain 49 % Anxiety 44 % Back pain 39 % Dizziness 15 % Increased fatigability 56 % Forgetfulness 15 %	Age Gender Vocation Crash factors (self reported) Anxiety Pre-traumatic pain Intensity of initial pain Radiographic findings Psychosocial stress Psychological scales Cognitive variables Factors associated with with poor recovery: Older age Rotated/inclined head position Concern for illness Greater variety of symptoms Pre-traumatic headache More intense initial pain Degenerative changes Lower attentional functioning	Recovered = no symptoms Symptomatic, non-disabled = symptoms but working Symptomatic, disabled = not working or working at reduced level due to injury	24 % symptomatic after 1year 18 % symptomatic after 2 years 4 % disabled	Not described if definition of recovery was based on standard outcome measures.
Richter, Germany [35]	Prospective clinical trial. Inclusion from trauma centre. 6 months follow-up.	n = 43 (51 % ♂) ½- 23 hours after injury 11 lost for follow-up	Pain 81 % Neck pain 49 % Neck stiffness 42 % Vertigo 18 % Visual disturbances 5%	Age Gender Collision type Position in vehicle Airbag and restraint Change in vehicle velocity Pre-existing disease Initial symptoms Tenderness/ pain on palpation Radiological findings	Duration of symptoms (days retrospectively reported) cut-point long > 7 days. Severity of symptoms (VAS 0-10). Cut-point severe >4.5.	19 % impairment during work and leisure. None sick listed at 6 months follow-up.	Predictive factors determined by decision tree analysis. Predictive values not provided.

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

(continued)				Neurological findings Treatment prescribed Psychological assessment Factors associated with increased risk for severe pain and long duration: psychological assessment (SF-36, pain control, everyday life quality)			
Ryan, Australia [108]	Prospective clinical trial. Inclusion from general practitioners and physiotherapists clinics. 6 months follow-up.	n = 32 (41 % ♂) 3 lost for follow-up	Not provided	Gender Impact direction Head position Velocity change Deformation (vehicle examined for deformation and crash site inspected) Factors associated with increased risk of non-recovery: Unaware of the coming collision	Recovered (= no symptoms)	34 % recovered	Not consecutive inclusion (subjects volunteered) Not described if definition of recovery was based on standard outcome measures.
Satoh, Japan [109]	Prospective cohort trial. Data obtained from interviews conducted by insurance personnel. 6 months follow-up.	n = 6167 (62 % ♂)	Not provided	Gender Age Crash factors Occupation Factors associated with increased risk for prolonged treatment: Female gender Higher age Self-employed Immediate debut of symptoms Remained in vehicle after collision	Duration of treatment at hospital	11 % received treatment at 6 months	Reasons / indications for continued treatment not described
Scott, England [102]	Prospective clinical trial. Recruitment via emergency department. 3 months follow-up.	n = 25 (64 % ♂) None lost for follow-up.	100 % neck pain due to inclusion criteria	Serum creatine kinase Not associated with outcome	Neck pain Sleeping disturbances Sick leave	15/25 = 60 % neck pain, 8/ 20 = 40 % on sick leave after 3 months	Elevated serum creatine kinase observed in only 2 participants. Assessment of outcome measures not described

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Soderlund, Sweden [158]	Prospective clinical trial. Recruitment via an orthopaedic clinic 1 year follow-up.	n = 59 (41 % ♂) 6 lost for follow-up.	Grade 1: 14 % Grade 2: 83 % Grade 3: 3 %	Coping strategy questionnaire Prognostic value not tested	Pain disability index (0- 70)	Not provided	
Sterling, Australia [55;96]	Prospective clinical trial. Recruitment via emergency department, primary care practice and public advertisement. 6 months follow-up.	n = 80 (30 % ♂) 4 lost for follow-up.	Grade 2 +3 Neck pain 100 % Headache 59 % Shoulder pain 32 % Arm pain 24 % Lumbar pain 38 % Dizziness 15 %	Emotional distress (GHQ) Kinesphobia (TSK) Post Traumatic Stress (IES) General health (SF-36) Tests of hypersensitivity Factors associated with increased risk of non-recovery: Higher GHQ (anxiety/insomnia, social dysfunction, somatic symptoms) Higher TSK score Higher IES Lower SF-36 Generalised hypersensitivity early after injury	Recovered (NDI <8) Mild pain & disability (NDI 10-28) Moderate/severe pain & disability (NDI >30)	Neck Disability Index (NDI, 0-100) 38 % recovered and 22 % moderate/severe pain and disability at 6 months follow-up 97 % returned to work at 3 months follow-up	Concludes that the overlap of all psychological distress scores so large that scores were not useful as predictors. Close correlation between pain/disability and psychological distress
Sterner, Sweden [92].	Prospective trial. Data collection from questionnaires. Recruitment from emergency department and general practitioners. 16 months follow-up.	n = 356 (51 % ♂) 60 lost for follow-up (68 % ♂)	not provided	Age Gender Education Clinical signs (WAD grade) Collision type Prior neck complaints, back pain or headache Factors associated with persistent disability: Female gender Lower education Clinical signs in addition to symptoms Prior neck complaints	Disability 1: none or minor 2: complaints affecting activity but no sick leave 3: change of work task 4: sick leave due to injury	32 % disability>1 2 % on sick leave 2 % changed work task	

Table 3. Overview of prospective trials concerning prognosis after whiplash injuries.

Author, country	Setting and design	Study sample	Summary of baseline symptoms	Evaluated risk factors + results	Outcome measures	Prognosis	Comments
Suissa, Canada [110]	Prospective cohort trial. Recruitment insurance company. Data from claim reports. Cohort only including subjects who received compensation. 5 years follow-up.	n = 2627 (34 % ♂)	9 % muscle pain 12 % neck pain on palpation 12 % headache 2 % dizziness/ vertigo 1 % visual disturbances	Muscle pain + stiffness Decreased mobility Pain on palpation Radiating symptoms Loss of consciousness Anxiety or insomnia Factors associated with prolonged duration of compensation: Radiating symptoms to arms or hands Slightly increased risk with neck pain on palpation, muscle pain, pain radiating to shoulders.	Time from injury to last date of compensation.	12 % not recovered at 6 months	Data on signs and symptoms from physician, emergency room or the subject (8 %). Baseline symptoms very low frequencies – non systematic registration suspected. No standardisation of registrations described.
Warren & Warren, England#	From emergency department or medicolegal assessment. 3 years follow-up.	n = 1030 Number lost for follow-up unclear		Sociodemographic Physical Crash Treatment Factors associated with poor outcome: Age Early onset of neck pain Radiating pain in upper limbs Driving occupation	Symptoms Time off work		

♂= male, ♀= female
AIS: Abbreviated Injury Scale. 1= minor injury level.
GHQ = general health questionnaire
Grade 1, 2, 3: WAD grade according to the Quebec Task Force classification
IES = Impact of Event Scale
NRS = numeric rating scale
PPV: positive predictive value, NPV: negative predictive value
RR risk ration, [ ] 95 % confidence interval
information from review [69]

Table 4. Overview of trials concerning oculomotor test in WAD

Author	Design	Study sample	a. Method of SPEM registration b. Method of signal analyses	a. Outcome measures b. Results	Comments
Burke [38]	Prospective cohort study. Recruitment from emergency unit. No blinding regarding symptoms described. 6 weeks follow-up.	WAD: n = 39 17 ♂ grade 1:16 grade 2: 22 grade 3: 1 Max 7 days after injury.	a. OK test by hand-held optokinetic drum. No further description. b. ND.	a. ND b. 4/ 39 abnormal SP (1in group 1 + 3 in group 2). Resolution within 1-3 mo	No tracking test, tests and analyses not described. Most common abnormality: Disturbed accommodation and/ or convergence. Abnormal not defined.
Chester [125]	Cohort study. Patients referred for chronic pain management.	WAD: n = 48 18 ♂ 7 mo – 7 years after injury. n = 28 had ENG test. No control group.	a. Tympanometric Fistula Test, platform fistula test, rotation chair, electronystagmographic tests. References to test protocols.	a. ND b. 2/28 abnormal oculomotor screening test 16/28 nystagmus suggestive of benign paroxymal positional nystagmus 12/48 probably perilymph fistula,	Oculomotor tests not described. No data presented.
Fischer [133]	Controlled clinical trial. Recruitment from general practitioners. Blinding not described.	WAD: n = 32 15 ♂ 1- 26 mo after rear-end injury. Symptoms not described. Non-contact injury, not rear-end: n = 7 Control: n = 75	a. Smooth pursuit tracking: EOG recordings. Sinusoidal signal, 0.33 Hz max. 20°/ s. b. ND	a. ND b. no data provided. States that smooth pursuit eye movements within normal range. 7/32 hyperactive vestibule-ocular reflex and hyperventilation syndrome.	Saccade velocity, vestibular function, COR and OKN response also tested. Abnormal COR in one patient. Altered caloric response one patient. Other tests normal. Inadequate description tests and obtained data. Exclusion if use of relevant drug (not specified) Handling of blinks not described.
Gimse [117]	Controlled clinical trial. Subjects referred for neuropsychological examination. Blinding not described.	WAD: n = 26 7 ♂ 1 – 15 years after injury All had visual problems and vertigo. Control: n = 26 age, gender, education, occupation matched.	a. Smooth pursuit tracking: incl. SPNT. EOG. Sinusoidal signal, max. 20°/ s visual angle 40°. b. ND	a. Mean velocity gain (eye velocity/ target velocity) b. Neutral position WAD/ controls gain = 0.76/ 0.88 Rotated positions WAD / controls gain = 0.65 / 0.85 (from figure) SPNT-diff WAD/ controls: diff = 0.1/ 0.02 Pathologic SPNT defined as SPNT-diff > (control mean value + 3 SD). Pathologic test in 24 /26	Selected study sample. Group differences statistical significant. Effect of head position significant. Caloric test, test of occipital lobe function, auditory brain stem response and saccade test also performed: No group differences. Handling of blinks not described.

Table 4. Overview of trials concerning oculomotor test in WAD

(continued)				patients.	No sensitivity/ specificity reported Not mentioned whether medication was stopped prior to examination
Heikkilä [132]	Cohort included by review of patients admitted to emergency unit.	WAD: n = 26 13 ♂ 1 - 2 years after injury WAD grade 2 +3 Control: n = 25 healthy subjects.	a. Smooth pursuit tracking:: EOG. Constant speed 20°/ s + 30°/ s b. Computerised. Ref. to Bergenius.	a. Gain (eye velocity/ target velocity) Number of superimposed saccades. b. 16/26 pathologic smooth pursuits (pathologic not defined). Gain WAD 20°/ s: 0.66 Gain WAD 30°/ s: 0.66 No data presented from control group.	Outcome described as gain, which is not consistent with the referred method. Abnormal SP associated with decreased cervical mobility and repositioning dysfunction. Handling of blinks not described. Not mentioned whether medication was stopped prior to examination
Hildingsson [128]	Prospective controlled clinical trial. No blinding described.	WAD: n = 40 16 ♂ 1st test: ½ - 3 mo after injury. 2nd test: 8 – 28 mo after injury Symptoms not described 2 lost for follow-up Control: n = 25.	a. Smooth pursuit tracking:: EOG. Constant speed 20°/ s + 30°/ s. 60° visual angle b. reference to Bergenius.	a. Gain (eye velocity/ target velocity). Number of superimposed saccades. Normal gain defined as control group's mean +/- 2 SD. Clinical outcome not defined. b. 1st test 8/40 WAD abnormal oculomotor test. Initial symptoms did not differ between normal and abnormal oculomotor tests (registration of symptoms ND). Abnormal 1st test ⇒ 8/8 disabling symptoms. Normal 1st test ⇒ 10/ 30 disabling symptoms. 2nd test 13/ 38 WAD abnormal tests. Abnormal 2nd test ⇒ 13/13 disabling symptoms. Normal 2nd test ⇒ 5/25 disabling symptoms. 1st test: 4 normal gain but increased number of saccades. 2nd test: 3 normal gain but increased number of saccades	Gain values not provided. Outcome described as gain, which is not consistent with the referred method. Handling of blinks not described. Patients with abnormal smooth pursuits had also lowered saccade performance. 5 cases only saccade abnormalities. 1st test: 100 % NPV, 44 % PPV. (er det PVs?) 2nd test: 100 % specific, 72 % sensitive. Not mentioned whether medication was stopped prior to examination
Hildingsson [130]	Controlled clinical trial. Chronic patients consecutively enrolled when referred to the department. No blinding described.	WAD: n = 20 7 ♂ > 1 year since injury. All had neck pain + stiffness and headache. 18/20 had vertigo/ dizziness.	a. Smooth pursuit tracking:: EOG. Constant speed 20°/ s + 30°/ s. 60° visual angle b. reference to Bergenius.	a. Gain (eye velocity/ target velocity) Number of superimposed saccades. Normal gain defined as control group's mean +/- 2 SD. b. Asymptomatic had test results as recovered. 14/ 20 WAD reduced velocity gain. 16/ 20 increased number of superimposed saccades.	Patient group referred due to severity of symptoms. Outcome described as gain, which is not consistent with the referred method. Voluntary saccade test performed in addition to SP. Prolonged latency and reduced peak velocity in the WAD

Table 4. Overview of trials concerning oculomotor test in WAD

(continued)		Asymptomatic group exposed to whiplash injury min 6 mo previous: n = 19 10 ♂ Control: n = 25		18/20 WAD abnormal results of either SP and/or saccade tests. No sensitivities / specificities	group. Stated that 4 patients had pronounced disturbances and 14 moderate (not defined). Handling of blinks not described. Not mentioned whether medication was stopped prior to examination
Hinoki [34]	Controlled clinical trial.	WAD: n = 19 Unclear whether more cohorts were assessed. No further description of the cohort. Controls: n = 30	a. OKN test and smooth pursuit tracking during pulse stimulation of the neck + with the neck fixed in a cervical collar. Test procedures not described. b. ND	a. ND b. No abnormal tests in controls. 13/19 lowered test performance on one or more test with pulse stimulation of the neck + improved function with neck collar.	Test procedures not described. No data presented. Abnormal not defined. Not mentioned whether medication was stopped prior to examination
Mallison [32;159]	Retrospective cohort study. Participants referred for assessment of dizziness	WAD n = 19 Minor head injury n = 17 15 ♂ Minimum 2 years after accident. All had dizziness	a. Standard electronystagmography. Not further described. b. ND	a. ND b. 0/19 WAD patients had ENG abnormalities 3/ 15 with minor brain injury had ENG abnormalities	Tests not described, abnormal not defined. Not mentioned whether medication was stopped prior to examination
Mosiman [160]	Controlled clinical trial. Setting not described.	WAD: n = 11 symptomatic, all had dizziness 3 ♂ 1 mo - 6 years after injury control: n = 10 recovered 6 ♂ 1 mo - 7 years after injury n = 16 unexposed, healthy subjects, age matched. 4 ♂	a. Cortical control of saccades. Antisaccade test + memory guided saccade test. Recordings performed with infrared reflection	a. mean saccade latency + median percentage error in amplitude b. WAD decreased performance on for both tests. Normal performance in reflexive saccades.	All medication stopped 24 h before testing. Author concludes that the findings were suggestive of frontal dysfunction.

Table 4. Overview of trials concerning oculomotor test in WAD

Author	Design	Study sample	a. Method of SPEM registration b. Method of signal analyses	a. Outcome measures b. Results	Comments
Oosterveld [138]	Cohort study, hospital setting. Not described if inclusion consecutive.	WAD: n = 262 105 ♂ ½- 5 years after injury 85 % had dizziness No control group	a. Vestibular + visual tracking tests. ND of method. b. ND	a. ND b. 113/ 261 had disturbances in visual pursuit movements (disturbance not defined). No data presented.	No description of method or basis for diagnosis of disturbed SP. Also findings of abnormal vestibular tests, but description of test procedures and results were not provided. Not mentioned whether medication was stopped prior to examination.
Prushansky [139]	Controlled clinical trial. Setting unclear. No blinding described.	WAD: n = 26 10 ♂ 6 -84 mo after injury WAD grade 2+ 3 Control: n = 23 7 ♂	a. Smooth pursuit tracking incl. SPNT. Name and supplier of equipment provided. Method ND. b. Computerised. Parameters not described.	a. Velocity gain (eye velocity/ target velocity). b. Lowered gain in WAD. Gain neutral position WAD/ control: 0.79 / 0.86. No difference in SPNT-diff: SPNT-diff WAD/ control 0.026/ 0.032	No information on test method or signal analysis. Not described how eye velocity was determined. Not mentioned whether medication was stopped prior to examination.
Tjell [33]	Controlled clinical trial. Hospital setting, patients referred for otoneurophysiologic examination. Blinded otoneurological interpretation.	WAD: n = 75 (25 not dizzy, 50 dizzy) WAD grade 2+ 3 27 ♂ 6 – 195 mo after injury. Control: n = 20 central vertigo n = 20 Meniere's disease n = 30 healthy subjects.	a. Smooth pursuit tracking incl. SPNT. EOG. Sinusoidal signal, visual angle 40°, max velocity 20°/s. b. Manual interpretation.	a. Mean velocity gain (eye velocity/ target velocity). Eye velocity calculated by subtracting the corrective saccades from the total excursion of the gaze. Abnormal SPNT-diff defined as healthy control group's mean + 2 SD. b. <u>Gain neutral</u> WAD dizzy 0.83 WAD not dizzy 0.85 Central vertigo 0.59 Meniere 0.83 Healthy 0.87 <u>SPNT-diff</u> WAD dizzy 0.14 WAD not dizzy 0.10 Central vertigo 0.00 Meniere 0.02 Healthy 0.02 Sensitivity of SPNT test: WAD with / without dizziness 90 % / 56 %, specificity 91 %.	SPNT-diff significantly higher in both WAD groups than in controls. Significantly higher SPNT-diff with than without dizziness. Not mentioned whether medication was stopped prior to examination.
Tjell [118]	Controlled clinical trial. WAD cohort selected by drawing lots from	WAD: n = 160 61 ♂ 6- 328 (median 15) months after injury	a. Smooth pursuit tracking incl. SPNT. EOG. Gaze-angle 40°, sinusoidal signal, max velocity 20°/sec.	a. SPNT-diff. Gain determined by subtracting the corrective saccades from the total excursion of the gaze. Pathological results defined as SPNT-diff> 99.5	Not mentioned whether medication was stopped prior to examination

Table 4. Overview of trials concerning oculomotor test in WAD

(continued)	patients at Dep. of Rehabilitation Medicine. Blinded clinical examinations and analyses of SP recordings.	WAD grade 2 + 3 Control: Cervical spondylosis (n= 52) Cervical dizziness (n = 46) Fibromyalgia (n =24) Healthy (n = 50)	b. manual interpretation	percentile of results of healthy controls. b. Neutral gain WAD/ healthy: 0.86/ 0.87 SPNT-diff WAD/healthy 0.11/0.02 Sensitivity: 72 %, specificity 92 % PPV 92 % NPV 71 % Odds ratio 28.6	
Toglia [161]	Cohort study. Patients at Neurosensory Laboratory.	WAD: n = 309 50 % ♂ All had dizziness as main complaint. No control group.	a. Vestibular tests. Inadequate descriptions b. ND	a. ND b. 29 % latent nystagmus 57 % abnormal caloric response 51 % abnormal rotatory test	Test procedures inadequately described. Abnormal not defined in relation to a control group
Wenngren [131]	Prospective clinical trial. Cohort admitted to hospital department within 8 hours of accident. 2 year follow-up.	WAD: n= 38 WAD grade 2 + 3 20 ♂ within 2 mo after the injury 4 lost to follow-up. Stated that results compared to control group, but control group not described.	a. Smooth pursuit tracking: EOG. Constant speed 20°/ s + 30°/ s. b. ND	a. Clinical outcome: *Group 1* no symptoms (n = 21) *Group 2* moderate/ intermittent symptoms (n = 8) *Group 3* severe daily symptoms and sick leave (n = 5) EOG outcome: Gain Number of superimposed saccades. b. 1st test: 5/ 38 pathologic SP 2nd test: 3/34 pathologic test (1 had previously a normal test) 2-year follow-up: 16/34 Group 1. Statistical lower gain in Group 3. 2/5 with lowered gain had increased number of superimposed saccades.	Data for prediction of persistent symptoms by 1st test not presented. Stated that initial test results did not reveal prognostic clinical signs for the whole group. Gain not defined. Not mentioned whether medication was stopped prior to examination

ND = not described
OK = optokinetic, OKN = optokinetic nystagmus
Grade 1, 2, 3 = Grading as suggested by the Quebec Task Force.
NPV = negative predictive value, PPV = positive predictive value.
SD = standard deviation(s)
COR = cervico-ocular reflex
EOG = electrooculography.
SPNT = smooth pursuit neck torsion test
SPNT-diff: Difference between gain obtained in neutral seated position and the mean of gains obtained in rotated neck positions.

Table 5. Scheme for allocation of participants into the intervention trial and the information trial

Score	0	1	2	3	4
A. Total cervical range of motion (0-360 degrees)	> 280		261-280		< 261
B. Pain intensity (box-scale 0-10)	0- 2	3-4			> 4
C. Number of non-painful complaints		3-5		6-11	
D. Gender	Male		Female		

Allocation score (A+B+C+D) $\geq 4 \Rightarrow$ inclusion in the intervention trial.

Allocation score (A+B+C+D) $< 4 \Rightarrow$ inclusion in the observation trial.

Table 6. Baseline characteristics of participants in the intervention trial in relation to follow-up status after one year

Characteristic Follow-up status	**Neck Collar** **n = 156**	**"Act-as-Usual"** **n = 153**	**Active Mobilisation** **n = 149**	**All participants** **n = 458**
Gender (% male of follow-up status):				
Included	29	27	29	28
Complete follow-up	28	26	25	26
Interview after 1 year	27	37	40	35
Lost for follow-up	50	20	40	29
Age, years median (IQR)				
Included				
Complete follow-up	33 (26-42)	34 (26-41)	33 (25-45)	34 (26-43)
Interview after 1 year	34 (28-46)	38 (32-40)	34 (32-37)	35 (28-46)
Lost for follow-up	33 (24-36)	33 (28-37)	30 (25-34)	32 (24-38)
	28 (22-33)	27 (22-35)	35 (20-37)	28 (22-35)
Occupation (% of participants within each follow-up status)				
Included:				
Self-employed	5	5	5	5
White-collar	38	34	42	38
Blue-collar	27	28	17	24
Student	18	18	27	21
Out of work force	12	15	9	12
Complete follow-up:				
Self-employed	4	6	6	5
White-collar	41	42	47	43
Blue-collar	26	27	14	22
Student	16	14	24	19
Out of work force	13	11	9	11
Interview after 1 year:				
Self-employed	3	3	3	3
White-collar	34	34	34	34
Blue-collar	34	37	23	31
Student	16	16	31	21
Out of work force	13	10	9	11
Lost for follow-up:				
Self-employed	25	8	0	11
White-collar	25	8	0	10
Blue-collar	0	20	20	16
Student	50	36	40	39
Out of work force	0	28	40	24

Table 6. (continued)

Characteristic Follow-up status	**Neck Collar**	**"Act-as-Usual"**	**Active Mobilisation**	**All participants**
Collision direction (% of participants within each follow-up status)				
Included:				
Rear-end, direct	56	48	61	55
Frontal, direct	14	18	18	17
Rear-end, oblique	17	17	14	16
Frontal, oblique	13	17	7	12
Complete follow-up:				
Rear-end, direct	58	53	60	58
Frontal, direct	13	14	18	15
Rear-end, oblique	17	17	14	16
Frontal, oblique	12	16	8	11
Interview after one year:				
Rear-end, direct	52	47	63	54
Frontal, direct	24	24	20	23
Rear-end, oblique	18	8	11	12
Frontal, oblique	6	21	6	11
Lost for follow-up:				
Rear-end, direct	50	28	60	37
Frontal, direct	0	28	20	21
Rear-end, oblique	0	32	0	21
Frontal, oblique	50	12	20	21
Sick listed at baseline (% of participants within each follow-up status)				
Included	53	52	54	53
Complete follow-up	58	56	51	53
Interview after 1 year	50	42	66	55
Lost for follow-up	50	48	60	50
Neck pain 0-10, median (IQR)				
Included	5 (4-6)	5 (4-7)	5 (4-7)	5 (4-6)
Complete follow-up	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)
Interview after 1 year	5 (4-6)	6 (4-7)	6 (3-7)	6 (4-7)
Lost for follow-up	5 (2-8)	5 (4-7)	7 (4-7)	5 (4-7)
Headache 0-10, median (IQR)				
Included	5 (3-7)	5 (4-7)	4 (3-6)	5 (3-7)
Complete follow-up	4 (3-6)	5 (3-7)	5 (3-7)	5 (3-7)
Interview after 1year	6 (4-8)	6 (4-7)	6 (4-8)	6 (4-8)
Lost for follow-up	5 (1-9	6 (4-7)	5 (3-7)	5 (4-7)

Table 6. (continued)

Characteristic Follow-up status	**Neck Collar**	**"Act-as-Usual"**	**Active Mobilisation**	**All participants**
Total cervical range of motion, degrees median (IQR)				
Included	252 (197- 294)	248 (190- 298)	244 (198- 286)	248 (197- 294)
Complete follow-up	254 (209- 298)	248 (204- 296)	259 (202- 299)	254 (208- 297)
Interview after 1year	242 (161- 280)	270 (186- 296)	226 (206- 277)	240 (182- 286)
Lost for follow-up	292 (182- 321)	236 (168- 304)	176 (117- 284)	234 (158- 304)
Number of non-painful complaints, 0-11 median (IQR)				
Included	4 (3-6)	4 (3-6)	4 (3-6)	4 (3-6)
Complete follow-up	4 (2-6)	4 (2-6)	4 (3-6)	4 (3-6)
Interview after 1 year	5 (4-6)	4 (3-6)	5 (3-7)	5 (3-6)
Lost for follow-up	3 (3-3)	4 (2-6)	7 (3-9)	4 (3-6)
Physical health summary SF-36 median (IQR)				
Included	55 (52- 58)	55 (50- 58)	56 (52- 58)	55 (51- 58)
Complete follow-up	55 (53- 58)	55 (49- 58)	56 (52- 57)	55 (51- 57)
Interview after 1 year	56 (52- 58)	55 (52- 58)	57 (54- 59)	56 (53- 58)
Lost for follow-up	53 (50- 57)	55 (50- 58)	50 (42- 55)	55 (50- 58)
Impact of Event, median (IQR)				
Included	12 (5- 24)	12 (5- 22)	10 (3- 20)	11 (4-22)
Complete follow-up	10 (5- 22)	11 (4- 19)	11 (3- 19)	11 (4- 20)
Interview after 1 year	12 (3- 24)	13 (5- 22)	9 (4- 23)	10 (4- 23)
Lost for follow-up	18 (9-26)	20 (8- 31)	5 (1- 17)	18 (6- 26)

IQR = inter quartile range

Table 7. Association between time since accident and smooth pursuit eye movements

	Rho
Session 1	
Neutral	0.09
Right	0.06
Left	-0.2
Extension	0.2
Session 2	
Neutral	0.2
Right	0.1
Left	0.01
Extension	0.1

The estimated correlation coefficients (rho) for the association between SPI-values in each of eight recordings and time passed since accident (n= 40).

Table 8. Smooth pursuit index in patients with "severe" and "non-severe" pain and in patients with and without dizziness

Session 1	**"Severe pain"**	**"Non-severe pain"**
Neutral	0.91 (0.88 - 0.99)	0.97 (0.88 – 0.99)
Right	0.94 (0.89 - 0.99)	0.94 (0.85 – 0.99)
Left	0.95 (0.85 - 0.98)	0.95 (0.89 - 1)
Extension	0.89 (0.84 – 1)	0.98 (0.88 - 1)
SPNT-diff	-0.002 (-0.03 - 0.02)	0.02 (-0.01 - 0.04)
Session 2		
Neutral	0.95 (0.84 - 1)	1.0 (0.93 – 1)
Right	0.96 (0.89 – 0.98)	0.96 (0.91 - 1)
Left	0.96 (0.88 – 0.97)	0.95 (0.88 - 1)
Extension	0.95 (0.88 – 0.98)	0.96 (0.90 - 1)
SPNT-diff	0 (-0.02 - 0.03)	0 (-0.01 - 0.04)

Session 1	**"Dizzy"**	**"Non-dizzy"**
Neutral	0.95 (0.91 –1.0)	0.92 (0.88 – 0.99)
Right	0.94 (0.87 –1.0)	0.94 (0.86 –0.99)
Left	0.98 (0.88 – 0.99)	0.94 (0.84 – 0.96)
Extension	0.95 (0.84 – 1.0)	0.91 (0.85 – 0-99)
SPNT-diff	0 (-0.02 - 0.03)	0 (-0.02 - 0.03)
Session 2		
Neutral	0.95 (0.72 –1.0)	0.97 (0.92 –1.0)
Right	0.96 (0.84 –1.0)	0.96 (0.91 –1.0)
Left	0.96 (0.82 –1.0)	0.96 (0.89 –1.0)
Extension	0.95 (0.74 –1.0)	0.95 (0.90 –1.0)
SPNT-diff	0 (-0.04 - 0.02)	0 (0 - 0.02)

"Severe pain" defined as: Severe self reported pain regularly or daily

"Dizzy" defined as: Severe self reported dizziness at least regularly

Table 9. Area under the curve for receiver operant curves analysing five different saccade definitions

Saccade definition Outcome	**AUC (95 % confidence interval)**
Saccade definition 1)	
Neutral	0.56 (0.44 - 0.69)
Right	0.54 (0.42 - 0.66)
Left	0.60 (0.48 – 0.73)
SPNT-diff	0.63 (0.41 – 0.66)
Saccade definition 2)	
Neutral	0.56 (0.44 - 0.68)
Right	0.58 (0.46 - 0.70)
Left	0.62 (0.50 – 0.74)
SPNT-diff	0.58 (0.46 – 0.70)
Saccade definition 3)	
Neutral	0.55 (0.43 - 0.67)
Right	0.56 (0.44 - 0.68)
Left	0.64 (0.52 – 0.75)
SPNT-diff	0.62 (0.50 – 0.73)
Saccade definition 4)	
Neutral	0.51 (0.40 - 0.63)
Right	0.56 (0.44 - 0.67)
Left	0.61 (0.49 – 0.73)
SPNT-diff	0.62 (0.50 – 0.73)
Saccade definition 5)	
Neutral	0.61 (0.49 - 0.72)
Right	0.62 (0.51 - 0.74)
Left	0.60 (0.48 – 0.72)
SPNT-diff	0.50 (0.37 – 0.63)

AUC = area under the curve.
Neutral/right/left = SPI in neutral/right rotation/left rotation.

The minimum saccade velocities relative to the target velocity in the saccade definitions:
1) 120 %, **2)** 140 %, **3)** 160 %, **4)** 180 %, and **5)** 220%
The minimum saccade velocities relative to the target velocity was 200 % in the saccade definition used in the main analyse