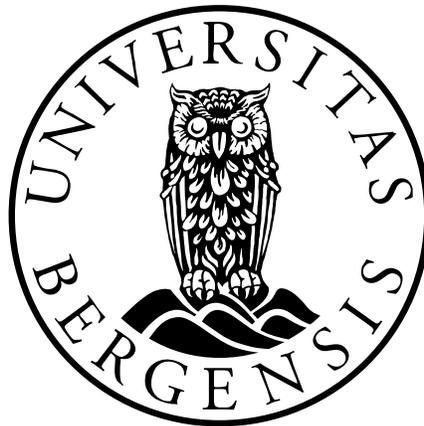


# **MRI of the alar and transverse ligaments in whiplash-associated disorders and rheumatoid arthritis**

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## Scientific environment



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## 2. Abbreviations

AADI	Anterior atlantodental interval
ACR	American College of Rheumatology
Anti-CCP	Anti-cyclic citrullinated peptide
CI	Confidence interval
CT	Computed tomography
DAS28	Disease activity score in 28 joints
ESR	Erythrocyte sedimentation rate
IES	Impact of event scale
MHAQ	Modified Health Assessment Questionnaire
MRI	Magnetic resonance imaging
NDI	Neck Disability Index
NRS-11	11-point numeric rating scale
RA	Rheumatoid arthritis
STIR	Short tau inversion recovery
TR	Repetition time
TE	Echo time
VAS	Visual analogue scale
WAD	Whiplash-associated disorders

### 3. List of publications

This thesis is based on the following papers, which will be referred to by their Roman numerals:

**I MRI of the alar and transverse ligaments in whiplash-associated disorders (WAD) grades 1-2: high-signal changes by age, gender, event and time since trauma.**

Vetti N, Kråkenes J, Eide GE, Rørvik J, Gilhus NE, Espeland A.

*Neuroradiology* 2009;51:227-35.

**II MRI of the transverse and alar ligaments in rheumatoid arthritis: feasibility and relations to atlantoaxial subluxation and disease activity.**

Vetti N, Alsing R, Kråkenes J, Rørvik J, Gilhus NE, Brun JG, Espeland A.

*Neuroradiology* 2010;52(3):215-23.

**III MRI of the alar and transverse ligaments in acute whiplash-associated disorders 1-2 – a cross-sectional controlled study.**

Vetti N, Kråkenes J, Damsgaard E, Rørvik J, Gilhus NE, Espeland A.

*Spine*, in press.

**IV Acute whiplash-associated disorders (WAD) grades 1-2: Are MRI high-signal changes of alar and transverse ligaments related to outcome?**

Vetti N, Kråkenes J, Eide GE, Rørvik J, Gilhus NE, Espeland A.

Submitted.

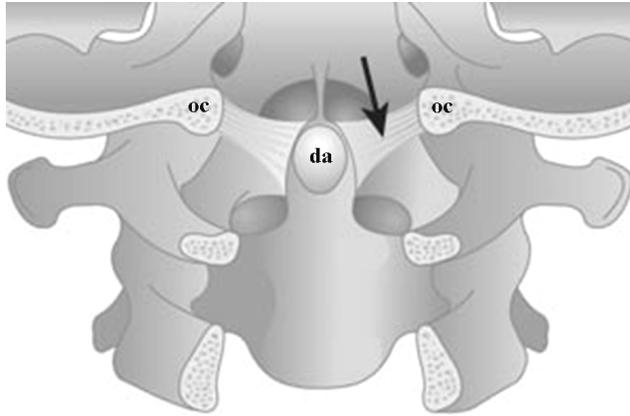
## 4. Introduction

The thesis concerns magnetic resonance imaging (MRI) of the upper neck alar and transverse ligaments in whiplash-associated disorders (WAD) and rheumatoid arthritis (RA). Non-injured, non-RA controls were also studied. In this introduction, I will present knowledge about the alar and transverse ligaments that existed prior to the writing of the thesis. The anatomical and biomechanical characteristics of the alar and transverse ligaments will be briefly outlined in the background part. I then explain the rationale for focusing on these ligament structures and summarize prior studies concerning imaging of alar and transverse ligaments. At the end of the introduction, the specific motivation for the project is presented. Studies by other authors focusing on the alar and transverse ligaments that were presented during the time it took to finish this work will be commented later in the discussion part.

### ***4.1. Background - alar and transverse ligaments***

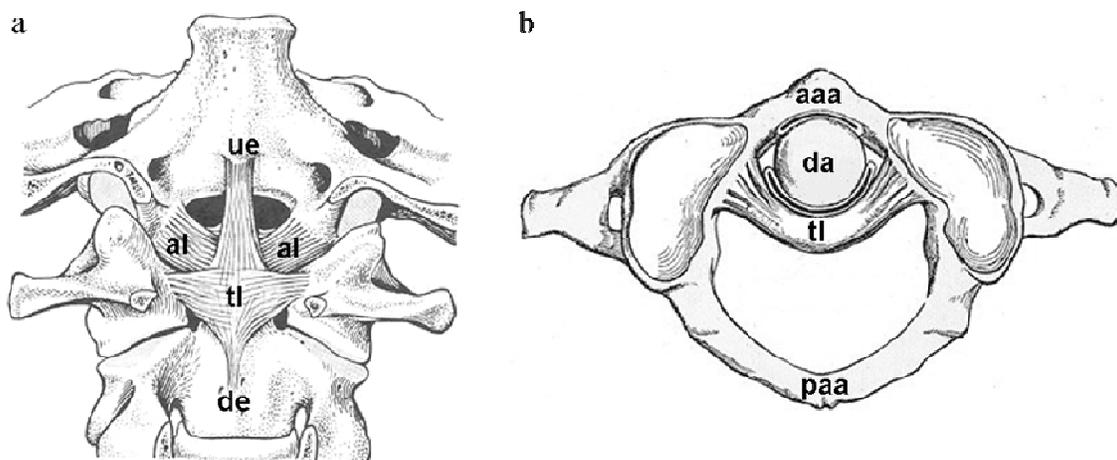
The alar and transverse ligaments are important ligament structures at the craniovertebral junction<sup>1-5</sup>. These ligaments are not available for biopsy or during surgery. They are usually not visualized on radiography, computed tomography (CT) or ultrasonography. Our knowledge about them has mainly been achieved by in vitro studies on cadavers or finite-element models. Recent years' advances in MRI technology have made MRI a potential tool for evaluating these ligaments and their role in disease manifestations at the craniovertebral junction.

The alar ligaments are paired rounded cords running from the upper posterolateral part of dens axis and inserting into the fovea on the medial side of the occipital condyles<sup>1</sup> (Figure 1). Each alar ligament has a length and diameter of about 10 mm and 5 mm respectively<sup>6-9</sup>. Alar ligaments usually pass slightly upwards and backwards on their course from the dens to the occipital condyle<sup>8</sup>, but their dimensions and orientations vary between individuals<sup>1,6,8,10</sup>.



**Figure 1.** Posterior view of the alar ligaments (transverse ligament removed), black arrow points at right alar ligament; **da** = dens axis, **oc** = occipital condyle (from Tidsskrift for Den norske legeforening 2005; 125:2939-41)

The transverse ligament is a flattened band about 20 mm long, 9 mm wide, and 3 mm thick running posterior to the dens axis and inserting into the tubercles on the medial sides of the lateral masses of atlas (Figure 2)<sup>6,8,11,12</sup>. One downward and one upward band extension stabilise the transverse ligament and together they form the cruciform ligament of atlas.



**Figure 2.** The transverse ligament (**tl**) from the posterior (a) and superior (b) view; **ue** = upward extension, **de** = downward extension, **al** = alar ligament, **aaa** = anterior atlantal arch, **da** = dens axis, **paa** = posterior atlantal arch (a from Platzer W: Color Atlas and Textbook of Human Anatomy, Vol 3: Locomotor system, Thieme, 1986; b from Gray's Anatomy, Churchill Livingstone 1995)

Histological studies have revealed compact collagen fibres to both the alar and transverse ligament structures with only a few elastic fibres found in the periphery<sup>2,5</sup>. The main function of the alar ligaments is to limit opposite neck rotation and lateral flexion at the craniovertebral junction<sup>1,2,4</sup>. The transverse ligament holds the dens against the anterior atlantal arch and prevents anterior dislocation of atlas on axis during flexion<sup>2,3,13,14</sup>. In biomechanical cadaver studies the mean strength load to failure has been reported to be between 210 newton and 370 newton for the alar ligaments and between 350 newton and 820 newton for the transverse ligament<sup>2,3,11,13</sup>.

## ***4.2. Rationale for imaging alar and transverse ligaments***

### **4.2.1. Rationale in whiplash-associated disorders (WAD)**

Whiplash injury constitutes a major health problem in many parts of the world and seems to be of increasing incidence<sup>15</sup>. In 1995 the Quebec Task Force provided a definition of the disease and introduced the whiplash-associated disorders (WAD) concept describing the clinical manifestations of whiplash injury (Table 1)<sup>16</sup>. The cause of such manifestations has been extensively debated during the last decades<sup>17,18</sup>, especially in chronic WAD, that means the continuation of symptoms or disability for 6 months or longer after the whiplash injury<sup>16</sup>. Some authors have postulated a mainly psychosocial explanation for chronic symptoms<sup>19,20</sup>. Others have focused their studies on different parts of the cervical spine intending to find a pathological morphologic correlate to such manifestations<sup>21-24</sup>. Most authors apply to a biopsychosocial explanation of the phenomenon<sup>25,26</sup>.

**Table 1. Classification of whiplash-associated disorders (WAD) according to the Quebec Task Force**

Grade	Clinical presentation
0	No complaint about the neck. No physical sign(s)
1	Neck complaint of pain, stiffness or tenderness only. No physical sign(s)
2	Neck complaint and musculoskeletal sign(s) <sup>a</sup>
3	Neck complaint and neurological sign(s) <sup>b</sup>
4	Neck complaint and fracture or dislocation

<sup>a</sup> Musculoskeletal signs include decreased range of motion and point tenderness

<sup>b</sup> Neurological signs include decreased or absent deep tendon reflexes, weakness and sensory deficits

It is well known that following severe cervical trauma, soft tissue injuries are more common than fractures<sup>27,28</sup>. Ligament structures at the craniovertebral junction have gained much attention. In cadaver studies, Dvorak et al described the importance of the alar ligaments in preventing rotational instability at the craniovertebral junction<sup>29</sup>, and they reported such instability in chronic WAD patients by using functional computed tomography (CT) examinations<sup>30-32</sup>. The histological and biomechanical properties of the alar ligaments could make these structures vulnerable for rupture during trauma especially if stretched by rotation of the head at impact<sup>1,2,5</sup>. Both alar and transverse ligament injuries have been documented in post mortem histopathological studies following fatal head / neck traumas<sup>27,33-35</sup>. In biomechanical experiments cervical spine cadaver specimens have been exposed to forces simulating whiplash traumas. The results have indicated that cervical spine soft tissue structures can be at risk of injury also following less severe trauma<sup>36-39</sup>. However, no in vitro study has been able to demonstrate alar or transverse ligament injuries at frontal, head turned rear end, or side impacts with a force below 8G<sup>40-42</sup>.

MRI is widely used for evaluation of ligaments throughout the musculoskeletal system. As normal ligaments are tough bands of connective tissue composed of densely packed collagen fibre bundles they are expected to show low signal on most MRI sequences<sup>43,44</sup>. In acute trauma, MRI high-signal intensity in ligaments is taken as a sign of injury and can be due to complete or partial disruption of fibres with intra-ligamentous haemorrhage and edema<sup>45-48</sup>. The ability to heal following acute injury varies between ligaments. Experimental and clinical studies have shown that complete rupture of the anterior cruciate ligament of the knee does not heal at all<sup>49-51</sup>. Some extra-articular ligaments like the medial collateral ligament of the knee and the anterior talofibular ligament of the ankle show excellent healing properties<sup>48,51-53</sup>. However, injured ligaments always heal with a scar which is histologically and biomechanically different from a normal ligament<sup>49,52</sup>. Persisting high-signal changes and altered morphology of ligaments have been reported in MRI follow-up studies on ankles and knees 3-36 months after injury<sup>48,53-56</sup>. Thus MRI ligament high-signal changes can be found both in the acute and the chronic phase after injury.

#### **4.2.2. Rationale in rheumatoid arthritis (RA)**

Rheumatoid arthritis (RA) is a chronic inflammatory disease mainly characterised by articular joint involvement. RA has a prevalence of about 0.5-1.0 %, 2-3 times higher in women compared to men<sup>14,57,58</sup>. The cervical spine, especially the craniovertebral junction, is often involved. Cervical subluxations are reported to occur in 23-86% of RA patients<sup>59-61</sup> and may cause spinal cord compression with major neurological impairment or even death<sup>62,63</sup>. Atlantoaxial subluxation accounts for more than three fourths of the cervical subluxations. Functionally intact transverse and alar ligaments are the most important structures to prevent such subluxation<sup>3,4,13,14,29</sup>.

Mechanical instability due to ligament dysfunction at the atlantoaxial level has been found to cause progressive osseous destruction even in the absence of active synovitis<sup>64</sup>. In RA the alar and transverse ligaments thus seem to have an important role in preventing osseous destruction at the craniovertebral junction.

Histopathological studies have reported presence of fibrocartilage in both the alar and transverse ligaments<sup>65</sup>. Fibrocartilage epitopes may act as targets in autoimmune reactions in RA<sup>66,67</sup>. These autoimmune reactions can result in inflammation and edema or structural ligament alterations which might cause high-signal changes on MRI. Alar and transverse ligament high-signal changes could therefore be an early sign of cervical RA and might predict atlantoaxial subluxation and osseous destruction.

### **4.2.3. Rationale in control individuals**

MRI ligament high-signal changes have been reported in subjects without any known trauma and without rheumatic diseases<sup>44,68</sup>. Degenerative changes are found to cause high signal in tendons and ligaments<sup>68-70</sup>, and such changes are expected to increase by age<sup>70,71</sup>. Fat tissue or loose connective tissue interspersed between fibres as normal variants or at insertions where fibres diverge can cause high signal in ligaments<sup>44,68,72</sup>. Furthermore, high signal in ligaments does not necessarily reflect morphologic, structural changes. Under certain circumstances ligament high-signal changes can be produced by MRI artefacts<sup>73-77</sup>.

## **4.3. Imaging of alar and transverse ligaments**

### **4.3.1. Imaging in WAD and controls**

Although the appearance of the alar and transverse ligaments has tentatively been described on CT<sup>78</sup>, soft tissue discrimination by the use of CT is too poor for evaluation of ligament structure. Based on that rotary instability at the craniovertebral junction is mainly being restricted by the alar ligaments<sup>2</sup>, Dvorak et al established a method for indirect assessment of these ligaments by using rotational functional CT on cadavers, WAD patients and volunteers<sup>29,31,32</sup>. They reported that 151 of 423 WAD patients (36%) had abnormal asymmetric rotation at the level of C0-C1<sup>30</sup>. Others have

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not been able to reproduce their findings<sup>79</sup>. Rotational functional CT seems difficult to standardise, and the criteria for rotational instability are controversial<sup>79,80</sup>. Consequently, this method has not gained broad acceptance as a reliable tool for evaluating the alar ligaments<sup>10,35</sup>.

MRI differentiates soft tissue better than CT and can directly visualize the soft tissues of the craniovertebral junction. Already in 1991 Dickman and his colleagues applied MRI for evaluation of the transverse ligament<sup>34</sup>. Using a 1.5 Tesla magnet, they performed sagittal and axial gradient echo sequences with a slice thickness of 3 mm slices on 20 uninjured adults and 10 trauma patients, who all had known upper neck injuries according to cervical radiographs. On axial images the transverse ligament was visualised in all cases. Tears appearing as regions of disruption with high-signal intensity were described in 3 patients. All 3 patients had documented atlantoaxial instability prior to the MRI examination. Due to the available MRI technology at that time and the use of T2-weighted sequences, the images had poor anatomic depiction and the detailed structure of an intact transverse ligament could not be evaluated.

At 1.5 Tesla, by using axial or sagittal gradient echo and paraxial T1-weighted spin echo sequences with a slice thickness of 2 mm, Willauschus et al in 1995 described the alar ligaments in 7 WAD patients, 8 non-trauma volunteers and 17 deceased accident victims<sup>35</sup>. The ligaments were visualized in all cases except one. They were reported to have a similar low to intermediate signal intensity in the WAD group, the volunteers and the deceased victims. Inter-individual differences in signal intensity were observed. No striking difference in signal characteristics as a possible sign of ligament injury was detected when comparing the right and left ligament for each individual. Ruptures produced artificially by cutting one alar ligament in deceased individuals were identified on MRI. The T1-weighted sequences used in that study probably produced poor signal to noise ratios, and the alar ligaments seem hard to discriminate from surrounding tissue on the published images.

In 2001, using a 0.5 Tesla machine, Wilmlink et al applied proton and T2-weighted spin echo sequences in the coronal plane with slice thickness of 3 mm on 12 WAD patients and 6 controls<sup>81</sup>. They examined unilateral thinning or interruption of the alar ligaments, but did not characterise signal intensity. All alar ligaments were visualized. No major differences in the appearance of ligaments between patients and controls were found. Twenty-five percent of the alar ligaments were registered as probably or clearly abnormal, but the criteria for these categories were poorly defined. Interobserver and intraobserver agreement was poor to fair (kappa 0.0 - 0.4). Asymmetric orientated images occurred in more than half the cases, and such images were more likely to be interpreted as abnormal.

The morphologic characteristics of the alar ligaments in 50 asymptomatic subjects were assessed by Pfirrmann and his group in 2001 by using coronal and axial T1-weighted and T2-weighted spin echo sequences with 3-4 mm slices in a 1.0 Tesla magnet<sup>10</sup>. The left and right alar ligaments could be detected in 84% and 76% of the subjects respectively. The signal intensity of ligaments was recorded as high, low or similar compared to adjacent muscle tissue. Alar ligament high-signal intensity was found in 21% (right) and 21% (left) on T1-weighted sequences and in 8% (right) and 24% (left) on T2-weighted sequences. Moderate to good interobserver agreement was reached (kappa 0.45 – 0.70). More than two thirds of the alar ligaments were reported to show heterogeneous signal intensity. The anatomic direction of the ligaments was asymmetric in 88 % of the examined subjects.

In 2001, Kråkenes et al established a high-resolution MRI protocol for imaging ligamentous and membranous structures at the craniovertebral junction<sup>8</sup>. They used a 1.5 Tesla magnet and proton-weighted fast spin echo sequences with slice thickness of 2 mm and voxel size of 0.45 mm<sup>3</sup> in three orthogonal planes; axial, coronal and sagittal. The alar and transverse ligament high-signal changes were graded 0-3 based on the ratio between any high signal part and the total cross-sectional area<sup>82,83</sup>. High signal had to be seen in at least two imaging planes to be graded 1-3, otherwise it was graded 0. In all 122 study participants both the alar and transverse ligaments could be

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evaluated. Interobserver agreement for assigning into grades 0-1 or grades 2-3 high signal was moderate to good (kappa 0.46 - 0.65) for the alar ligaments and moderate (kappa 0.43 - 0.46) for the transverse ligament. Grades 2-3 alar ligament high-signal changes were significantly more frequent in chronic WAD patients (61/92, 66%) compared to non-injured controls (2/30, 7%)<sup>22</sup>. It was concluded that soft tissue upper neck structures, particularly the alar ligaments, seem to play an important role in the understanding of chronic WAD and that the detailed structure of these ligaments can be characterised by the use of high-resolution proton-weighted sequences.

Kim et al, using a 1.5 Tesla magnet, found proton-weighted images with 2 mm slice thickness superior to other sequences (spin echo T1-weighted, fast spin echo T2-weighted, and gradient echo T1- or T2-weighted) for assessing the alar ligaments<sup>7</sup>. In 2002 they reported better visualisation in the coronal plane compared to the axial plane in a group of 22 asymptomatic volunteers. In the coronal plane, 95-100% of ligaments could be demonstrated both with the head in neutral position and with the head actively rotated to the left or right. The authors concluded that a reliable assessment of the alar ligaments can be achieved by this MRI method and that rotation studies may be valuable. However, ligament signal characteristics and observer agreements were not given.

A somewhat similar MRI protocol of proton-weighted sequences with a slice thickness of 3 mm on a 0.5 Tesla vertical open bore magnet was used for assessing the alar ligaments in a study by Roy et al presented in 2004<sup>77</sup>. Fifteen non-injured volunteers were examined with their head in neutral position (axial, coronal and sagittal), but also with their head laterally flexed (coronal). In the coronal plane both alar ligaments were identified in all subjects except one. Ipsilateral or contralateral neck flexion generally reduced ligament visibility. Ligament high-signal intensity was graded 1-3 using a modified version of Kråkenes' system<sup>82</sup>. High signal intensity was found in 8 of 26 ligaments identified on sagittal images. In no case did the high signal cover more than half of the cross-sectional area. Due to high prevalence of high signal in non-injured subjects and poor reliability of grading the signals, these authors implied that MRI

should not be used for routine investigation of alar ligaments in WAD. However, their main protocol of proton images with 3 mm slices in a vertical open bore low field (0.5 Tesla) magnet might be inadequate for evaluating these delicate ligament structures.

In a case control study presented in 2008, Myran et al evaluated the alar ligaments in 59 chronic WAD1-2 patients, 57 non-symptomatic controls and 57 symptomatic controls <sup>74</sup>. The symptomatic controls had chronic neck pain without a history of neck trauma. These authors used the same MRI protocol of high-resolution proton-weighted images and the same grading system of high-signal intensity as Kråkenes et al <sup>82</sup>. All ligaments were visualised and the image quality was subjectively rated as good in 89%. The interobserver agreement between two observers for grading high-signal changes as 0-1 or 2-3 was good (kappa 0.60 - 0.66). Although the chronic WAD1-2 patients had the highest frequency of grades 2-3 alar ligament high-signal changes (49%), no significant difference in such changes between the three groups was found. From their results the authors concluded that the clinical relevance of high-signal intensity in alar ligaments is unknown and should be evaluated further in prospective studies.

Volle et al developed a “functional” MRI method with the intention of evaluating the stability at the craniovertebral junction <sup>84,85</sup>. In a 0.2 Tesla open bore magnet using a special coil device they performed functional imaging by stepwise tilting the head in lateral flexion and later rotating the head to both sides. Fast spin echo (T1-weighted) and gradient echo sequences (T1- and T2-weighted) were applied for this purpose. Images were interpreted in video loops. Among 420 chronic WAD patients, complete or incomplete alar ligament ruptures were described in 72 (17.1%) <sup>85</sup>. Another 81 patients (19.1%) showed changes in their intraligamentous signal pattern and contemporary craniovertebral instability. However, the criteria for rupture and instability seemed to be poorly defined and they were not validated in control groups. The reproducibility of this “functional” MR method has not been evaluated and its diagnostic value in WAD is not clear <sup>40,86</sup>.

No MRI study describing the appearance of the alar and transverse ligaments in acute WAD1-2 had been performed before the present study. Prior MRI studies in acute WAD have focused on other findings of the cervical spine e.g. fracture or dislocation, traumatic disc or endplate changes, soft tissue bleeding / edema, posterior or anterior longitudinal ligament rupture and spinal cord injuries <sup>87-92</sup>. Such traumatic MRI changes have been reported to be rare and not related to prognosis in patients who have acute WAD1-2 based on evaluation without MRI <sup>87,89,90</sup>. Longitudinal MRI studies on acute WAD patients focusing on the craniovertebral ligaments have been requested <sup>89</sup>. If alar and transverse ligament high-signal changes should affect long-term prognosis after neck trauma, such MRI findings could represent an indication for, and perhaps even a target for, interventions to improve patient recovery.

#### **4.3.2. Imaging in RA**

High-resolution MRI techniques as described by Kråkenes et al <sup>8</sup> have not been applied to RA patients, and only one MRI study focusing on the alar or transverse ligaments in RA patients could be found prior to our paper. In that study, the transverse ligament was examined by sagittal and axial gradient echo sequences with 3 mm slices in a subsample of 4 symptomatic RA patients <sup>34</sup>. Anterior subluxations ranged from 8 to 11 mm. No ligament disruption was identified, but the authors described stretching, distortion, thickening or irregularity of all transverse ligaments. The criteria for these imaging findings were not given and the ligament signal characteristics were not reported.

#### **4.4. *Specific motivation for the study***

Before the writing of this thesis, high-resolution proton-weighted MRI sequences had been established that were capable of visualizing the detailed structures of the alar and transverse ligaments <sup>82,83</sup>. A reasonably reliable classification system for grading high-signal changes of these ligaments had been developed <sup>22,74</sup>. In one initial study, the alar

and transverse ligament high-signal changes were reported to be more frequent in chronic WAD2 patients compared to controls<sup>82,83</sup>. In the same study sample, such ligament changes were related to neck disability and trauma factors like impact direction and head position at the instant of collision<sup>22,93,94</sup>. However, these results had not been confirmed by others, and reports on the frequency of high-signal changes in non-injured volunteers were diverging<sup>22,74,77</sup>. More information on trauma factors and their relation to alar and transverse ligament high-signal changes as well as data from larger control groups were needed to clarify if such MRI findings were caused by the acute traumatic event.

Alar and transverse ligament high-signal changes had not been evaluated in acute WAD, and their prognostic role had not been assessed. Thus the nature and clinical relevance of these changes were not clear. Further studies were needed to find out if upper neck high-resolution MRI in the acute phase of injury could add information that was valuable in the treatment and follow-up of WAD patients. We hypothesized that alar and transverse ligament high-signal changes in WAD patients are caused by the acute traumatic event and therefore should occur more frequently than in controls and be related to symptoms and trauma factors at injury as well as to outcome at 12 months follow-up.

Joint dislocation and pain can make time demanding MRI protocols a challenge for the person examined. Upper neck high-resolution MRI had not previously been applied on RA patients. In RA, alar and transverse ligament dysfunction with instability at the craniovertebral junction can cause severe neurological manifestations<sup>62,63</sup>. Effective anti-rheumatic medical treatment exists<sup>95</sup>. A method for early detection of upper neck ligament affection could therefore be of great value. We hypothesized that ligament high-signal changes in RA are due to the inflammatory disease and therefore should be related to other imaging and clinical RA features such as larger atlantoaxial subluxation on radiographs and increasing severity and duration of RA.

## 5. Aims of study

In this project we intended to evaluate the alar and transverse ligaments on upper neck high-resolution MRI in WAD1-2 patients, RA patients and controls. Our aims in the different studies are given below.

**Paper I.** The aim was to describe the prevalence of MRI high-signal changes of the alar and transverse ligaments in WAD1–2 in relation to patient age and gender, cervical spine degeneration, type of trauma event and time since trauma.

**Paper II.** The aim was to examine the feasibility of high-resolution MRI of the alar and transverse ligaments in different stages of adult RA, and to explore whether high-signal changes of these ligaments are related to other imaging and clinical features.

**Paper III.** The aim was to describe alar and transverse ligament MRI high-signal changes in acute WAD1-2 in relation to clinical and accident related factors, and to compare such changes between the acute WAD1-2 cohort and a control group of uninjured volunteers.

**Paper IV.** The aim was to evaluate if MRI high-signal changes of the alar and transverse ligaments in the acute phase of whiplash injury are related to outcome after 12 months.

## 6. Materials and methods

The first study in this thesis (**paper I**) is a cross-sectional study with retrospective data collection in clinically referred WAD1-2 patients. In the remaining studies (**paper II-IV**) data were collected prospectively. These studies are termed prospective in the present thesis. The second study (**paper II**) is a cross-sectional study with consecutive and prospective recruitment of RA patients. The third study (**paper III**) is a case-control cross-sectional study with consecutive and prospective recruitment of acute WAD1-2 patients. The fourth study (**paper IV**) is a longitudinal follow-up study in which the patients in the acute WAD1-2 cohort from study 3 report their outcome 12 months after injury. A detailed description of the study samples is given below.

### 6.1. Study population

#### *Inclusion criteria*

In all studies on whiplash patients (**paper I, III-IV**) we concentrated on WAD1-2 (Table 1, page 12). Patients with information of neurological signs (WAD3) or neck fracture / dislocation (WAD4) were not included. WAD3-4 patients are usually evaluated, treated and followed at neurosurgical or orthopaedic hospital clinics, and were not focused on in the present studies. We did not include patients without neck complaints following a trauma (WAD0), as we assumed injury of the upper neck ligaments to be rare in such subjects. RA patients (**paper II**) were included only if fulfilling the American College of Rheumatology (ACR) criteria ensuring a correct RA diagnosis<sup>96</sup>. As we intended to describe the alar and transverse ligaments on MRI in adults, only patients and controls between the age of 18 and 80 years were included in the prospective studies (**paper II-IV**).

### *Exclusion criteria*

Cervical spine operated subjects were excluded in all sub-studies (**paper I-IV**). MRI in such subjects frequently reveals altered anatomic relations and disturbing artefacts due to metal implants. Pregnant and MRI incompatible subjects were not included. Due to questionnaires in Norwegian only, no foreign-speaking subjects were assigned for participation.

In the prospective studies (**paper II-IV**) we intended to avoid any influence of prior neck conditions and other relevant health problems on MRI findings and clinical features. Patients with cancer or other serious somatic or psychiatric diseases were not asked to join the study. Subjects with prior neck injury / whiplash trauma, reported treatment for neck problems during the last 10 years, or prior neck pain of more than 30 days in total, were excluded from the studies on acute WAD and controls (**paper III-IV**). Patients with prior severe head injuries may have unrecognised neck injuries and were also excluded. Subjects with established rheumatic diseases were not included in the WAD-studies. In the RA study (**paper II**), patients with prior neck injury or whiplash trauma were excluded, and so were those with known cervical nerve root syndrome or myelopathy. Such patients were regarded to be more likely to demonstrate symptoms that could mask potential symptoms originating from the upper neck ligaments. To avoid influence of surgery on serological laboratory results, RA patients with any surgery performed during the last 4 weeks were not asked to participate.

#### **6.1.1. Clinically referred WAD group (paper I)**

By searching the imaging database from the MRI institute Capio Røntgen, Bergen, 1403 consecutive patients examined with high-resolution upper neck MRI in the time period from 1 January 2005 to 31 May 2006 were identified. Our inclusion criteria - a history of neck trauma combined with neck complaints of pain, stiffness or tenderness - were confirmed from the referral letters in 1304. Patients with reported neurological signs (n = 0), neck fracture reported or seen at MRI (n = 6), neck mass / tumour at

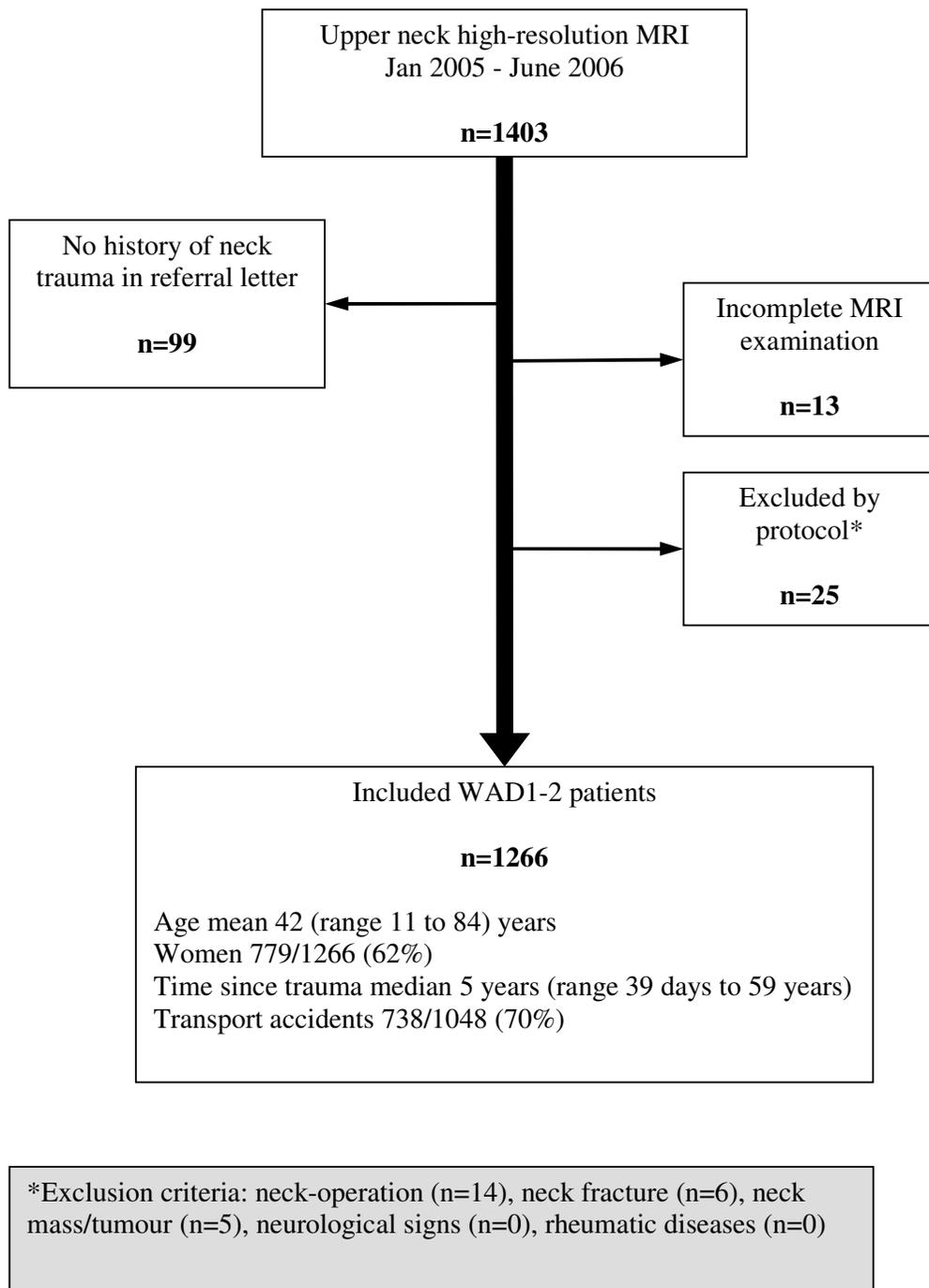
MRI (n = 5), reported previous neck operation (n = 14), or rheumatoid arthritis (n = 0) were excluded. Thirteen patients had not completed an adequate MRI, leaving 1266 includable WAD1-2 patients. A study flow chart is given in Figure 3.

The included patients' mean age was 42 years (range 11 to 84 years), 779 (62%) were women. All patients were referred from clinicians, 89 % from general practitioners. More than to thirds (70%) had sustained transport accidents. The time since trauma calculated as the time from the date of trauma to the date of MRI examination, was median 5.0 years (range 39 days to 59 years). In 95% of patients the time since trauma was more than 6 months.

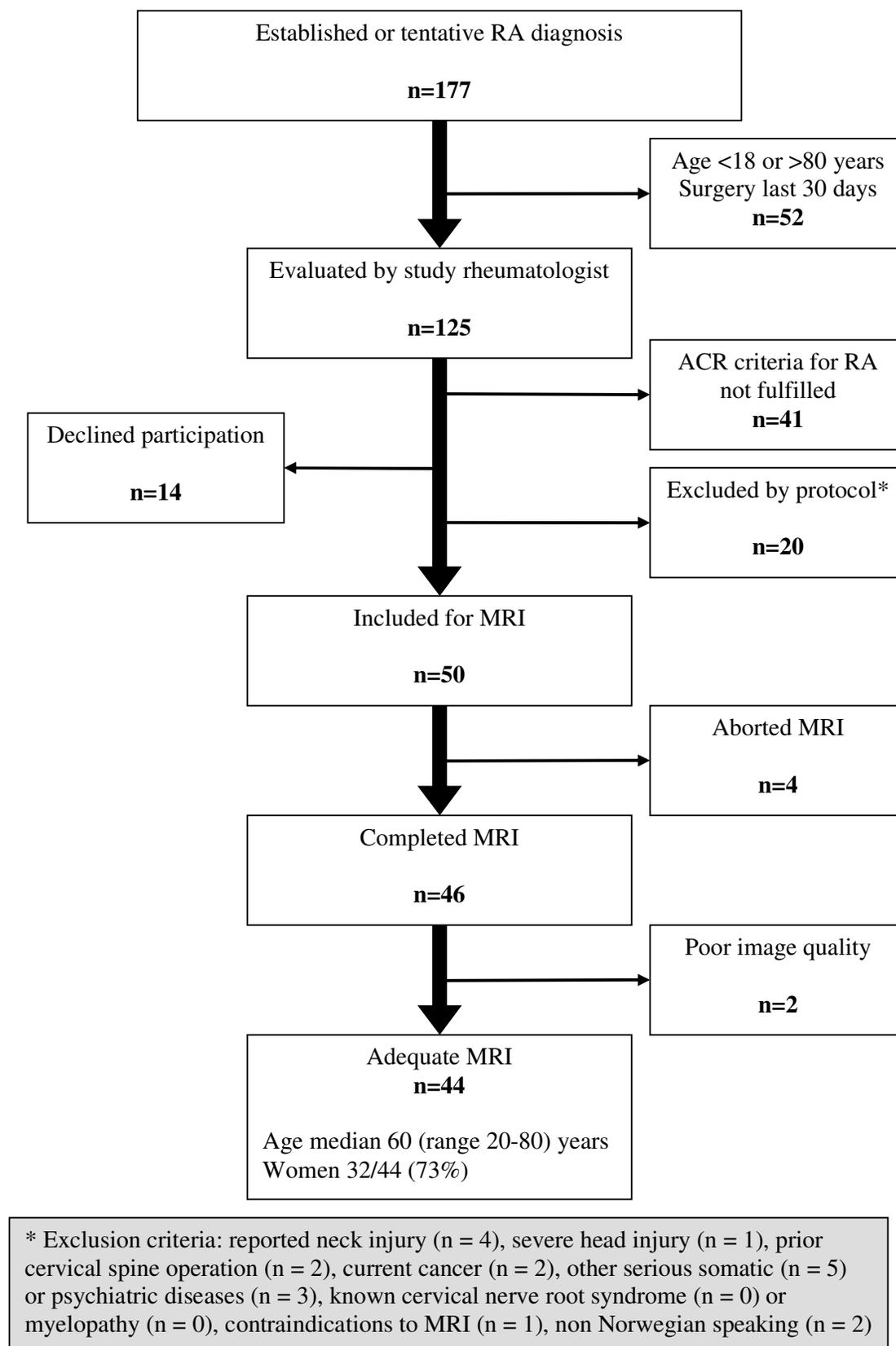
### **6.1.2. RA group (paper II)**

Patients admitted to the Department of Rheumatology, Haukeland University Hospital with an established or tentative diagnosis of RA, were prospectively and consecutively identified from admission records. From October 2006 to May 2007, 125 patients aged 18-80 years with no surgery during the last 4 weeks were recruited. They were all examined by the same study rheumatologist who confirmed the American College of Rheumatology criteria in 84. Fourteen of these RA patients declined participation, and 20 were excluded due to the before-mentioned criteria (see page 23). Another 4 patients had to abort the MRI examination due to claustrophobic discomfort. The MRI examination was thus completed by 46 RA patients. As two patients showed poor image quality and non-interpretable proton sequences, the final study sample included 44 RA patients. A study flow chart is given in Figure 4.

In the final sample, 32 patients (73%) were women, median age was 60.4 years, median RA duration 9.1 years, and median disease activity score in 28 joints (DAS28) 5.3. Positive rheumatoid factor was found in 25 (57%) and anti-cyclic citrullinated peptide (anti-CCP) in 35 (80%) of the 44 RA patients.



**Figure 3.** Study flow chart: clinically referred WAD group (**paper I**)

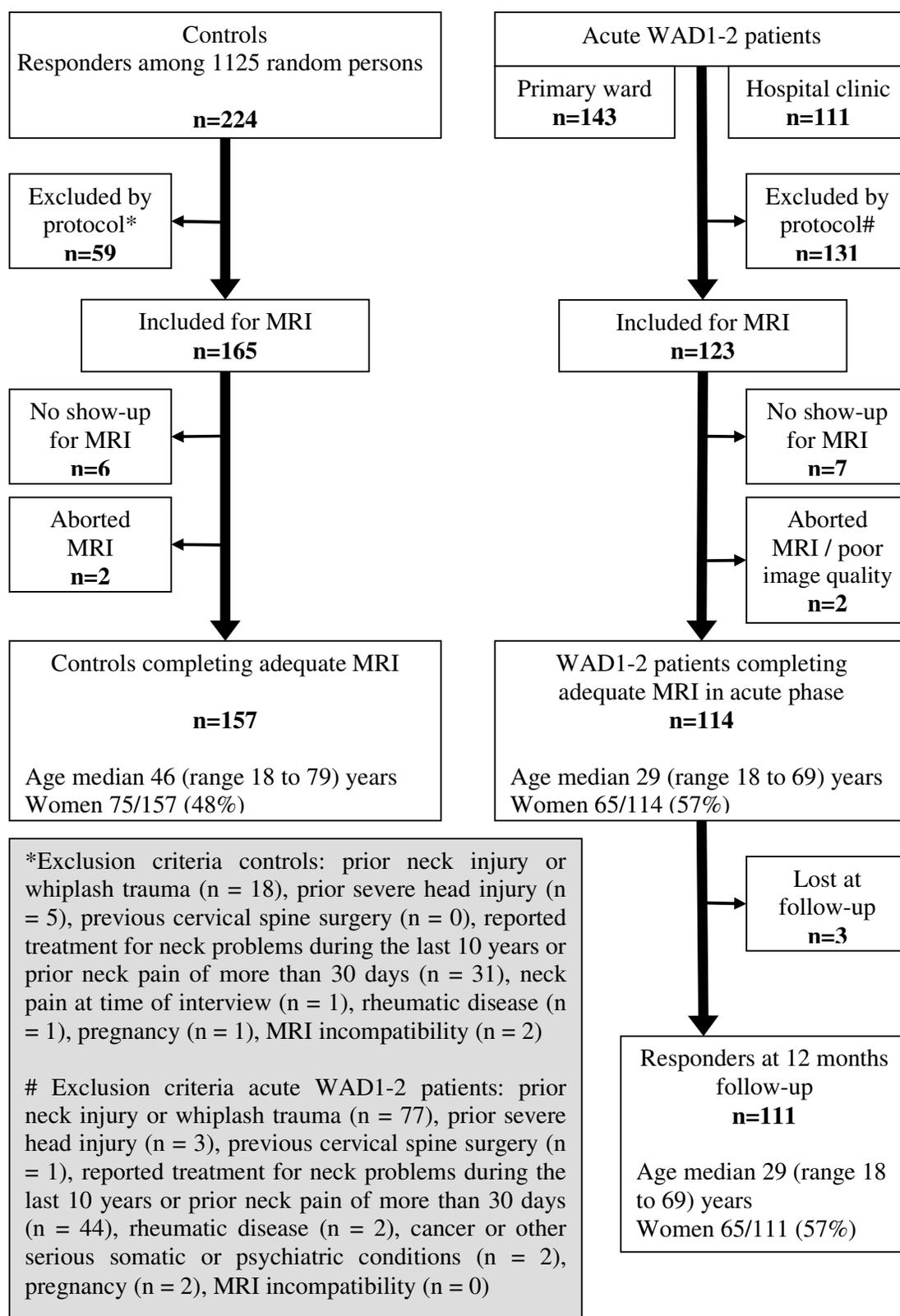


**Figure 4.** Study flow chart: rheumatoid arthritis (RA) group (**paper II**)

### **6.1.3. Acute WAD1-2 group and 12 months follow-up group (paper III and IV)**

The inclusion criteria were Norwegian speaking acute WAD1-2 patients, age 18-80 years, sustaining a car accident during the last 7 days and reporting onset of neck pain within 48 hours of the accident. From May 2007 until Mars 2009 we prospectively and consecutively recruited such patients both from persons attending a primary care clinic (Bergen Accident and Emergency Department) and from patients undergoing conventional radiography and / or CT of their cervical spine at a hospital clinic (Haukeland University Hospital). At the primary care clinic, nurses and physicians recruited the patients by using a prespecified inclusion form (appendix, page 87). At the hospital clinic, the author of this thesis identified eligible patients from imaging files. Patients at both institutions fulfilling the inclusion criteria were all interviewed by this same researcher (N.V.) using an interview guide (appendix, page 88). At these interviews, 131 of 254 patients were excluded according to the predefined criteria. Seven patients did not show up for MRI, and two patients had to abort the MRI examination due to claustrophobic discomfort or had uninterpretable images. Thus, 114 acute WAD1-2 patients completed an adequate MRI examination and were eligible for analysis. Their median age was 29 years, 65 patients (57%) were women. A study chart is given in Figure 5.

The 114 included WAD1-2 patients were contacted again by phone or mail 12 months after their car accident and asked to complete a written follow-up questionnaire. Three did not respond despite reminders, whereas 111 (97%) responded and form the follow-up study sample (**paper IV**).



**Figure 5.** Study flow chart: acute WAD1-2 group and controls (paper III-IV)

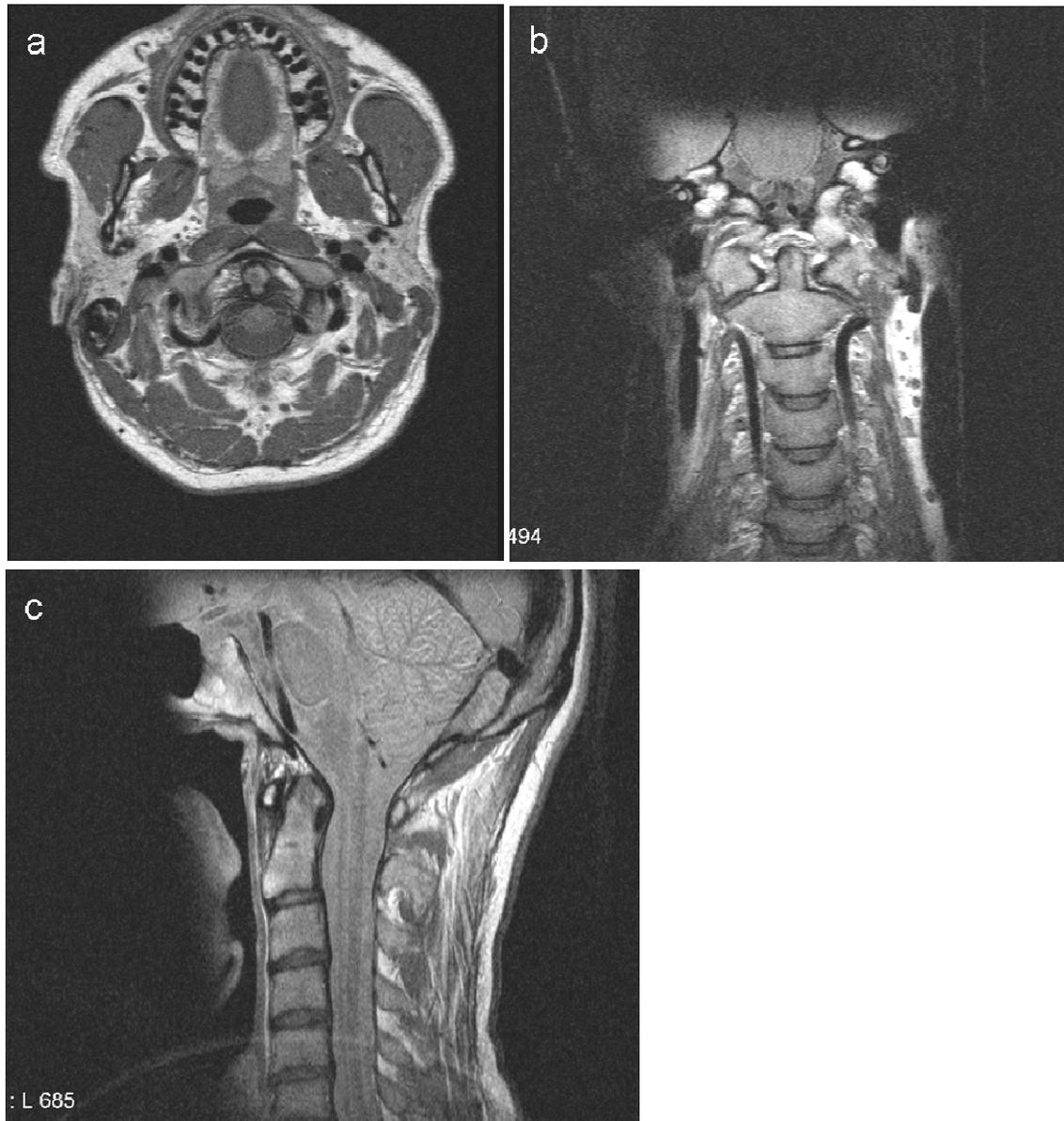
#### **6.1.4. Control group (paper III)**

Invitation letters were sent to 1125 random persons aged 18 to 80 years from the National Population Register of Bergen, Norway (appendix, page 89-91). In the letter we asked for volunteers without prior or current neck problems. All 224 responders were interviewed by the same researcher (N.V.) using an interview guide (appendix, page 92), and 59 subjects were excluded according to the predefined criteria (see page 23). Six subjects did not meet for MRI, and 2 subjects had to abort the MRI examination due to claustrophobic discomfort. A total of 157 responders completed adequate MRI and constitute the control group (Figure 5). Their median age was 46 years, 75 controls (48%) were women.

## **6.2. MRI protocol**

### *Proton-weighted sequences*

The retrospective study (**paper I**) was based on Kråkenes' MRI protocol<sup>8</sup>. Prior to the prospective studies (**paper II-IV**), we performed pilot studies on 24 volunteers in an attempt to improve the protocol for proton-weighted sequences and to experiment with other sequences. Ligament visualisation was assessed subjectively. We modified several acquisition parameters without achieving improved proton images (see Discussion, page 54). Thus, in both the retrospective and the prospective studies, the protocol included the same high-resolution proton-weighted sequences in three orthogonal planes; axial, coronal, and sagittal (Figure 6). The MRI parameters are given in Table 2. All subjects were imaged with head and neck in a neutral position by using the same 1.5 Tesla scanner (Symphony Mastroclass, Siemens Medical System, Erlangen, Germany) and a standard circular polarised one-channel receive-only head coil.



**Figure 6 a-c.** High-resolution proton-weighted 1.5 Tesla MRI sections of the upper neck in axial (a), coronal (b) and sagittal (c) plane. Images are shown with their full field of view

**Table 2. Magnetic resonance imaging (1.5 Tesla) parameters for upper neck proton-weighted sequences in three orthogonal planes and sagittal short tau inversion recovery (STIR) sequences**

	Proton			Sagittal STIR		
	Axial	Coronal	Sagittal	Upper neck	Whole spine	Cervical spine
Repetition time (TR)/ Echo time (TE), ms	2660 / 15	2870 / 15	2150 / 15	6990 / 88	5680 / 51	
Echo train length (ETL)	13	13	13	13	13	
Number of acquisitions / concatenations	5 / 1	5 / 1	4 / 2	3 / 1	2 / 1	
Number of slices	12 interleaved	13 interleaved	20 interleaved	20 interleaved	19 interleaved	
Matrix	291×512	271×512	246×512	192×384	240×320	
Field of view (FOV), mm	175×200	200×200	175×200	175×200	180×180	
Slice thickness/interslice gap, mm	1.5 / 0	1.5 / 0	1.5 / 0.3	1.5 / 0.3	3.0 / 0.3	
Voxel size, mm	0.6×0.4×1.5	0.7×0.4×1.5	0.7×0.4×1.5	1.0×0.5×1.5	0.8×0.6×3.0	
Receiver bandwidth	136 Hz / pixel	136 Hz / pixel	136 Hz / pixel	130 Hz / pixel	195 Hz / pixel	
Phase-encode direction	Right to left	Right to left	Head to feet	Head to feet	Head to feet	
Saturation pulses	None	Left, superior	right, Anterior, superior	Anterior, superior	None	
Acquisition time	5 min 23 s	5 min 06 s	7 min 16 s	6 min 47 s	6 min 33 s	
Coverage	Below foramen magnum to base of <i>dens axis</i>	Anterior arch of <i>atlas</i> to through canal	Right to left of occipital condyle	Right to left of occipital condyle	Right to left apophyseal joint	
Inversion time (TI)				150 ms	160 ms	
Flip angle				160 degrees	160 degrees	

*“Focused” STIR sequence*

Acute traumatic changes like bleeding or edema and the extent of fat tissue may be better evaluated when including sequences with fat suppression techniques<sup>72,97</sup>. All such sequences are burdened with reduced MRI signal, especially when imaging at high resolutions. In the pilot studies, we found that short tau inversion recovery (STIR) sequences were superior to proton-weighted sequences with chemical shift selective fat suppression for evaluation of the upper neck ligaments. We created a “focused” sagittal STIR sequence (Table 2, Figure 7). By using the same field of view, slice number / thickness and interslice gap, the “focused” STIR images and sagittal proton-weighted images could be coupled. Adequate anatomic depiction could thus be ensured during interpretation of the “focused” STIR images, despite their reduced MRI signal.

*“Large” STIR sequence*

The proton-weighted sequences and the sagittal “focused” STIR sequence covered only the medial parts of the upper four to five cervical spine levels. The lower cervical spine was not visualised on these sequences. To evaluate potentially relevant findings of the whole cervical spine, a sequence with a larger field of view was required. In the RA patients we wanted to assess possible rheumatic changes at the lateral apophyseal joints and at all cervical levels. We therefore included a “large” sagittal STIR sequence with a larger field of view and slice thickness covering the apophyseal joints bilaterally for the whole length of the cervical spine (Table 2, Figure 7). In addition to the standard head coil, a standard circular polarised neck array coil and the upper two elements of a standard spine array coil were used for this purpose. This sequence was evaluated by the study radiologists for the RA patients only, but was performed on all study groups, providing data for future research.

The final MRI protocol which was applied in all our prospective studies thus included five sequences with a summarised acquisition time of 31 min 5 s. All five sequences were successively evaluated by a separate neuroradiologist to rule out clinically relevant incidental findings. The two study radiologists were blinded to the separate radiologist’s findings.



**Figure 7 a-b.** “Focused” (a) and “large” (b) mid-sagittal 1.5 Tesla MRI STIR images shown with their full field of view. The “focused” STIR images could be coupled to the corresponding sagittal proton images

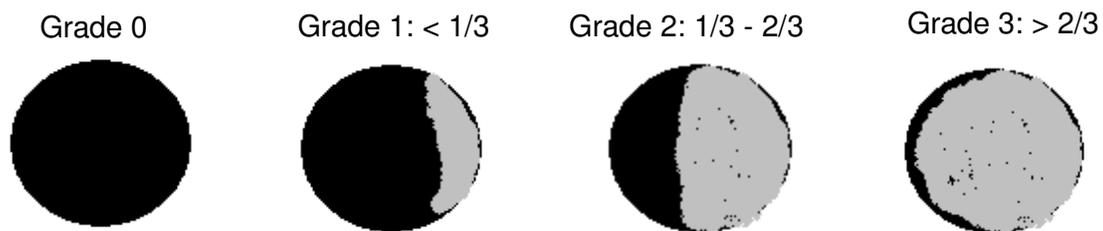
No STIR sequences were applied in the retrospective study. A standard sagittal T2-weighted fast spin echo sequence with 3 mm slice thickness covering the whole cervical spine was included, enabling a fair assessment of degenerative changes at all cervical spine levels.

### **6.3. MRI interpretation**

#### **6.3.1. Prospective studies (paper II-IV)**

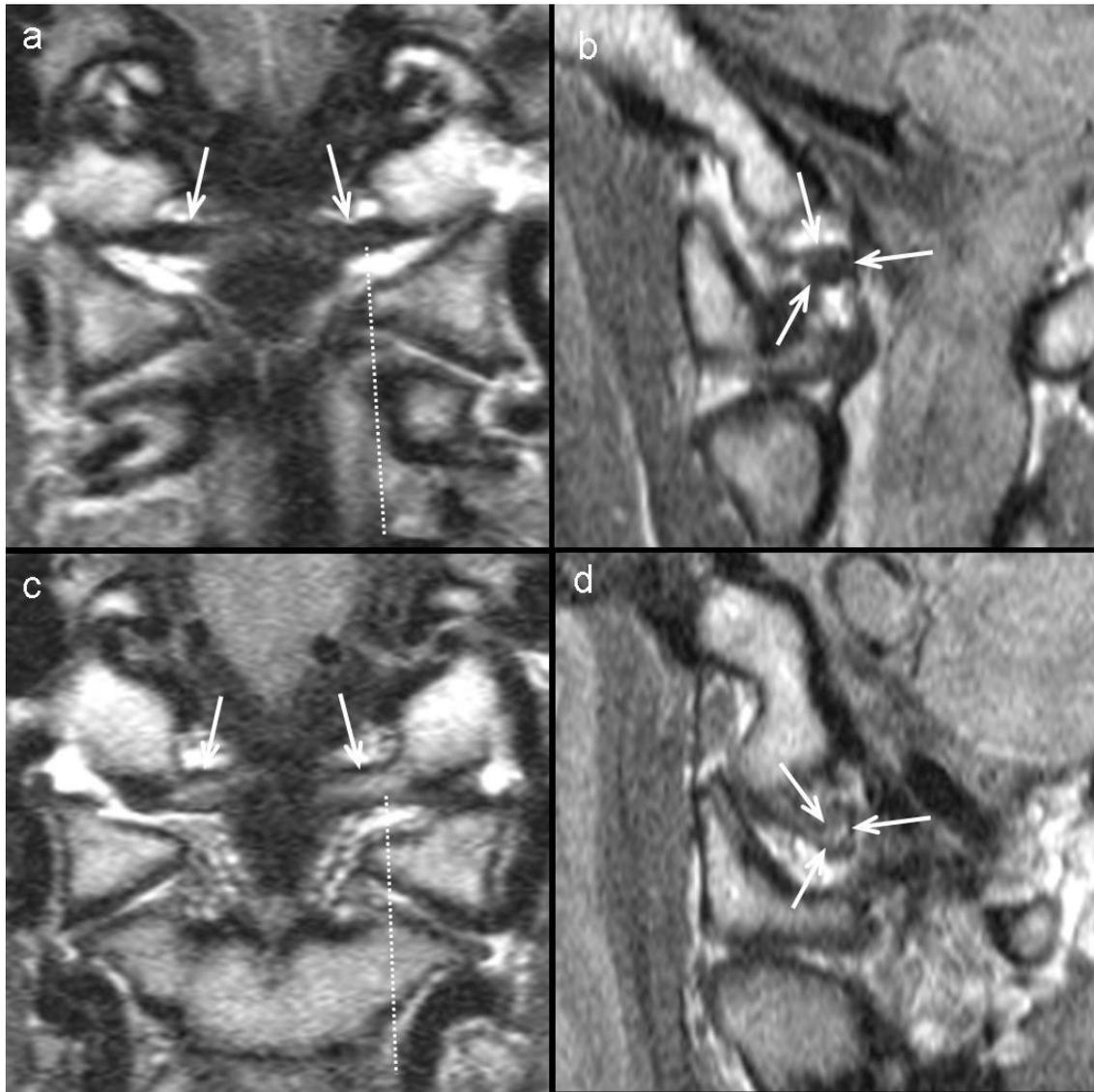
##### *Criteria for grading of ligaments*

Using the classification system proposed by Kråkenes, high-signal changes of the alar and transverse ligaments were graded 0-3 on the proton sequences based on the ratio between any high-signal part and the total cross-sectional area of the ligament<sup>22,82</sup>. No high signal was graded 0, high signal in 1/3 or less of the total cross-section was graded 1, high signal in 1/3 to 2/3 of the total cross-section was graded 2, and high signal in 2/3 or more of the total cross-section was graded 3 (Figure 8).

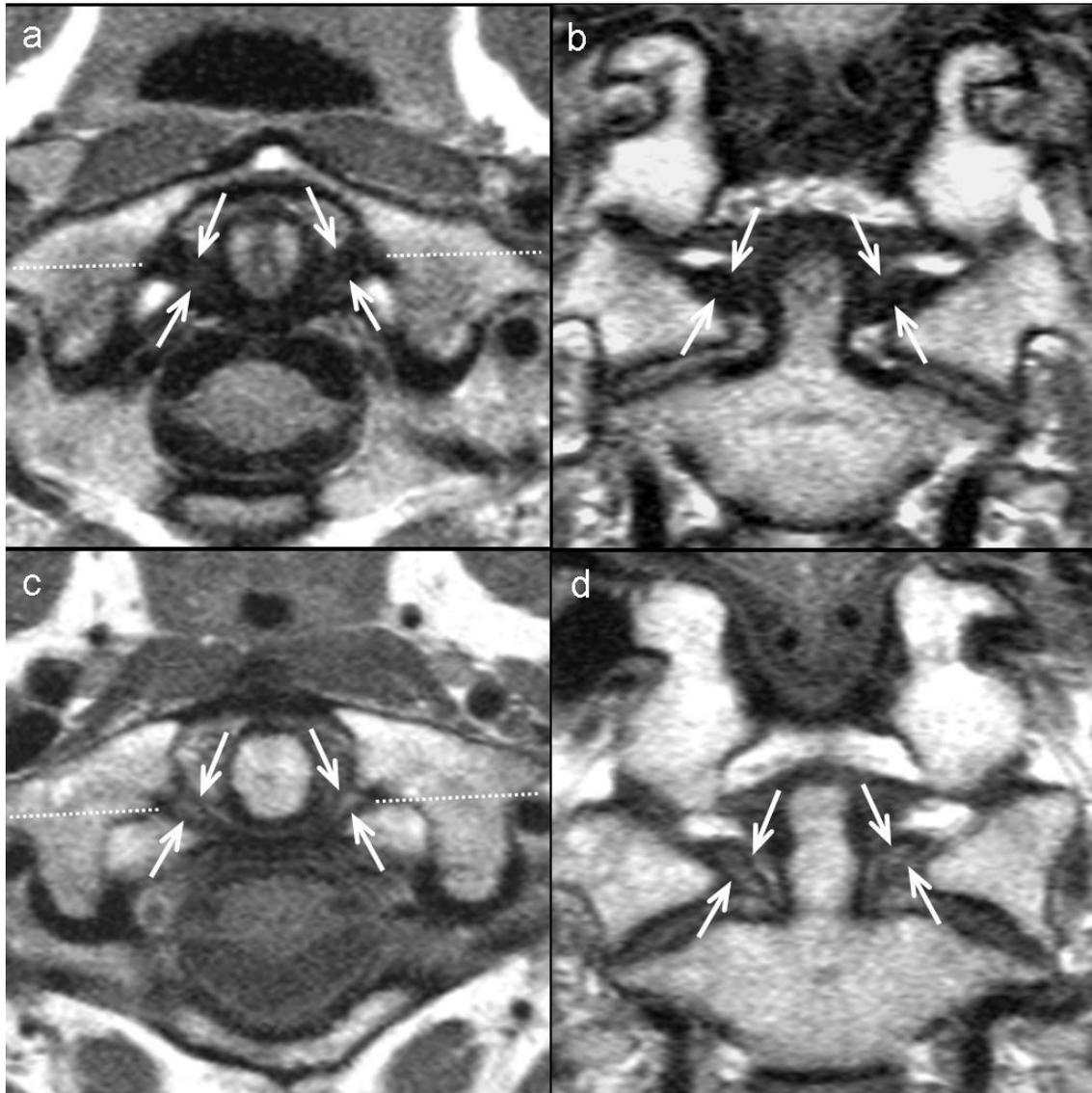


**Figure 8.** The grading system was based on the ratio between any high-signal part and the total cross-sectional area of the ligament

The image with the largest cross-sectional area of high signal was used for grading, alar ligaments on sagittal sections (Figure 9) and transverse ligaments on sagittal or coronal sections (Figure 10). Any high signal had to be seen in at least two imaging planes to be graded 1-3; otherwise it was graded 0 (no high signal). Homogenous grey ligaments were graded 2. The right and left sides were graded separately to analyse possible side differences.



**Figure 9 a-d.** Grade 0 (a, b) and grade 3 (c, d) alar ligament changes (arrows) on coronal (a, c) and sagittal (b, d) high-resolution proton-weighted MRI sections. Dotted lines mark the sagittal plane



**Figure 10 a-d.** Grade 0 (a, b) and grade 3 (c, d) transverse ligament changes (arrows) on axial (a, c) and coronal (b, d) high-resolution proton-weighted MRI sections. Dotted lines mark the coronal plane

On the “focused” STIR sequence, the signal intensity of these ligaments was compared to the signal of adjacent craniovertebral bone marrow and cerebrospinal fluid (Figure 11).



**Figure 11 a-d.** Alar ligaments (arrows) with low signal intensity (a) and signal intensity higher than adjacent bone marrow (b) on “focused” STIR images in two different subjects. Their coupled proton-weighted images of the alar ligaments (arrows) are shown below (c, d)

#### *Evaluation of MRI features in RA*

In the RA patients, the whole cervical spine was assessed for rheumatic changes on MRI. Anterior atlantodental interval (AADI) was measured on the mid-sagittal proton

image with the patient's neck in neutral position. Erosion was defined as a bone defect with sharp margins visible in at least two planes, synovitis as intermediate to high-signal intensity on STIR images in a region thicker than the width of the joint capsule, and bone edema as a poorly defined area within the trabecular bone with high-signal intensity on STIR consistent with increased water content <sup>98,99</sup>. Absent cerebrospinal fluid in both anterior and posterior subarachnoidal spaces on sagittal STIR images was regarded as stenosis at the spinal cord or brain stem level. Decreased cord / brainstem diameter at the stenotic level indicated cord / brainstem compression <sup>99</sup>. Signal changes within the spinal cord and brainstem were evaluated on STIR sequences.

#### *Image quality*

In the prospective studies, the overall image quality for visualisation of the ligaments was classified as good, reduced (interpretable images) or poor (not interpretable images) by one radiologist (N.V.). For the RA patients, image quality was assessed by both radiologists in consensus.

#### *Blinding*

All images were completely de-identified, also for patient age and gender, for study group allocation, and for examination date and time, since some study groups were more likely to be examined during weekends or in the evening. Unknown to the interpreters, all proton images were randomly presented in collections containing the same relative proportions of subject groups (WAD patients, RA patients and controls). To prevent any findings on STIR images (e.g. findings suggesting RA) to influence the grading of ligament high-signal changes on proton images, this grading was completed before any STIR images were made available. Two radiologists (6 and 26 years experience), who were also blinded to clinical data and functional radiography findings, independently graded all proton images. This provided the data for the observer agreement analysis. The radiologists thereafter solved all disagreements by joint reinterpretation of images. Their consensus grading was used in all further analyses, where the four grades were dichotomised by combining grades 0 and 1 and grades 2 and 3.

The “focused” STIR sequence was evaluated with the consensus proton ligament grading available. In the acute WAD patients and controls, the “focused” STIR sequence was interpreted by one radiologist only (N.V.), blinded to group allocation and clinical data. This interpretation was used in the analyses. However, the second radiologist (J.K.) independently interpreted the “focused” STIR images in a total of 45 randomly selected acute WAD patients and controls in order to assess interobserver agreement. When evaluating the “focused” and “large” STIR sequences in the RA study, the interpreters knew that the images belonged to RA patients. These STIR images were interpreted first independently and later in consensus by both radiologists. The consensus interpretation was used for analyses.

### **6.3.2. Retrospective study (paper I)**

The 4-level classification system for grading high-signal changes of the alar and transverse ligaments on proton-weighted sequences given above (see page 34) was also used in the retrospective study on clinically referred WAD patients. In addition the number of cervical spine levels (0, 1, 2 or more) with degeneration (e.g. disc bulge / herniation, low disc height, narrow facet joint, osteophytes) was assessed on the standard T2-weighted sequence covering the whole cervical spine. All images were prospectively interpreted by one radiologist only (J.K.). He had clinical data available but interpreted the images prior to the formation of study hypotheses. The result of this interpretation was used in the analyses. A second radiologist (N.V.) blinded to clinical data, independently graded high-signal changes in a random subsample of 100 examinations providing data for calculating interobserver agreement. Image quality was not evaluated in the retrospective study.

## **6.4. Radiography protocol and interpretation**

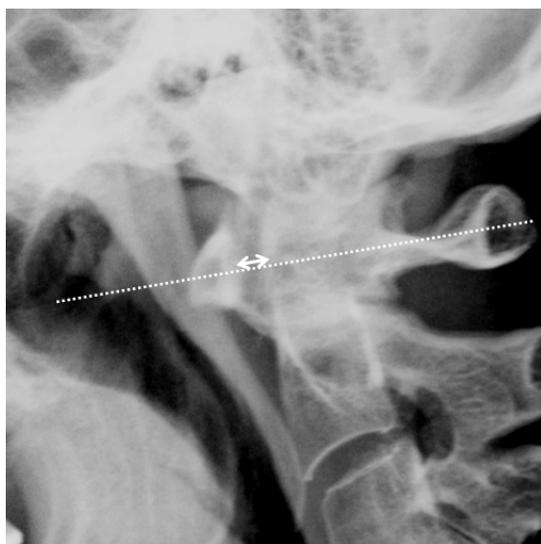
The included WAD patients were not routinely examined with conventional cervical spine radiography. The need for such conventional radiography or CT in excluding

neck fracture or dislocation was independently evaluated by the cooperative physician clinically responsible for each patient, and such examinations were not interpreted by our study radiologists.

### *RA patients*

In all our included RA patients functional cervical spine radiographs were taken within 33 (median 2) days after the clinical examination. Patients were imaged in upright position while sitting or standing. Lateral radiographs in both neck flexion and extension and an anterior-posterior open-mouth view were taken with a tube distance 1.50 and 1.00-1.15 meters respectively.

One radiologist (N.V.) blinded to clinical data and MRI findings interpreted the RA patients' radiographs in random order. AADI was measured on the lateral views taken during flexion and defined as the midline distance between the posterior part of the anterior tubercle of atlas and the anterior surface of the odontoid process (Figure 12)<sup>62,100,101</sup>. Vertical dislocation was evaluated on the lateral radiographs according to Kauppi<sup>102</sup>. Vertical subluxation was defined as present when the sclerotic ring of C2 reached the inferior line of atlas.



**Figure 12.** The anterior atlantodental interval, AADI, (double-arrow) in RA patients was assessed on lateral radiographs taken during flexion and measured along the line between the central part of the posterior and the central part of the anterior arch of atlas (dotted line)

## **6.5. Questionnaires and clinical data**

In the prospective studies (**paper II-IV**) WAD and RA patients filled in questionnaires containing relevant clinical instruments, see below. Although not all questionnaire data were analysed in the present studies, the entire questionnaires applied on acute WAD1-2 patients and RA patients are shown in the appendix (page 93-106). Acute WAD patients were evaluated for neck pain and neurological findings by cooperative clinicians (appendix, page 87), enabling WAD classification. No other clinical examination was performed on the WAD patients as a part of this study. Control individuals were interviewed to ensure that they fulfilled the inclusion criteria, but they were not asked to fill in any questionnaires or to undergo a clinical examination. An experienced rheumatologist performed a comprehensive clinical examination on all RA patients. Information on RA disease duration and any medical anti-rheumatic treatment was taken from the patients' hospital medical journals. In the retrospective study (**paper I**) no patients were contacted and all clinical information was taken from the referral letters.

### **6.5.1. Clinical data in WAD**

#### *Clinical data- acute phase*

Within 0 - 13 (median 4) days after their car accident all included acute WAD1-2 patients filled in a questionnaire (appendix, page 93-99). It included an 11-point numeric rating scale (NRS-11) of average neck pain since injury (initial neck pain); 0 = no pain and 10 = worst possible pain<sup>103,104</sup>, a pain drawing for the localization of maximum neck pain<sup>105</sup>, questions regarding accident-related factors, and a modified version of the Neck Disability Index (NDI)<sup>106,107</sup>. The NDI contains 10 different items each with a possible score of 0-5 reflecting increasing neck pain or difficulties during daily life activities. NDI was calculated only when at least 8 of 10 items were answered and then given as a percentage of the highest achievable score<sup>93,106</sup>. Patients' post traumatic stress response, expectations of recovery and concomitant head injury are potential risk factors for developing chronic disability or pain in acute WAD1-2<sup>108-112</sup>. Post traumatic stress response was evaluated by the impact of event

scale (IES, theoretic range 0-75) <sup>113</sup> (appendix, page 99), which has been validated in WAD <sup>108,109,114</sup>. The mean value of completed questions replaced any missing items when calculating the total IES score. At least 13 of 15 items had to be answered for a total IES score to be calculated. Patients also answered to what extent (little, some, great) they expected to get rid of their pain after the accident (appendix, page 96). These expectations of recovery were dichotomized into high (great extent) and low (little / some extent). Patients' subjective reports of concomitant head injury were registered at the interview.

#### *Clinical outcome data*

The acute WAD patients were contacted again 12 months after the accident. Uninformed of their MRI results, the responders completed a follow-up questionnaire 51-56 (median 52) weeks after the accident. Primary outcome was neck disability as measured by the NDI. According to previously validated cut off values, NDI was dichotomized into  $NDI \leq 8\%$  and  $NDI > 8\%$  <sup>107,115,116</sup>. Neck pain during the preceding week was registered by an NRS-11 and categorized into NRS-11 0-4 or NRS-11 5-10 <sup>89,103</sup>. All 111 patients responding at follow-up returned valid data for both disability (NDI) and neck pain (NRS-11).

### **6.5.2. Clinical data in RA**

RA patients' questionnaire (appendix, page 100-106) contained the Modified Health Assessment Questionnaire (MHAQ) <sup>117</sup> (page 101, point 2) and visual analogue scales (VAS) -scores covering the last 7 days' RA disease activity and neck pain. Immunological laboratory test results regarding rheumatoid factor and anti-CCP were obtained. Serological laboratory tests, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were taken within 6 days before or after the clinical examination. A Disease Activity Score in 28 joints (DAS28 score) was calculated based on a 28-joint count, ESR and the VAS-score of last 7 days' RA disease activity

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## **6.6. Statistical analysis**

### **6.6.1. Observer agreement**

Intra- and interobserver agreement was assessed by calculating kappa coefficients. When using all four grades of high-signal changes, weighted kappa with linear weights was applied. We dichotomised the grading system by combining grades 0 and 1 and grades 2 and 3. Such combined grades had shown reasonable interobserver agreement<sup>22,74</sup> and were used in the prior studies reporting relations between MRI ligament high-signal changes and trauma factors<sup>94</sup>. Ordinary kappa was calculated for agreement regarding the presence of grades 2-3 high-signal changes. As recommended by Altman<sup>119</sup>, agreement beyond chance was interpreted as poor (kappa < 0.20), fair (kappa 0.21 - 0.40), moderate (kappa 0.41 - 0.60), good (kappa 0.61 - 0.80) or very good (kappa 0.81 - 1.00). McNemar's test was applied for assessing systematic differences in ligament grading between observers. SPSS 14.0-16.0 and Medcalc version 9.5.1.0 were used to calculate ordinary and weighted kappa values, respectively.

### **6.6.2. Unadjusted analyses**

Difference in frequency of right- and left-sided ligament high-signal changes was analysed using McNemar's test. In all other analyses the highest assigned grade of ligament high-signal changes was applied if the grade differed between the two sides. Fisher's exact test was applied to compare proportions between groups. To compare means, we used an independent t-test or, if normality could not be assumed, the Mann-Whitney U test. Mantel-Haenszel's exact chi-square test for trend (linear-by-linear association) was applied to assess linear trends between ordered groups. SPSS 14.0-16.0 was used to analyse data.  $P \leq 0.05$  indicated statistical significance.

### **6.6.3. Adjusted analyses - regression models**

To assess relations between ligament high-signal changes and relevant clinical or imaging characteristics we built regression models<sup>120</sup>. Stepwise, backward, binary logistic regression was performed with grades 2-3 ligament high-signal changes as

outcome variable and mutual adjustments done for relevant explanatory continuous and categorical variables, using likelihood-ratio tests. In the longitudinal follow-up study we analysed the prognostic role of alar and transverse ligament high-signal changes in acute WAD1-2. Logistic regression analyses with NDI and neck pain NRS-11 as binary outcome variables were performed. Grades 2-3 ligament high-signal changes were our explanatory variable of main interest. Mutual adjustments were done both for age and gender and for all factors potentially related to outcome with  $p < 0.2$  in the crude analysis. Interaction between variables significantly related to outcome was looked for. All regression analyses were performed by SPSS 14.0-16.0.

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## 7. Results

### 7.1. *Interobserver agreement*

Interobserver agreement on grading alar and transverse ligament high-signal changes was reported in all papers (**paper I-IV**). Dichotomized grades were used for all within and between group analyses of ligament changes, and the highest assigned grade was chosen if the grade differed between the left and right side (see page 43). In the prospective studies we therefore calculated kappa values for agreement regarding the presence of grades 2-3 high-signal changes in a given patient. For the alar ligaments, good agreement was reported both in the RA group (kappa = 0.78, **paper II**) and in the acute WAD group and control group combined (kappa 0.71, **paper III**). For the transverse ligament, moderate agreement was reported both in the RA group (kappa 0.59, **paper II**) and in the acute WAD group and control group combined (kappa 0.54, **paper III**). In RA patients we specifically aimed to evaluate the feasibility of the high-resolution MRI examination, why we also reported kappa values for interobserver agreement per patient when applying all four grades of ligament high-signal changes (weighted kappa 0.52 alar, 0.57 transverse, **paper II**).

Additional calculations were made during the writing of this thesis to establish kappa values for each study group: the clinically referred WAD group, RA group, acute WAD group, and control group. Regarding the presence of grades 2-3 changes in a given patient, interobserver agreement was good for the alar ligaments (kappa 0.69-0.78) and moderate for the transverse ligament (kappa 0.53-0.59) in all groups. When using all four grades, interobserver agreement was moderate or good both for the alar and the transverse ligaments, depending on group (weighted kappa 0.52-0.69 alar, 0.52-0.65 transverse). Interobserver agreement regarding the presence of grades 2-3 changes calculated separately for the right and the left side was good for the alar ligaments in all groups (kappa 0.62-0.86 right side, 0.63-0.78 left side) and fair to

good for the transverse ligament, depending on group and side (kappa 0.34-0.63 right side, 0.51-0.61 left side).

## ***7.2. Alar and transverse ligament MRI high-signal changes***

### **7.2.1. In clinically referred WAD patients (paper I)**

In this study on clinically referred WAD1-2 patients, 95% of included patients had chronic symptoms (time since trauma > 6 months). The prevalence of grades 2–3 high-signal changes on high-resolution upper neck MRI in all included patients was 35.5% for the alar ligament (95% confidence interval (CI), 32.8% to 38.1%) and 24.6% for the transverse ligament (95% CI, 22.2% to 26.9%) (Table 3). Grades 2–3 high-signal changes were more common in men than women, odds ratio 1.9 (95% CI, 1.5 to 2.5) for alar and 1.5 (95% CI, 1.1 to 2.0) for transverse ligament changes. Ligament high-signal changes were not related to age ( $p = 0.198$ -0.874), spinal degeneration ( $p = 0.663$ -0.751), type of trauma event ( $p = 0.521$ -0.635) or time since trauma ( $p = 0.432$ -0.671). Grades 2-3 alar and transverse ligament high-signal changes were bilateral in about half of the cases; 238/449 (53%) and 164/311 (53%), respectively. Unilateral changes were more often left- than right-sided ( $p < 0.001$ ).

### **7.2.2. In RA patients (paper II)**

MRI images had good quality for evaluating the ligaments in 42 (91.3%) and were interpretable in 44 of the 46 RA patients. The prevalence of MRI grades 2–3 high-signal changes in the 44 eligible RA patients was 34.1% (95% CI, 19.5% to 48.7%) for the alar ligament and 31.8% (95% CI, 17.5% to 46.1%) for the transverse ligament (Table 3). According to the adjusted analyses, such ligament changes were more frequent with larger AADI on radiography ( $p = 0.028$  alar,  $p = 0.012$  transverse), higher ESR ( $p = 0.003$  transverse), positive rheumatoid factor ( $p = 0.002$  alar), and higher scores of last week neck pain ( $p = 0.004$  alar). No statistically significant

association was found between grades 2-3 ligament changes and RA duration, DAS28 score, MHAQ score, positive anti-CCP, or rheumatic MRI features. On the focused STIR sequence, only one transverse ligament and no alar ligament had signal intensity higher than bone marrow.

### **7.2.3. In acute WAD patients and control subjects (paper III)**

This study included 271 subjects: 114 WAD1-2 patients and 157 control individuals. The image quality was rated as good in 94.5% (256/271) of subjects for the proton sequences and in 85.9% (231/269) for the STIR sequence. These proportions did not differ between patients and controls ( $p = 0.106$  proton,  $p = 0.596$  STIR).

Among all 114 acute WAD1-2 patients, grades 2-3 high-signal changes on MRI were found in 35.1% (95% CI, 26.2 to 44.0%) for the alar ligaments and in 23.7% (95% CI, 15.8% to 31.6%) for the transverse ligament (Table 3). According to the multiple regression analyses such high-signal changes were related to contemporary head injury ( $p = 0.041$  alar), neck pain ( $p = 0.042$  transverse) and male gender ( $p = 0.033$  transverse), but not associated to NDI or any accident related factor. Unilateral grades 2-3 changes were more often left- than right-sided in the transverse ligament (17 left / 2 right,  $p = 0.001$ ) but not in the alar ligaments (11 left / 12 right,  $p = 1.000$ , McNemar's test).

Among the 157 non-injured asymptomatic controls, MRI showed grades 2-3 alar high-signal changes in 30.6% (95% CI, 23.3% to 37.9%) and grades 2-3 transverse high-signal changes in 29.9% (95% CI, 22.7% to 37.2%) (Table 3). Control individuals with vs. without such changes did not differ regarding gender ( $p = 0.225$  alar,  $p = 0.486$  transverse) or age ( $p = 0.888$  alar,  $p = 0.176$  transverse). As for the acute WAD1-2 patient group, unilateral grades 2-3 changes were significantly more frequent on the left side in the transverse (13 left / 4 right,  $p = 0.049$ ) but not in the alar ligaments (16 left / 8 right,  $p = 0.152$ , McNemar's test).

No difference in frequency of grades 2-3 ligament high-signal changes between WAD1-2 patients and controls was found in the unadjusted analysis ( $p = 0.434$  alar,  $p = 0.272$  transverse) (Table 3) or when adjusting for age and gender in a logistic regression analysis ( $p = 0.433$  alar,  $p = 0.254$  transverse). STIR ligament signal intensity higher than bone marrow was found in 3 patients and 1 control. Such STIR signal was registered for the alar ligaments only, and its frequency did not differ between patients and controls ( $p = 0.311$ ).

**Table 3: MRI grades 2-3 ligament high-signal changes in different study groups**

Group	Alar ligament grades 2-3 high signal <sup>a</sup>			Transverse ligament grades 2-3 high signal <sup>a</sup>		
	n	%	p <sup>b</sup>	n	%	p <sup>b</sup>
Clinically referred WAD1-2 (n = 1266)	449	35.5	0.249	311	24.6	0.145
RA (n = 44)	15	34.1	0.714	14	31.8	0.854
Acute WAD1-2 (n = 114)	40	35.1	0.434	27	23.7	0.272
Control (n = 157)	48	30.6	<sup>b</sup>	47	29.9	<sup>b</sup>

MRI = magnetic resonance imaging; WAD = whiplash-associated disorders; RA = rheumatoid arthritis

<sup>a</sup> Highest assigned grade if different between right and left side

<sup>b</sup> p value based on Fisher exact test comparing to the control group

#### **7.2.4. In WAD follow-up group (paper IV)**

Among the 111 responders (median age 29.8 years; 63 women), 34.2% had grades 2-3 alar ligament changes and 22.5% had grades 2-3 transverse ligament changes at injury. At 12 months follow-up, 49 (44.1%) reported disability (NDI > 8), and 23 (20.7%) reported neck pain (NRS-11 > 4). Grades 2-3 ligament changes in the acute phase of injury were not related to disability or neck pain at 12 months follow-up. More severe

posttraumatic stress response (higher IES score) and low expectations of recovery increased the odds for disability (odds ratio 1.46 per 10 IES points,  $p = 0.007$  and odds ratio 4.67,  $p = 0.005$ , respectively) and neck pain (odds ratio 1.93 per 10 IES points,  $p = 0.001$  and odds ratio 21.56,  $p = 0.006$ , respectively). Female gender increased the odds for neck pain (odds ratio 3.25,  $p = 0.038$ ).

## **8. General discussion**

### ***8.1. Methodological considerations***

#### **8.1.1. Study populations**

Prospective and consecutive recruitment according to a predefined study protocol prevented bias during enrolment of acute WAD patients, control individuals and RA patients. Acute WAD patients and controls were interviewed by the same researcher (N.V.) who applied the same exclusion criteria in both groups. This ensured comparable groups. All included whiplash patients could be classified as WAD1-2, but we had insufficient data to discriminate between WAD1 and WAD2. Possible effects of prior neck conditions on MRI findings and clinical features were avoided, since acute WAD patients and controls with previous neck trauma or prior neck complaints were excluded. RA patients with neck trauma were also excluded to avoid any effect of trauma in the RA group.

Inclusion of acute WAD1-2 patients both from a primary ward clinic (Bergen Accident and Emergency Department) and a hospital clinic (Haukeland University Hospital) ensured a relevant range of trauma severity in the acute WAD group. This increased the ability to detect important associations between MRI ligament changes and trauma factors or clinical features in the acute phase of injury.

The total number of adult subjects in the Bergen County population who experienced neck complaints after a car accident during our study period is unknown. We did not record the number of acute WAD patients declining to participate at Bergen Accident and Emergency Department. About one third (82/263) of the potentially includable patients from the hospital clinic could not be reached by phone or mail or had severe injuries precluding upper neck MRI examination. Some subjects probably did not seek medical care or contacted other primary ward clinics in Bergen County or their general

practitioner. Nevertheless, in Bergen County, all patients admitted for hospitalisation after traffic accidents are received at the study hospital clinic, and the remaining subjects with suspected traffic injuries are usually evaluated at Bergen Accident and Emergency Department. Consequently, we are convinced that the vast majority of patients sustaining high-velocity accidents or demonstrating severe symptoms were considered for participation. This made the current acute WAD1-2 sample appropriate for demonstrating a higher frequency of ligament high-signal changes in acute WAD1-2 than in non-injured controls, provided such changes were caused by the actual mechanic incident.

All controls were informed in the invitation letter (appendix, page 89-91) that current or prior neck trauma or neck complaints precluded participation. Being aware of this, some controls might have denied neck trauma and neck complaints in order to get a cervical spine MRI examination. If subjects with neck problems were faulty included in the control group, the prevalence of ligament changes in controls could theoretically be overestimated. Since the responsible researcher performed a thorough telephone interview of each control person before the final inclusion, denial of any current or prior neck problem would be unexpected. However, information on such problems could be lacking due to recall bias.

All included RA patients were hospitalised at a rheumatology department. Although patients with recently diagnosed RA disease were also hospitalised ensuring a wide range of rheumatic features, most included patients had active RA disease (median DAS28-score 5.3, range 2.9-7.9) and long RA disease duration (median 9.1 years, range 0.0-34.6 years) (**paper II**). Our sample should therefore be appropriate to demonstrate the feasibility of upper neck high-resolution MRI in different stages of adult RA disease.

In the retrospective study (**paper I**), all clinical data were taken from referral letters. Such data may be imprecise. However, these particular referral letters were often extensive and were unlikely to lack crucial data on neurological signs or neck fracture (WAD3-4) or to falsely report neck complaints in WAD0. The report of WAD1-2

should therefore be quite certain. WAD1-2 patients who reported more severe symptoms may have been more likely to be referred for MRI. Our sample may therefore not be representative for WAD1-2 patients in general, but rather for patients with more pronounced symptoms.

A major strength of the longitudinal study (**paper IV**) was the high proportion of responders at 12 months follow-up (97%, 111/114) which prevented selection bias. This high response rate was reached partly because the same researcher who included the patients at the time of injury (N.V.) also contacted the patients 12 months later. Patients could send their follow-up questionnaires by mail and were encouraged to fill in the questionnaires even if they could not attend for the follow-up MRI (results in preparation). Furthermore, all patients were informed about the 12 months follow-up when giving their initial written consent to participate. Ligament findings on MRI were not communicated to the participants or their health care providers, avoiding possible influence of such information on the patients' response rates and reports of outcomes<sup>121,122</sup>.

### **8.1.2. Sample size**

During the early planning of this study, sample size calculations were performed using a significance level of 5% and a power of 80% (nQuery Advisor 6.0). At that time, prevalence data on alar ligament high-signal changes in WAD and controls were scarce. Kråkenes et al had reported the prevalence of grades 2-3 alar ligament changes to be 66.3% in a chronic WAD2 group and 6.7% in a control group<sup>22,94</sup>. The clinically relevant difference in prevalence between WAD patients and controls was unknown. By using a 2:1 design, we estimated that 150 controls and 75 acute WAD1-2 patients would be needed if a difference in prevalence from 5% in the control group to 18% in the acute WAD group should be detected as statistically significant. To account for inadequate MRI examinations and to increase the ability to detect relevant associations within the WAD group, we somewhat increased the number of acute WAD patients (n = 114, **paper III**).

In RA patients, no data on the prevalence of MRI upper neck ligament high-signal changes existed prior to the current studies. Pre-study calculations showed that with 31 RA patients and a prevalence of transverse ligament changes in these patients of 15% or 50%, the width of the 95% confidence interval for the prevalence would be 25% (2.5% to 27.5%) or 35% (32.5% to 67.5%), respectively. Based on these calculations, around 40 RA patients were regarded as adequate in this initial MRI study on alar and transverse ligaments in RA, also for evaluating feasibility and marked associations within the RA group. In the retrospective study on clinically referred WAD patients (**paper I**), a large number of MRI examinations were available from imaging files, and no pre-study sample size calculations were performed.

Post-study power calculations were performed based on the current observed prevalence of alar ligament high-signal changes in control individuals (30.6%, **paper III**), using a significance level of 5% and a power of 80% (SPSS SamplePower 2.0). In a 2:1 design, we estimated that to detect a difference in prevalence of 20% (between 30.6% in the control group and 50.6% in the acute WAD group), 138 controls and 69 WAD patients would be needed. A smaller difference would hardly be clinically relevant. Thus, the final numbers of included acute WAD patients and controls were adequate. In the 44 included RA patients, the prevalence of transverse ligament changes was found to be 31.8% with a width of the 95% confidence interval of 28.6% (17.5% to 46.1%, **paper II**).

### **8.1.3. MRI protocol**

#### *Proton-weighted sequences*

Due to their high signal to noise ratio, proton-weighted sequences can produce adequate images even at the high resolutions needed to visualize the small craniovertebral ligament structures <sup>8</sup> (Figure 9 and 10, page 35 and 36). All our prospectively recruited subjects completing the MRI examination (n = 318) had interpretable proton images except for two RA patients and one acute WAD patient, who were excluded due to poor image quality. Only 7 subjects had to abort the MRI examination, all because of claustrophobic discomfort. This clearly shows that the

protocol is robust and well accepted by different patient groups despite the long acquisition times. Kråkenes et al reported that proton images were superior to T1- and T2-weighted spin echo sequences, T2-weighted gradient echo sequences and STIR sequences, both in discriminating ligaments from surrounding tissue and in evaluating their structure <sup>8</sup>. That proton-weighted sequences can demonstrate the alar and transverse ligaments has also been confirmed in several other studies <sup>7,74,77,123</sup>.

In the pilot studies on 24 volunteers, we experimented by modifying MRI parameters (TR, TE, echo train length (ETL), number of acquisitions, receiver bandwidth, and phase-encode direction) in order to optimise the proton sequences. We also applied an eight-channel head coil and a parallel imaging technique, generalized autocalibrating partially parallel acquisition (GRAPPA), that can reduce acquisition times allowing a higher number of acquisitions <sup>124,125</sup>. These modifications did not produce proton images showing the ligaments more clearly than the proton images obtained using the standard one-channel receive-only head coil. We also experimented by using a 3.0 Tesla scanner (GE Signa Excite HD) which is known to create a stronger MRI signal <sup>126,127</sup>. However, no advantages of 3.0 Tesla compared to 1.5 Tesla were found when applying proton-weighted sequences on the upper neck ligaments.

### *SPACE sequences*

In a study published in 2009, Baumert et al examined the upper neck ligaments in a 1.5 Tesla scanner applying SPACE (Sampling Perfection with Application optimized Contrast using different flip-angle Evolution), a T2-weighted three-dimensional turbo spin echo sequence with variable flip-angle distributions <sup>128</sup>. A single set of 0.9 mm slices with isotropic resolution that allowed multiplanar reconstruction, was acquired. The alar and transverse ligaments were identified in all of 52 volunteers. This method seems promising but has not been applied on WAD patients. The long acquisition time of the SPACE sequence (8 minutes versus 5-7 minutes for our proton sequences) might reduce its feasibility in subjects with neck pain. On the other hand, since only a single SPACE sequence was needed, the total examination time was considerably reduced (our three proton sequences took 17 min and 45 s). By using SPACE sequences, Baumert et al described increased signal intensity in the central portion of

the alar ligaments in about half of their volunteers. It is unknown how increased signal intensity on SPACE images corresponds to high-signal changes on proton-weighted images.

#### *Gradient echo sequences*

Gradient echo sequences are widely used in MRI assessment of spine injuries<sup>129,130</sup> and have also been applied for visualisation of the upper neck ligaments<sup>34,35,85</sup>. Shorter acquisition times and multiplanar image reconstructions are possible advantages of such sequences. However, the craniovertebral junction involves tissue at close anatomic proximity with great differences in magnetic properties, which again can induce magnetic field inhomogeneity and susceptibility artefacts, causing poor image quality. Gradient echo sequences are especially prone to such artefacts<sup>131</sup>. In our pilot study we experimented with different gradient echo sequences both on 1.5 Tesla and 3.0 Tesla scanners but were not able to produce images superior to the established proton images regarding the visualisation of the alar and transverse ligaments.

#### *Gadolinium enhanced sequences*

Gadolinium enhanced T1-weighted sequences increase the sensitivity for rheumatic features, especially synovitis<sup>99</sup>. It has been suggested that contrast enhancement can add valuable information on upper neck ligaments<sup>123</sup>. However, no MRI study focusing on these structures has reported on gadolinium enhanced imaging. The usefulness of adding contrast enhanced sequences for evaluation of the alar and transverse ligaments is therefore unknown and should be weighted against the disadvantages of longer examination times and the administration of gadolinium.

#### *“Functional” MRI*

All our patients and controls were imaged with their head and neck in a neutral position. Other researchers<sup>7,77,80,84,132</sup> have performed MRI of the craniovertebral junction during lateral neck flexion or neck rotation which stretches the alar ligaments<sup>1,2,4</sup>. As changes in tension can affect the MRI signal from ligaments<sup>133</sup>, adding such “functional” sequences could give valuable information. In RA patients, MRI during cervical flexion and extension would have been of interest as the transverse ligament is

stretched during flexion and prevents anterior dislocation of atlas on axis <sup>2,3,13,14</sup>. Special MRI compatible devices have been developed for this purpose <sup>134,135</sup>. “Functional” MRI is often difficult to perform and standardise in closed scanners, and decreased image quality and ligament visibility compared to images taken in neutral position has been reported <sup>77</sup>. Adding more sequences to our MRI protocol would also imply a longer total imaging time that might be unacceptable to some patients.

Volle et al. performed “functional” MRI of the craniovertebral junction by first tilting WAD patients’ head stepwise in lateral flexion, and later rotating the head stepwise to both sides <sup>84,85</sup>. Images were partly studied in video loops. Alar ligaments and craniovertebral instability were assessed. Although a similar protocol was recently applied on WAD patients and controls <sup>132</sup>, this method is still not properly validated. The criteria for alar ligament rupture and craniovertebral instability are poorly described, and the reproducibility of such findings is unknown <sup>40,86</sup>.

### *STIR sequences*

For evaluation of blood / edema and the presence of fat tissue on MRI, fat suppression techniques can be used <sup>72,97</sup>. In their study of craniovertebral structures, Dullerud et al used proton-weighted sequences both with and without chemical shift selective fat suppression <sup>123</sup>. They reported better delineation of craniovertebral structures, especially membranes, when applying fat suppression. However, chemical shift selective fat suppression techniques are hampered by reduced signal to noise ratio and are sensitive to magnetic field inhomogeneity <sup>97</sup>. In the pilot studies, we found STIR sequences superior compared to proton-weighted sequences with chemical shift selective fat suppression. Both sequences showed poorer anatomic depiction than the proton-weighted images. Our included sagittal “focused” high-resolution STIR images were therefore coupled to the corresponding proton-weighted images during interpretation.

#### 8.1.4. MRI interpretation

All prospectively included patients and controls (**paper II-IV**) were examined using the same MRI protocol and the same 1.5 Tesla scanner, providing comparable images between groups. The retrospective study (**paper I**) was based on images obtained using the same scanner and a nearly identical protocol containing the same high-resolution proton-weighted sequences but no STIR sequence.

To ensure a truly blinded and unbiased grading of ligament high-signal changes in the prospective study groups, all images were completely de-identified, also for patient age and gender and for examination date and time. The observers remained blinded for study group also when incidental findings needed further evaluation. Such findings were looked for by a different neuroradiologist shortly after the images had been produced and were not conveyed to the observers. Findings on STIR images did not influence the grading of ligament high-signal changes on proton images. The STIR images were not made available before the interpretation of the proton images had been completed. RA patients might have been identified due to specific rheumatic changes on the proton images (e.g. anterior atlantoaxial dislocation, visible in the neutral position), but such changes were rare in the current RA group. In all prospective studies double reading and consensus grading in cases of disagreement were performed, an approach previously shown to be beneficial compared to single reading of images <sup>136</sup>.

In the retrospective study (**paper I**), all images were interpreted by one study radiologist only (J.K.), and the result from this interpretation was used in the analyses. Clinical data from referral letters were available which might have biased the ligament grading. The second radiologist (N.V.) blinded to such clinical data and to the first radiologist's grading, interpreted a random subsample of 100 examinations. The two radiologists achieved reasonable agreement (see page 45) and did not report a significantly different prevalence of ligament high signal changes. The grading results in the retrospective study should therefore be comparable to the consensus grading results in the prospective studies. However, in the retrospective study both observers knew that all presented images were taken from clinically referred WAD1-2 patients.

If this knowledge influenced the grading, it would be expected to result in an overestimation of the prevalence of ligament high-signal changes. Consequently, the true difference in prevalence of such changes between the clinically referred WAD1-2 patients and the control individuals might be even smaller than reported (Table 3, page 48).

In the acute WAD group, time from accident to MRI was median 5 days (range 0-13 days) and 87 % of the patients underwent MRI within 7 days after their accident. Although it has been postulated that post injury edema can resolve within the first week<sup>87,137,138</sup>, it is unlikely that we have missed important MRI ligament changes in the acute phase due to delayed MRI examination.

In all sub-studies high-signal ligament changes were graded according to Kråkenes<sup>22</sup>. Our findings of moderate to good interobserver agreement (kappa 0.53 – 0.78) for grades 2-3 versus grades 0-1 ligament changes in a given subject indicate reasonably reliable grading of ligaments on high-resolution proton-weighted upper neck MRI. The kappa values for agreement regarding grades 2-3 alar ligament changes, calculated separately for the right and the left side (kappa 0.62 – 0.68), are in line with comparable reports on WAD patients and controls from Myran (kappa 0.60 – 0.66)<sup>74</sup> and Kråkenes (kappa 0.46 – 0.65)<sup>22</sup>. Similar kappa values have been reported for many MRI examinations in daily use, for example to assess foraminal lumbar spinal stenosis (kappa 0.58)<sup>139</sup>, herniated or bulging lumbar discs (kappa 0.59)<sup>140</sup> and bone marrow changes at the vertebral endplates (Modic changes) (kappa 0.53)<sup>141</sup>.

Previous reports on kappa values for grading upper neck ligament high-signal changes on MRI have indicated insufficient observer reliability when using all four grades<sup>74,123</sup>. As found in our study, improved agreement can be achieved by dichotomizing grades<sup>22,74</sup>. Despite this, we chose to apply all four grades throughout the image interpretation to be methodologically comparable to previous studies.

### 8.1.5. Clinical data and outcomes

Almost complete datasets were achieved in the prospective studies (**paper II-IV**). When acute WAD patients returned incomplete questionnaires at injury or at 12 months follow-up, the author of this thesis re-contacted the patients by telephone within a few days in order to obtain more complete data. In the RA group, the study rheumatologist (R.A1.) checked that all RA patients had completed relevant items before she collected their questionnaires.

Recall bias may have affected the clinical information given by the study participants in the prospective studies, but hardly differed between participants with and without high-signal ligament changes. Thus, such bias was unlikely to affect the associations between ligament high-signal changes on MRI and clinical factors within the study groups.

The key instruments used to obtain clinical information on the prospectively included acute WAD1-2 patients have all been validated in prior WAD groups. Neck pain NRS-11, NDI and IES are reported and recommended in several recent WAD studies<sup>89,109,114,115,142</sup>. The acute WAD1-2 patients completed the questionnaires containing these instruments within 0-13 (median 4) days after injury. They would therefore be expected to report accurate information on accident related factors and symptoms in the acute phase. However, some of the items included in NDI and IES might be difficult to answer immediately following an accident, e.g. regarding sleep, work, driving (appendix, page 97-98). Nevertheless, only one of the 114 acute WAD1-2 patients had not answered an adequate number of NDI items in the acute phase of injury. In all other acute WAD patients both the NDI score and the IES score could be calculated.

In the follow-up study (**paper IV**) we used NDI and last week's neck pain NRS-11 as outcome variables. Outcome measures often differ between WAD studies, but most often either neck disability or neck pain is applied<sup>143</sup>. Since disability and pain are considered two distinct outcomes<sup>144</sup>, we analysed each separately (**paper IV**). When dichotomising these continuous outcome variables for logistic regression analyses, we

used validated cut off values <sup>89,103,107,115,116</sup>. In the logistic regression analysis, we adjusted for age, gender, initial neck pain (NRS-11), posttraumatic stress (IES) and expectation of recovery. Data on anxiety or depression were not included <sup>114,145</sup>. Potential residual confounders could not have changed our result for prognostic value of MRI ligament high-signal changes unless they were unequally distributed between patients with and without such changes. In a cross-sectional study on chronic WAD2 by Kaale et al <sup>146</sup>, alar ligament high-signal changes were related to decreased maximal active cervical spine flexion and rotation. We had no data on cervical range of movement in our acute WAD1-2 cohort.

### **8.1.6. Statistical methods**

#### *Unadjusted analysis*

The significance level was set to 0.05 (5%) in all studies. Several within group analyses of associations between ligament high-signal changes and other variables were performed in the RA group and in the acute WAD1-2 group. If one does not apply corrections for multiple comparisons, the risk of observing a difference when in truth there is none (type 1 error) increases. The use of such multiple testing corrections is controversial <sup>147</sup>. We thought it would be more important to avoid failing to observe a difference when in truth there is one (type 2 error). As a consequence, no corrections for multiple comparisons were performed in the crude analyses. In all studies, the results from the regression analyses with mutual adjustment for relevant explanatory factors (see below) were considered to be the conclusive results.

Many tests exist for assessing associations between categorical variables. We applied Fisher's exact test for this purpose, also in the larger study groups. Some authors claim that this test is too conservative and advocate the use of unconditional tests or in large samples, the traditional asymptotic Pearson's chi-squared test <sup>148</sup>. These different tests would usually produce rather similar p-values in samples that are as large as our WAD1-2 and control groups; the main results would hardly be changed if a different test was chosen, neither in the within-group analyses nor in the between-groups analyses.

If a normal distribution of continuous variables could not be ascertained, means were compared by using the Mann-Whitney U test. An independent t-test assuming normality is more powerful <sup>149</sup>. In cases where normality could be questioned we therefore checked that the t-test gave a similar result to ensure that the result was robust.

### *Adjusted analysis*

To control for confounders and measure independent effects of different explanatory factors on ligament high-signal changes (**paper I-III**) or neck disability and neck pain (**paper IV**), we performed stepwise backward, binary logistic regression analyses by using likelihood-ratio test. The numbers of explanatory variables that can be included in regression models depend on the total sample size and the distribution of the outcome variable <sup>150</sup>. In our prospective studies the number of potential explanatory factors was high and therefore only variables potentially related to the outcome variable with  $p < 0.2$  in the crude analysis were included in the regression models. The procedures for including explanatory variables in regression models and the use of stepwise selection of variables are controversial <sup>120,151</sup>. Stepwise selection is still widely used and recommended, particularly when as in our case the outcome variable is new and all important covariates are not known <sup>151</sup>. In all regression analyses continuous explanatory variables were treated and presented uncategorized. Corresponding regression models were built to check that similar results were achieved if such continuous variables were treated categorized.

## ***8.2. Discussion of alar and transverse ligament high-signal changes***

### **8.2.1. Prevalence in WAD1-2 and controls**

When evaluating the prevalence of high-signal changes of alar and transverse ligaments one has to take into account the different MRI protocols and grading

systems applied. Although high-signal changes have been described on both T1-weighted and T2-weighted sequences<sup>10,35,128,151</sup>, the results from our studies should best be compared to findings in studies where high-resolution proton-weighted sequences have been applied.

#### *Alar ligaments - WAD1-2*

In our large group of clinically referred WAD1-2 patients (**paper I**), of whom 95 % had a time since trauma of more than 6 months suggesting chronic WAD, the prevalence of grades 2-3 alar ligament high-signal changes was 35% (449/1266). By using similar sequences, roughly comparable prevalence results were reported in chronic WAD groups by Myran et al (49%, 29/59)<sup>74</sup> and Dullerud et al (29%, 16/56)<sup>123</sup>. Kråkenes et al reported a higher prevalence of alar ligament changes in their chronic WAD patients (66%, 61/92)<sup>22</sup>. Since the patients in this latter study fulfilled the WAD2 criteria both in the acute phase and 12-16 weeks later, they might have experienced more severe neck traumas. However, the frequency of alar ligament changes was not related to type of trauma event (transport accidents or non-transport accidents) in our clinically referred WAD1-2 patients (**paper I**). Also, we found no relation between trauma factors and ligament findings in acute WAD1-2 (**paper III**). Thus, the difference in prevalence of alar ligament changes between the patients of Kråkenes et al and our clinically referred WAD1-2 patients seems hard to explain. No previous study has reported on the prevalence of alar ligament high-signal changes in acute WAD1-2 patients. This prevalence was 35% (40/114) in our study (**paper III**).

#### *Alar ligaments - controls*

The prevalence of alar ligament changes in uninjured controls varies between studies. In our control group, grades 2-3 alar ligament changes had a prevalence of 31% (48/157, **paper III**). Kråkenes et al reported such changes in only 7% (2/30)<sup>22</sup>. Myran et al included both 57 symptomatic (neck pain) and 57 asymptomatic uninjured individuals and found a prevalence of 33% and 40%, respectively<sup>74</sup>. In a study by Dullerud et al, grades 2-3 high-signal changes were found in 30% (16/54) of control alar ligaments<sup>123</sup>. A similar result (31%, 8/26) was also found in a small group by Roy et al<sup>77</sup>, but they applied a somewhat different MRI protocol and grading system (see

page 17). By using T2-weighted high-resolution SPACE sequences, Baumert et al recently reported high-signal changes in 44% of the alar ligaments of their 52 healthy volunteers <sup>128</sup>. Kråkenes et al used a small control group (n = 30) <sup>82</sup>, and random variation may have contributed to their lower estimated prevalence of alar high-signal changes in controls compared to the present and other studies.

#### *Transverse ligament – WAD1-2 and controls*

Data regarding MRI findings of the transverse ligament are sparse. The prevalence of grades 2-3 high-signal changes in our clinically referred WAD1-2 patients was 25% (311/1266, **paper I**). This figure is comparable to the prevalence estimated by Dullerud et al in their chronic WAD group (29%, 16/56) <sup>123</sup>. Kråkenes et al found a somewhat higher prevalence (40%, 37/92) in chronic WAD2 patients <sup>22</sup>. The prevalence of grades 2-3 transverse ligament high-signal changes in our control group (30%, 47/157) is in line with the results of Dullerud et al (26%, 14/54) <sup>123</sup> and Kråkenes et al (20%, 6/30) <sup>22</sup>. No data exist for comparison with the prevalence of transverse ligament high-signal changes in our acute WAD1-2 group (24%, 27/114, **paper III**).

#### *WAD1-2 versus controls*

The prevalence of grades 2-3 alar and transverse ligament high-signal changes did not differ between the clinically referred WAD1-2 patients (**paper I**) and the uninjured controls (**paper III**) (Table 3, page 48). This is in line with the results from controlled studies on chronic WAD1-2 patients by Myran et al <sup>74</sup> and Dullerud et al <sup>123</sup>. Kråkenes et al reported that alar and transverse ligament high-signal changes were significantly more frequent in chronic WAD2 patients than in controls <sup>22</sup>. The discrepancy is difficult to explain.

The prevalence of grades 2-3 ligament high-signal changes similarly did not differ between the acute WAD1-2 patients and the controls (**paper III**) (Table 3). As argued earlier in this thesis (see page 51), a significant difference would have been expected if upper neck ligament high-signal changes in the acute phase of injury were due to the acute, mechanic incident.

### 8.2.2. High-signal changes: associations within WAD1-2 groups

#### *Gender*

We observed a male preponderance for alar and transverse ligament MRI high-signal changes in the clinically referred WAD1-2 group (**paper I**). Such a male preponderance was also found for the transverse ligament in acute WAD1-2 patients, but was not found in the controls (**paper III**). A potential explanation for the male preponderance could be that males are more often involved in high energy accidents<sup>152-156</sup>. However, transport accidents, which might involve higher energy than non-transport accidents, were actually less frequent in males (**paper I**). Higher car speed at impact did not imply more ligament high-signal changes in the acute WAD1-2 patients (**paper III**). Furthermore, alar ligament high-signal changes were more prevalent in males also in the RA group (**paper II**). The male preponderance can therefore most probably not be explained by trauma-related factors.

#### *Right-left differences*

Unilateral alar ligament high-signal changes were more often left- than right-sided in clinically referred WAD1-2 patients (**paper I**). The alar ligaments may be more vulnerable when tightened by the opposite rotation of the head<sup>1,2,5,94</sup>. The left ligament could therefore theoretically be more vulnerable in right-hand driving countries, where car drivers might more often have their head turned right. However, we observed this left preponderance for alar ligament changes both in transport accidents and in non-transport accidents (**paper I**). In the acute WAD1-2 group, no such side difference of alar changes was observed, and unilateral alar changes were not related to having the head rotated at impact (**paper III**). Consequently, a left side predominance of alar ligament changes can probably not be explained by trauma factors such as head rotation. Regarding the transverse ligament, a left predominance of high-signal changes was found in both the acute and the clinically referred WAD groups, but also in the non-injured controls. A reasonable explanation for the side difference is therefore hard to find. Chemical shift artefact<sup>76,157</sup> is not a plausible explanation, since

our MRI protocol did not include sequences with a frequency direction of left to right (or right to left).

*Clinical symptoms in the acute phase of injury and accident-related factors*

Associations between MRI grades 2-3 ligament high-signal changes and head position at impact as well as between such changes and neck disability, have been reported in chronic WAD2<sup>93,94</sup>. In the present study on acute WAD1-2, alar ligament high-signal changes were not associated with neck disability, neck pain intensity, head position, impact direction, speed at impact or other accident related factors (**paper III**). Alar ligament changes were found somewhat more often in patients subjectively reporting concomitant head injury. Head injury may imply more severe trauma and higher loads on the craniovertebral structures<sup>158</sup>. In the same acute WAD1-2 group, high-signal changes of the transverse ligament were weakly related to neck pain but not to neck disability or accident related factors (**paper III**). In general, no strong associations were found that convincingly connected the ligament high-signal changes to clinical symptoms or accident-related factors.

*Outcome at 12 months follow-up*

Our acute WAD cohort should be representative of acute WAD1-2 patients without previous neck problems who seek medical care shortly after a car accident. The outcomes at 12 months were somewhat better than reported for cohorts that were comparable but also included WAD3 patients<sup>114</sup> or patients prioritized for MRI due to more severe initial symptoms<sup>89</sup>. Female gender, more severe post traumatic stress response, and reduced expectations of recovery were associated with poor outcome, as in previous reports<sup>108-112</sup>. An independent effect of degree of initial pain<sup>110,114,159,160</sup> was not confirmed, probably because pain just after the accident may be intense but temporary.

Thus, in the present cohort, it was possible to identify relations between clinical factors and outcomes. However, no relation between ligament high-signal changes in the acute phase and outcomes at 12 months could be found despite a representative sample, sufficient sample size, adequate distribution of MRI ligament high-signal

changes and outcomes, and adjustment for relevant factors (**paper IV**). This lack of prognostic value of MRI high-signal changes in the acute phase of injury has important implications. First, such changes are unlikely to represent an indication for treatment, regardless of whether they are traumatic or represent morphologic ligament variants. Second, routine use of high-resolution MRI of these ligaments is not warranted in acute WAD1-2. Third, the high-signal changes are unlikely to be injury-induced. If they were due to the acute, mechanic incident, we would expect at least some prognostic effect.

The present study was the first to evaluate the prognostic value of alar and transverse ligament high-signal changes in WAD. Previous studies have reported that MRI findings like vertebral fracture or dislocation, traumatic disc or endplate changes, prevertebral soft tissue bleeding / edema, posterior or anterior longitudinal ligament rupture, and spinal cord injuries rarely occur in patients who have acute WAD1-2 based on assessment without MRI <sup>88-92,161</sup>. Such MRI findings, when occurring, were not related to outcome, and cervical spine MRI has not been recommended as a standard procedure in WAD1-2 patients <sup>87,109,162,163</sup>. Our results show that adding MRI sequences capable of visualising craniovertebral ligaments does not change this recommendation.

### **8.2.3. High-signal changes in RA**

We were the first to describe the prevalence of alar and transverse ligament high-signal changes on MRI in RA patients and the relations of such changes to other imaging findings and clinical features (**paper II**). Dickman et al described abnormalities of the transverse ligament in all of 4 RA patients examined using T2-weighted gradient echo sequences, but did not report exact signal characteristics <sup>34</sup>.

Our results suggest that MRI ligament changes are related both to general and local RA disease activity (**paper II**). Patients with transverse ligament changes had higher ESR. Patients with alar ligament changes were more often rheumatoid factor positive. Both groups tended to show more dens erosions on MRI. MRI ligament changes were

not significantly related to DAS 28, anti-CCP or disease duration. The scores of the 28-joint count and patients' assessment of global health contribute importantly to the total DAS28 score, which therefore to a lesser degree reflects cervical RA activity. The large majority (79.5%) of the RA patients were anti-CCP positive, making any relation to ligament changes more difficult to prove. The long disease durations (median 9.1 years) may have reduced the chance to detect any relation between ligament changes and disease duration, since cervical spine changes can usually be demonstrated within 2 years of RA disease onset if the cervical spine is involved in RA<sup>164</sup>.

A functionally intact transverse ligament prevents AADI from exceeding 3 mm<sup>2,3,13,14</sup>. The association we found between transverse ligament high-signal changes and larger AADI suggests that such high signal might reflect involvement of the transverse ligament in cervical RA. However, longitudinal studies are needed to find out if high-signal changes increase the risk of larger AADI and later subluxation. If so, high-resolution MRI might become a tool for predicting cervical RA and clinically relevant complications at an early stage of disease before it can be demonstrated on functional radiography.

The similar prevalence of grades 2-3 ligament high-signal changes in the 44 RA patients and in the 157 non-rheumatic non-injured controls (Table 3) reduces the clinical importance of such findings in RA. If ligament high-signal changes in RA patients were due to the inflammatory disease, a difference in prevalence between RA patients and controls would have been expected.

#### **8.2.4. Cause of high-signal changes - morphologic correlate**

##### *MRI Artefacts*

High-signal intensity in ligaments on MRI is expected to reflect morphologic, structural changes<sup>68</sup>, but may also be due to MRI artefacts. The alar and transverse ligaments are delicate structures surrounded by epidural fat, which shows high signal on proton images. These ligaments often run obliquely to the standard imaging planes,

and high signal can appear as a result of volume averaging<sup>74,77</sup>. Such partial volume artefacts were reduced by using high-resolution sequences in three orthogonal planes. Only high signal seen in at least two imaging planes was graded 1-3. A previous study suggested that volume averaging was not an important reason for interobserver disagreement in grading of alar ligaments<sup>82</sup>. In the only study comparing high-signal intensity and ligament thickness, high-signal intensity tended to be more frequent in thicker ligaments<sup>8</sup>. The opposite would be expected with partial volume artefacts. Also, such artefacts cannot explain our finding of left side predominance of high-signal changes (**paper I**), since symmetrical thickness and obliquity on the right and left side have been reported both for the alar ligaments and for the transverse ligament<sup>1,6,9</sup>.

The magic angle effect can cause high-signal changes of ligaments and tendons running at angles close to 55 degrees to the main magnet field (B0)<sup>73,75</sup>. B0 in a standard closed MRI scanner is orientated in the cranio-caudal direction of a supine patient. Considering the normal anatomy and directions of the alar and transverse ligaments<sup>8,9</sup>, an angle close to 55 degrees between these ligaments and B0 is rare, especially for the transverse ligament. The magic angle effect is most pronounced when applying short echo times (TE) as in proton sequences. However, upper neck ligament high-signal changes have been reported to be frequent also when applying long echo times as in T2-weighted sequences<sup>10,128</sup>. Both partial volume artefacts and magic angle artefacts should be considered during interpretation, but such artefacts can not explain the vast majority of upper neck ligament high-signal changes on high-resolution MRI.

#### *Age dependent degeneration*

It is well documented that age-dependent degeneration appears in tendons throughout the musculoskeletal system<sup>70,71</sup> and can cause high-signal changes on MRI<sup>69,70</sup>. Less is known about MRI and degeneration in ligaments. Cases of mucoid degeneration causing high-signal changes have been reported, predominantly in the anterior cruciate ligaments of the knee<sup>165-167</sup>. Focal regions of MRI high signal intensity in ligaments have been correlated to histological eosinophilic and mucoid degeneration in uninjured

cadaveric specimen<sup>68</sup>. MRI studies on ligaments of asymptomatic, non-injured subjects have shown low frequencies of high-signal changes<sup>168,169</sup>. Histological degeneration of ligaments has not been found to increase by age in uninjured individuals<sup>170,171</sup>.

The present alar and transverse ligament high-signal changes can not be explained by age dependent degeneration. No association to age was found in any study group (**paper I-III**), and ligament changes were not related to time since injury or to age-dependent cervical spine degeneration on MRI in the clinically referred WAD group (**paper I**). Such high-signal changes therefore most probably represent permanent tissue morphologically different from the expected compact collagen structure of alar and transverse ligaments<sup>5</sup>.

#### *Edema / inflammation*

In acute injuries, ligament high-signal changes can be caused by edema or bleeding<sup>45-48</sup>. If the alar and transverse ligaments were injured in the present acute WAD1-2 patients, the proton and STIR sequences in our MRI protocol were not capable of demonstrating this. No difference in grades 2-3 high-signal changes between patients and controls and no convincing relations between such changes and symptoms or accident related factors could be proven. On the focused STIR sequence which is highly sensitive for edema<sup>72,97</sup>, only 3 acute WAD1-2 patients and 1 control had ligament signal intensity higher than the intensity of the adjacent bone marrow.

In the RA group, such ligament high-signal intensity on STIR was found in one patient only. A previous study evaluating the MRI signals of the cervical peridental tissue in chronic RA has suggested that it represents fibrous tissue and does not reflect ongoing inflammation<sup>172</sup>. Similarly, post-mortem and post-operative histopathological studies of bone and soft tissue specimen from the upper cervical spine in chronic RA have revealed predominantly fibrous tissue with little or no evidence of active inflammation<sup>63,64</sup>. Neither in acute WAD1-2 nor in RA can edema, bleeding, or acute inflammation explain the majority of alar or transverse ligament high-signal changes.

*Post traumatic chronic changes*

It has been postulated that high-signal intensity in alar and transverse ligaments can represent chronic post traumatic changes<sup>82</sup>. Even if not detectable on MRI in the acute phase (**paper III**), ligament injury might through a subsequent repair process and replacement of collagen fibres with fibrosis or fat tissue produce high-signal changes in a later stage of injury. The expected result would then be more frequent high-signal changes in chronic WAD patients than in controls. This was found in the study by Kråkenes et al<sup>22</sup> on chronic WAD2 patients but not in our study on clinically referred WAD1-2 patients (**paper I**) or in the studies on chronic WAD1-2 patients by Myran et al<sup>74</sup> or Dullerud et al<sup>123</sup>. Overall, it seems unlikely that high-signal changes in a late stage of whiplash injury are caused by the previous trauma. However, the repeated MRI examination of our acute WAD1-2 cohort at 12 months follow-up will probably add information on how such MRI ligament findings might or might not change over time (results in preparation).

*Fat or loose connective tissue in normal morphologic ligament variants*

Alar and transverse ligament high-signal changes were common in the present uninjured non-RA controls and occurred with similar frequency in this group and in the WAD and RA groups. Such changes therefore most probably represent normal morphologic ligament variants. Histological studies, performed on a few cadavers only, have revealed that these ligaments consist of compact collagen fibres without evidence of adipose tissue<sup>2,5</sup>. However, differences in signal intensity between the anterior and the posterior cruciate ligaments in the knee, despite their histologically similar compact fibre structure, have been explained by interfascicular fat and variations in macroscopic anatomy<sup>68</sup>. Fat interspersed between fibres could also cause high-signal changes of alar and transverse ligaments. This would be compatible with the low signal observed on STIR (**paper II-III**) and with the findings of Dullerud et al who reported reduced number of ligaments graded 2 or 3 when applying fat suppression<sup>123</sup>.

If alar and transverse ligament high-signal changes represent morphologic variants with loose connective tissue or fat, the affected ligaments could have reduced strength

and increased vulnerability during neck trauma, resulting in worsened prognosis. However, our longitudinal study of WAD1-2 patients revealed that neither alar nor transverse ligament high-signal changes were related to neck pain or disability 12 months following injury. Thus high-resolution MRI seems of limited clinical value in WAD1-2, at least in the acute phase.

Studies comparing imaging and histological findings of these upper neck ligaments could be performed to establish the true morphologic correlate of the high-signal changes. Such data on the underlying morphology would provide insight into the MRI evaluation of ligaments, but are unlikely to aid clinical decisions in acute WAD1-2.

## 9. Summary and conclusions

High-resolution proton-weighted MRI provided overall high-quality images and adequate visualisation of the alar and transverse ligaments in clinically referred WAD1-2 patients (**paper I**), RA patients (**paper II**), acute WAD1-2 patients (**paper III-IV**), and uninjured non-RA control individuals (**paper III**). High-signal changes of these ligaments were reliably graded with moderate to good interobserver agreement for grades 2-3 versus grades 0-1 changes.

In both WAD1-2 groups, about one third (35%) had grades 2-3 alar ligament changes and one fourth (24%-25%) had grades 2-3 transverse ligament changes (**paper I, III**). The prevalence of grades 2-3 changes in WAD1-2 patients did not differ significantly from the prevalence in uninjured controls (30% for alar and 30% for transverse ligament changes, **paper III**). Trauma-related factors can not explain the male or left side preponderance of ligament changes in WAD1-2 (**paper I, III**). In the clinically referred WAD1-2 patients, the ligament changes were not related to type of accident (transport or non-transport) or time since trauma (**paper I**). In the acute WAD1-2 group, no strong association convincingly connected ligament changes to accident related factors or acute clinical symptoms (**paper III**). Such changes in the acute phase of whiplash injury were not related to outcome at 12 months (**paper IV**). These results indicate that the ligament changes in WAD1-2 patients are not caused by the acute mechanic incident.

Our studies show that alar and transverse ligament high-signal changes in most cases can not be due to MRI artefacts and rather reflect morphologic, structural changes. The high-signal changes can not be explained by age dependent degeneration. They were not related to age (**paper I-III**) or cervical spine degeneration on MRI (**paper I**). We found no evidence that high-signal changes on proton-weighted sequences in acute WAD1-2 patients reflect edema or bleeding from an acute ligament injury (**paper III**).

Based on our findings, alar and transverse ligament high-signal changes represent normal morphologic ligament variants.

Regardless of their morphologic background, alar and transverse ligament high-signal changes in acute WAD1-2 patients had no prognostic value (**paper IV**) and are unlikely to represent an indication for treatment. Only female gender, more severe post traumatic stress response, and low expectations of recovery were related to poor outcome 12 months after injury (**paper IV**). Upper neck high-resolution MRI is therefore of limited value in the initial treatment and follow-up of WAD1-2 patients, and can not be recommended for routine use.

In this first study of alar and transverse ligament high-signal changes in RA, such changes were reliably graded, and high-resolution MRI was feasible at different stages of adult RA. This provides new opportunities for research on these ligaments in RA patients. Associations to larger anterior atlantoaxial subluxation, higher ESR, positive rheumatoid factor, and neck pain indicated that ligament high-signal changes can be related to local and general RA disease activity. However, the similar prevalence of grades 2-3 changes in RA patients and controls (alar: 34% vs. 30%, transverse: 32% vs. 30%) makes the clinical relevance of such MRI findings questionable. Further studies would be needed to clarify if high-resolution MRI of the alar and transverse ligaments can predict, diagnose, and help to treat cervical RA.

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## 11. Appendix

Dette skjema oppbevares på legevakten

**INKLUSJONSSKJEMA**  
**MR ved akutt nakkesleng-prosjekt**

Fylles ut av sykepleier evt lege før:

**ALLE PAS 18-80ÅR MED NAKKESYMTOMER ETTER BILULYKKE (ikke buss)**

Mann:  Kvinne:

Fødselsår:.....

	Ja	Nei
1. Er det <b>mindre enn en uke</b> siden ulykken? Ulykkesdato: .....		
2. Har pas <b>smerter i nakke el. bakhode</b> som oppstod <b>innen 48 timer</b> etter ulykken?		
3. Forstår pas <b>norsk</b> ?		

**Ja på alle spm 1-3 (og kun da):** Pas får Informasjonsskriv og Samtykkeerklæring, og spørres om kan tenke seg å bli kontaktet (oftest neste dag per tlf) for info og evt deltakelse i prosjektet

**Kan pas tenke seg å bli kontaktet/ evt delta?** Ja  Nei

Fylles ut og **SIGNERES AV LEGE** før:

**DE SOM KAN TENKE SEG Å BLI KONTAKTET/ EVT DELTA**

Pas Navn: ..... Fødselsdato: .....

	Ja	Nei
4. <b>Neurologiske funn:</b> pareser, sensibilitetsutfall eller reduserte dype reflekser? (utstrålende smerter/parestesier regnes <b>ikke</b> som et neurologisk funn)		

Pas **n/neurologisk funn** kan **ikke delta** (informeres om det). Forskeren kontakter øvrige pas.

**Pas kan delta selv om henvist rtg/inleggelse.** Rtg inngår **ikke** i prosjektet og MR-bildene vil **ikke** inngå i den vanlige diagnostikken. **Vurder derfor rtg/ henvisning på vanlig måte.**

Lege gir dette skjema og evt signert Samtykkeerklæring til teamleder/sykepl for oppbevaring.

Evt kommentarer: .....

**OBS!!! FØR PAS GÅR MÅ LEGE SJEKKE AT:**

- SIGNERT SAMTYKKEERKLÆRING med TLF NR/ kontakinfo er innhentet.
- INFORMASJONSSKRIV og et eget SPØRRESKJEMA er sendt med pas hjem.

-----  
Sykepleiers signatur

-----  
Legens signatur

-----  
Dato

**1 NAKKEPROSJEKT – HUS AKUTT INTERVJUGUIDE**

Løpenr: \_\_\_\_\_

Fylles ut for 18-80år tatt rtg eller et av nakken HUS etter bilulykke

Fødselsdato : \_\_\_\_\_

Personens navn : \_\_\_\_\_ Postnr: \_\_\_\_\_

**GENERELL INFORMASJON:** (Frivillig, du kan la være å svare på spørsmål du ikke vil svare på.)**INKLUSJON:** (strek under hvert kontrollerte punkt) ulykkesdato:.....

-18-80, bilulykke, nakke-/bakhode smerter, 48t, TSI 1 uke (blv), norsk?

-Neurologiske funn? Andre akutte skader? Ønsker pas å være med?

-Har pasienten fortsatt smerter i nakken/bakhodet? Ja  Nei **SPØRSMÅL OM TIDLIGERE NAKKESMERTE/NAKKESKADE:****1. I løpet av de siste 12 månedene før ulykken, hvor lenge har du samlet hatt nakkesmerter?**

1. Ingen (0) dager  
 2. Mellom 1 og 7 dager(uke)  
 3. Mer enn 7 dager (1 uke)

	Ja	Nei
2. Har du noen gang før ulykken hatt smerter i nakken samlet i mer enn 1 måned?		
3. Har du noen gang før ulykken blitt behandlet for nakkeplager?		
4. Hvis ja: Har du i løpet av de siste 10 år blitt behandlet for nakkeplager?		
5. Har du noen gang vært operert i nakken?		
6. Har du noen gang tidligere vært utsatt for nakkeskade eller nakkesleng? (hvis ja: symptomgivende nakkesleng? Kontakt helsevesen?)		
7. Har du noen gang hatt en hodeskade? Hvis ja:(bevissthetstap>5 min?, nakkepl?)		

**SPØRSMÅL OM GENERELL HELSE:**

	Ja	Nei
8. Har du av lege fått diagnosen revmatoid artritt (leddgikt) eller annen revmatisk sykdom (for eksempel Bechterew, Psoriasis leddgikt)		
9. Har du noen gang hatt kreft? (type?, kurasjon?)		
10. Har du en alvorlig sykdom / skade som gjør det vanskelig for deg å delta?		

**REGISTRERING AKUTT SKADE**

	Ja	Nei
11. Hodeskade i forb m ulykken? Hvis ja: tid bevisstløs:..... min		
12. Herrvist rtg? hvor?ct/rtg?.....funn?.....		
13. Innlagt? Hvor lenge?.....Flavn?.....		

**OPPSUMMERING:**

	Ja	Nei
14. Er personen MR-KOMPATIBEL?(MR-SJEKKLISTE)		
15. Er personen inkludert		
16. Transport >200 kr avtalt?		
17. Spørreskjema/santynkke- husket å minne pas om spørreskjema/smertestillende		

Kommentar:

Dato

Underskrift lege

**HELSE BERGEN**

Haukeland Universitetssykehus

**UNIVERSITETET I BERGEN***Institutt for kirurgiske fag, Seksjon for radiologi*

Bergen 6. mars 2007

Til deg som mottar denne henvendelsen

I et samarbeid mellom Haukeland universitetssykehus og Universitet i Bergen skal det utføres en MR-undersøkelse av tilfeldig utvalgte personer i Bergen. Hensikten er å undersøke den normale struktur i leddbåndene øverst i nakken hos nakkefriske personer. Det vil gi oss bedre grunnlag for å bedømme sykdom og skader, særlig hos personer som har vært utsatt for nakkesleng.

Dette er henvendelse om frivillig deltakelse i denne undersøkelsen. Du er tilfeldig utvalgt fra Folkeregisteret utfra bosted. Jeg har ingen opplysninger om din helse eller om eventuell deltakelse i andre forskningsprosjekt. Vi ønsker en kontrollgruppe av personer som ikke har hatt nakkeskade / nakkesleng og heller ikke har hatt nakkesmerter som har vært behandlet eller som har vært i mer enn 1 måned. Dersom du er en slik person håper jeg du vil være positiv til å delta i kontrollgruppen etter å ha lest informasjonen på neste side. Det er ønskelig med svar innen 2 uker.

Vedlagt følger:

- Informasjonsskriv
- Samtykkeerklæring
- Svarkonvolutt – fri porto

Vennlig hilsen

Nils Vetti  
Lege / stipendiat  
Radiologisk avdeling  
Haukeland universitetssykehus

## FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT

Denne forespørselen gjelder deltakelse i en **kontrollgruppe** i et nakkeprosjekt og går til personer som er tilfeldig utvalgt fra Folkeregisteret.

Ved hjelp av magnetisk resonans-tomografi (MR) har man i Bergen utviklet en metode for å undersøke leddbåndene øverst i nakken. Hovedformålet med dette prosjektet er å undersøke disse leddbåndene hos **nakkeslengpasienter**. For å få enda bedre innsikt i nakkeslengskadene vil vi også kartlegge leddbåndenes normale struktur i en kontrollgruppe av personer uten nakkeplager. Prosjektet er tilrådd av Regional komite for medisinsk forskningsetikk, Vest-Norge og av Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

**Kontrollgruppen** skal bestå av deltakere som ikke har hatt nakkeskade / nakkesleng og heller ikke har hatt nakkesmerter som har vært behandlet eller som har vart i mer enn 1 måned. Hvis dette passer på deg og du er villig til å delta, kan du returnere samtykkeerklæringen i vedlagte svarkonvolutt, så tar jeg kontakt. Du er også velkommen til å kontakte meg på telefon.

Deltakerne vil få time til MR-undersøkelse av nakken ved Cipro Røntgeninstitutt (se vedlagte kart). Undersøkelsen tar ca 30-50 minutt, gir ingen røntgenstråling og har ingen påviselige, skadelige biologiske effekter. Under billedtakingen oppstår tidvis sterk lyd, som dempes ved musikk i øreklokker, og du vil måtte ligge stille i en trang tunnel. De fleste takler dette greitt, men enkelte kan føle ubehag. Du kan samtale med personale under hele undersøkelsen, og du kan trekke deg når som helst.

Som deltaker i kontrollgruppen bidrar du til at vi får ny kunnskap om den normale struktur i nakkens leddbånd, og dermed bedre kan bedømme skader og sykdom. Hvis bildene av nakken unntaksvis skulle vise forandringer som krever oppfølging, vil vi informere deg om det.

Alle data behandles konfidensielt, er underlagt taushetsplikt, og vil være tilgjengelige kun for prosjektmedarbeiderne. Bilder og opplysninger vil bli lagret til 31.12.2018 og så anonymisert.

Det er frivillig å delta i studien. Du trenger ikke å oppgi noen grunn dersom du ikke ønsker å delta eller ønsker å trekke deg underveis. Det vil ikke ha konsekvenser for eventuell medisinsk behandling eller oppfølging fra fastlege eller andre om du deltar eller ei.

Undersøkelsen som utføres vil ikke koste deg noe. Eventuelle reiseutlegg og lignende vil du få dekket med et fast beløp kroner 200,-.

Hvis du lurer på noe, er du velkommen til å ta kontakt med meg på telefon.

Med vennlig hilsen

Nils Vetti  
Radiologisk avdeling  
Haukeland universitetssykehus

Telefon: 55 97 27 47

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## NAKKEPROSJEKT – DELTAKELSE I KONTROLLGRUPPE

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### Samtykkeerklæring

Denne erklæringen kan returneres i vedlagte svarkonvolutt (porto er betalt).

Mitt navn:

-----  
Fornavn                      Etternavn                      Født: dag    mnd    år

Adresse: ..... (gate/vei)                      ..... (postnr / sted)

Telefon: (privat).....    (arbeid).....    (mobil).....

E-postadresse (evt).....

Undertegnede har lest vedlagte informasjonsskriv og sier meg villig til å delta i prosjektet.

-----  
Underskrift

-----  
Dato

## 1 NAKKEPROSJEKT – INTERVJUGUIDE KONTROLLGRUPPE Løpenr: \_\_\_\_\_

Fødselsdato : \_\_\_\_\_

Personens navn : \_\_\_\_\_

## GENERELL INFORMASJON:

Du kan la være å svare på spørsmål du ikke vil svare på.

## SPØRSMÅL OM NAKKESMERTE/NAKKESKADE:

	ja	nei
1. Har du smerter i nakken nå for tiden?		

2. I løpet av de siste 12 månedene, hvor lenge har du samlet hatt nakkesmerter?

1. Ingen (0) dager  
 2. Mellom 1 og 7 dager(uke)  
 3. Mer enn 7 dager (1 uke)

	ja	nei
3. Har du nå eller tidligere hatt smerter i nakken samlet i mer enn 1 måned?		
4. Har du noen gang blitt behandlet for nakkeplager?		
5. Har du noen gang vært operert i nakken?		
6. Har du noen gang vært utsatt for nakkeskade eller nakkesleng?		
7. Har du noen gang hatt en hodeskade? (bevissthetstap?nakkeplager?)		

## SPØRSMÅL OM GENERELL HELSE:

	ja	nei
8. Har du av lege fått diagnosen revmatoid artritt (leddgikt) eller annen revmatisk sykdom (for eksempel Bechterew, Psoriasis leddgikt)		
9. Har du en alvorlig sykdom / tilstand som gjør det vanskelig for deg å delta?		
10. Har du noen gang hatt kreft? (type?, kurasjon?)		
11. Kan du ligge flatt på rygg i 30-40 minutt? (den tid MR-undersøkelsen tar)		

## OPPSUMMERING:

	Ja	nei
12. Er personen MR-KOMPATIBEL?(MR-SJEKKLISTE)		
13. Er personen inkludert		

\_\_\_\_\_  
Dato\_\_\_\_\_  
Underskrift lege

# SPØRRESKJEMA

## PROSJEKT: MR VED AKUTT NAKKESLENG

Kjære prosjektdeltaker.

Dette skjemaet fylles ut hjemme og leveres ved MR-undersøkelsen på **Capio/Unilabs** i vedlagt konvolutt.

Prøv å besvare alle spørsmålene. Det finnes alltid et svar som passer for din situasjon.

Skriv dato for utfylling av skjemaet her: .....

Ditt navn: .....

Fødselsdato: .....

Eventuelle spørsmål kan rettes til:

Dr Nils Vetti  
Radiologisk avdeling  
Haukeland universitetssykehus  
Tlf 55 97 27 47



1. Når skjedde ulykken? Dato:....., omtrent klokken:.....

2. Hvor lang tid gikk det fra ulykken til du fikk nakkesmerter? ..... timer

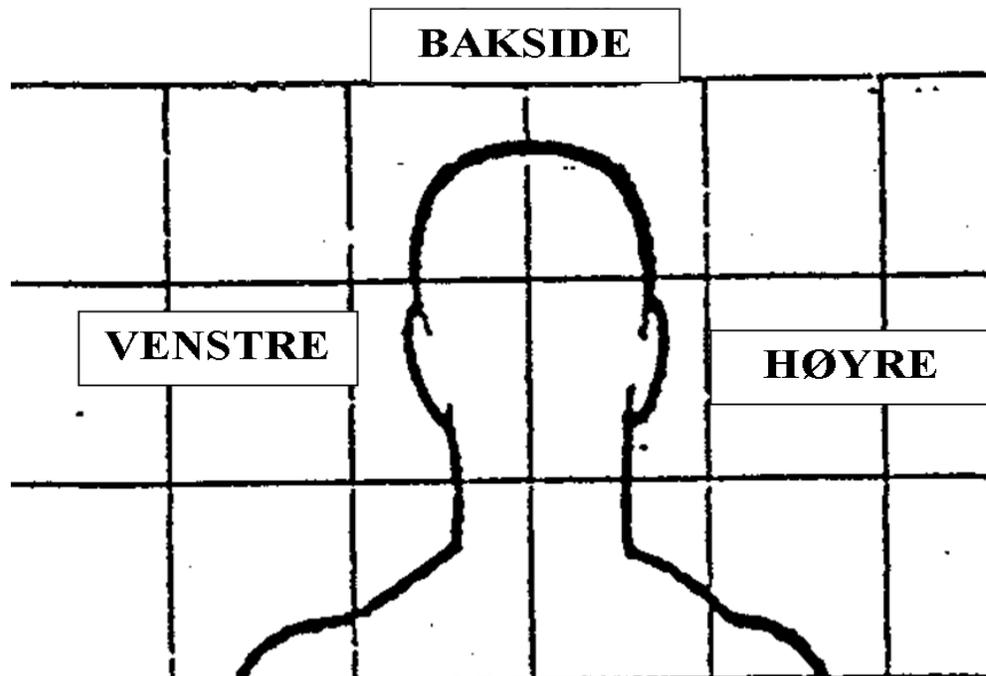
Hvis det gikk 1 døgn eller mer, skriv antall døgn her: ..... døgn

3. Hvordan vil du gradere de nakkesmerter du har hatt etter ulykken og frem til nå?  
(sett ring rundt ett tall)

0 1 2 3 4 5 6 7 8 9 10  
ingen smerter så vondt som det går an å ha

4a) Skraver på tegningen nedenfor de områder hvor du har hatt smerter siden ulykken.

4b) Sett så ett X på det punktet der du har følt mest intense smerter siden ulykken



**5. Bilen jeg satt i ved ulykken ble truffet (sett ett kryss):**

- 1. forfra
- 2. bakfra
- 3. fra siden
- 4. på annen måte (for eksempel rundvelt)
- 5. vet ikke/husker ikke

**6. I ulykkesøyeblikket hadde jeg (sett ett kryss):**

- 1. ansiktet snudd mot venstre
- 2. ansiktet snudd mot høyre
- 3. ansiktet rett frem
- 4. vet ikke/husker ikke

**7. Brukte du bilbelte? (sett ett kryss):**

- 1. Ja
- 2. Nei
- 3. Vet ikke/husker ikke

**8. Hadde du hodestøtte? (sett ett kryss):**

- 1. Ja
- 2. Nei
- 3. Vet ikke/husker ikke

**9. Ble airbag utløst på din plass? (sett ett kryss):**

- 1. Ja
- 2. Nei, det var ingen airbag på min plass
- 3. Nei, det var airbag på min plass, men den ble ikke utløst
- 4. Vet ikke/husker ikke

**10. Omtrentlig hastighet i ulykkesøyeblikket for bilen du satt i:**

Ca ..... km/t

- vet ikke

**11. Omtrentlig hastighet i ulykkesøyeblikket for det andre kjøretøyet ved kollisjonen:**

Ca ..... km/t

- ingen andre kjøretøy var involvert  
 vet ikke

**12. Hva var din arbeidsstatus ved ulykkestidspunktet?**(sett kryss i **den ruten eller de rutene** som passer for deg)

- |   |   |
|---|---|
| <input type="checkbox"/> 1. Fullt i jobb          | <input type="checkbox"/> 6. Full uføretrygd                       |
| <input type="checkbox"/> 2. Delvis i jobb         | <input type="checkbox"/> 7. Delvis uføretrygd                     |
| <input type="checkbox"/> 3. Fullt sykmeldt        | <input type="checkbox"/> 8. Annet (utdannelse, verneplikt etc...) |
| <input type="checkbox"/> 4. Delvis sykmeldt       | <input type="checkbox"/> 9. Arbeidssøkende                        |
| <input type="checkbox"/> 5. Yrkesrettet attføring | <input type="checkbox"/> 10. Alderspensjonist                     |

**13. Hvilken utdanning har du? (sett ett kryss)**

1. Grunnskole (1-9 år)  
 2. Videregående skole (10-12 år)  
 3. Høgskole/Universitet (mer enn 12 år)

**14. I løpet av de siste 12 månedene før ulykken, hvor lenge har du samlet hatt nakkesmerter?**(sett **ett** kryss)

1. Ingen (0) dager  
 2. Mellom 1 og 30 dager  
 3. Mellom 1 og 3 måneder  
 4. Mellom 3 og 6 måneder  
 5. Mer enn 6 måneder men ikke hele året  
 6. Hele året (12 måneder)

**15. I hvor stor grad har du tro på at du vil bli kvitt dine plager etter ulykken?**(sett **ett** kryss)

1. I liten grad.  
 2. I noen grad.  
 3. I stor grad.

## 16. Nakkefunksjonsindeks (NDI)

Dette skjemaet er utformet for å gi oss informasjon om hvordan dine nakkesmerter **ETTER ULYKKEN** har påvirket din evne til å klare deg i hverdagen. Vennligst besvar hver del, og sett kryss i den **ENE** rubrikken innenfor hver del som passer for deg.

Vi er oppmerksomme på at du kan mene at to av utsagnene i enkelte deler kan gjelde deg, men vennligst kryss av i den rubrikken som best beskriver ditt problem eller din situasjon.

### Del 1: Intensitet av nakkesmerter

- 0. Jeg har ingen smerter i nakken nå.
- 1. Nakkesmertene er milde nå.
- 2. Nakkesmertene er moderate nå.
- 3. Nakkesmertene er ganske sterke nå.
- 4. Nakkesmertene er meget sterke nå.
- 5. Nakkesmertene er de verst tenkelige nå.

### Del 2: Personlig stell (vask, påkledning etc.)

- 0. Jeg kan stelle meg selv som vanlig uten at det medfører ekstra nakkesmerter.
- 1. Jeg kan stelle meg selv som vanlig, men det medfører ekstra nakkesmerter.
- 2. Det er smertefullt i nakken når jeg steller meg selv, det tar lang tid og jeg må være forsiktig.
- 3. På grunn av nakkesmerter trenger jeg noe hjelp, men klarer det meste av mitt personlige stell.
- 4. På grunn av nakkesmerter trenger jeg daglig hjelp til det meste av mitt personlige stell.
- 5. På grunn av nakkesmerter klarer jeg ikke å vaske og kle meg selv, og jeg holder sengen.

### Del 3: Løfting

- 0. Jeg kan løfte tunge ting uten at det medfører ekstra nakkesmerter.
- 1. Jeg kan løfte tunge ting, men det medfører ekstra nakkesmerter.
- 2. Nakkesmerter hindrer meg fra å løfte tunge ting fra gulvet, men jeg klarer det hvis de er plassert lett tilgjengelig, for eksempel på et bord.
- 3. Nakkesmerter hindrer meg fra å løfte tunge ting, men jeg kan løfte lette til middels tunge ting hvis de er lett tilgjengelig plassert.
- 4. På grunn av nakkesmerter klarer jeg kun å løfte lette ting.
- 5. På grunn av nakkesmerter klarer jeg ikke å løfte eller bære noe i det hele tatt.

### Del 4: Lesing

- 0. Jeg kan lese så mye jeg vil/ønsker uten smerter i nakken.
- 1. Jeg kan lese så mye jeg vil, men med lette smerter i nakken.
- 2. Jeg kan lese så mye jeg vil, men med moderate smerter i nakken.
- 3. Jeg kan ikke lese så mye jeg vil, på grunn av moderate smerter i nakken.
- 4. Jeg kan nesten ikke lese, på grunn av sterke smerter i nakken.
- 5. Jeg klarer ikke å lese i det hele tatt, på grunn av sterke smerter i nakken.

### Del 5: Hodepine

- 0. Jeg har aldri hodepine.
- 1. Jeg får av og til lett hodepine.
- 2. Jeg får av og til moderat hodepine.
- 3. Jeg får ofte moderat hodepine.
- 4. Jeg får ofte sterk hodepine.
- 5. Jeg har hodepine nesten hele tiden.

**Del 6: Konsentrasjon**

- 0. Jeg kan konsentrere meg fullt ut når jeg vil uten nakkesmerter.
- 1. Jeg kan konsentrere meg fullt ut når jeg vil, men med lette nakkesmerter.
- 2. Jeg har litt vanskeligheter med å konsentrere meg når jeg vil, på grunn av nakkesmerter.
- 3. Jeg har store vanskeligheter med å konsentrere meg når jeg vil, på grunn av nakkesmerter.
- 4. Jeg har veldig store vanskeligheter med å konsentrere meg når jeg vil, pga nakkesmerter.
- 5. Jeg klarer ikke å konsentrere meg i det hele tatt, på grunn av nakkesmerter.

**Del 7: Arbeid**

- 0. Jeg kan arbeide så mye jeg vil /ønsker.
- 1. Jeg klarer å utføre mitt vanlige arbeid, men ikke mer enn det, på grunn av nakkesmerter.
- 2. Jeg klarer å utføre det meste av mitt vanlige arbeid, men ikke mer, på grunn av nakkesmerter.
- 3. Jeg klarer ikke å utføre mitt vanlige arbeid, på grunn av nakkesmerter.
- 4. Jeg klarer nesten ikke å utføre noe arbeid, på grunn av nakkesmerter .
- 5. Jeg klarer ikke å utføre noe arbeid i det hele tatt, på grunn av nakkesmerter.

**Del 8: Bilkjøring**

- 0. Jeg kan kjøre bil uten smerter i nakken.
- 1. Jeg kan kjøre bil så lenge jeg vil/ønsker, men med lette smerter i nakken.
- 2. Jeg kan kjøre bil så lenge jeg vil, men med moderate smerter i nakken.
- 3. Jeg kan ikke kjøre bil så lenge jeg vil, på grunn av moderate smerter i nakken.
- 4. Jeg klarer nesten ikke å kjøre bil, på grunn av sterke smerter i nakken.
- 5. Jeg klarer ikke å kjøre bil i det hele tatt, på grunn av nakkesmerter.
- Ingen av påstandene over passer for meg.

**Del 9: Søvn**

- 0. Jeg har ingen problemer med å sove.
- 1. Min søvn er minimalt forstyrret av nakkesmerter (mindre enn 1 times søvnløshet).
- 2. Min søvn er noe forstyrret på grunn av nakkesmerter (1-2 timers søvnløshet).
- 3. Min søvn er moderat forstyrret på grunn av nakkesmerter (2-3 timers søvnløshet).
- 4. Min søvn er veldig forstyrret på grunn av nakkesmerter (3-5 timers søvnløshet).
- 5. Min søvn er fullstendig forstyrret på grunn av nakkesmerter (5-7 timers søvnløshet).

**Del 10: Fritid**

- 0. Jeg kan delta i alle mine vanlige fritidsaktiviteter uten smerter i nakken.
- 1. Jeg kan delta i alle mine vanlige fritidsaktiviteter, men med noe smerter i nakken.
- 2. Jeg kan delta i de fleste, men ikke i alle mine vanlige fritidsaktiviteter, pga smerter i nakken.
- 3. Jeg kan kun delta i noen få av mine vanlige fritidsaktiviteter, på grunn av smerter i nakken.
- 4. Jeg kan nesten ikke delta i noen fritidsaktivitet, på grunn av nakkesmerter.
- 5. Jeg klarer ikke å delta i noen fritidsaktivitet i det hele tatt, på grunn av nakkesmerter.

Nedenfor finner du en liste over utsagn fra mennesker etter traumatiske hendelser. Vennligst les hvert utsagn og indiker (med ring rundt **ett** tall) hvor ofte disse kommentarene har vært riktige for deg når det gjelder denne hendelsen. Hvis du ikke har opplevd noe av dette i denne perioden, vennligst marker det ved å ringe rundt «ikke i det hele tatt» alternativet.

	Ikke i det hele tatt	Sjelden	Av og til	Ofte
1. Jeg har tenkt på ulykken også når jeg ikke har villet det	0	1	3	5
2. Jeg har unngått å uroe meg når jeg har tenkt på eller blitt minnet om det som skjedde	0	1	3	5
3. Jeg har forsøkt å slette det som skjedde fra hukommelsen	0	1	3	5
4. Jeg har hatt vansker med å sovne eller forbli sovende p.g.a. tanker og bilder om ulykken	0	1	3	5
5. Jeg har hatt perioder med sterke følelser om hendelsen	0	1	3	5
6. Jeg har hatt drømmer om hendelsen	0	1	3	5
7. Jeg har holdt meg unna ting som kan minne meg om hendelsen	0	1	3	5
8. Jeg har kjent det som virkelig eller som om det ikke har skjedd	0	1	3	5
9. Jeg har forsøkt å la være å snakke om hendelsen	0	1	3	5
10. Bilder fra hendelsen har dukket opp i tankene mine	0	1	3	5
11. Andre ting har stadig fått meg til å tenke på det	0	1	3	5
12. Jeg har vært klar over at jeg enda har mange følelser omkring hendelsen, men jeg har ikke sluppet dem til	0	1	3	5
13. Jeg har forsøkt å ikke tenke på det som skjedde	0	1	3	5
14. Enhver påminnelse har vekket følelser knyttet til det som skjedde	0	1	3	5
15. Følelsene omkring hendelsen har vært som numne (bedøvet)	0	1	3	5

MR NAKKE – PASIENTSKJEMA RA

LØPENR: .....

**FORSKNINGSPROSJEKT:  
MR AV NAKKE VED REVMATOID ARTRITT****SKJEMA SOM FYLLES UT AV PASIENT**

Kjære prosjektdeltaker.

Dette skjemaet fylles ut og leveres til dr. Rikke Alsing, Revmatologisk avdeling.  
Alternativet kan skjemaet leveres ved fremmøte til MR – undersøkelse.

Skriv dato for utfylling av skjemaet her: .....

Ditt navn: ..... Fødselsdato: .....

Telefon: (privat)..... (arbeid)..... (mobil).....

Eventuelle spørsmål kan rettes til:

Dr Rikke Alsing  
Revmatologisk avdeling  
Tlf 55 97 54 00

eller

Dr Nils Vetti  
Radiologisk avdeling  
Tlf 55 97 27 47



**HELSE BERGEN** - ALT HANDLAR OM MENNESKE  
Haukeland Universitetssjukehus

## SPØRSMÅL OM REVMATOID ARTRITT

Spørsmålet nedenfor gjelder din **revmatoide artritt** (leddgikt). Du besvarer det ved å sette en strek på tvers av linjen under spørsmålet, på det sted som du selv mener er passende.

For eksempel slik:



### 1. Forsøk å vurdere hvor **aktiv** sykdommen din har vært i løpet av **den siste uken**.

Når du tar alle symptomer med i betraktning, hvordan synes du tilstanden har vært siste uken?

Bra, ingen symptomer |-----| Svært dårlig

## SPØRSMÅL OM FYSISK FUNKSJON

### 2. I løpet av **den siste uken**, kunne du: (sett kryss)

	UTEN problemer	Med VISSE problemer	Med STORE problemer	Kunne IKKE
Kle på deg selv, inkludert å knytte skolisser og kneppe knapper?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Komme opp i og ut av sengen?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Løfte en full kopp eller et fullt glass til munnen?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gå utendørs på flat mark?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vaske og tørke deg over hele kroppen?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bøye deg for å ta opp klær fra gulvet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Skru vanlige kraner opp og igjen?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Komme inn i og ut av en bil?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

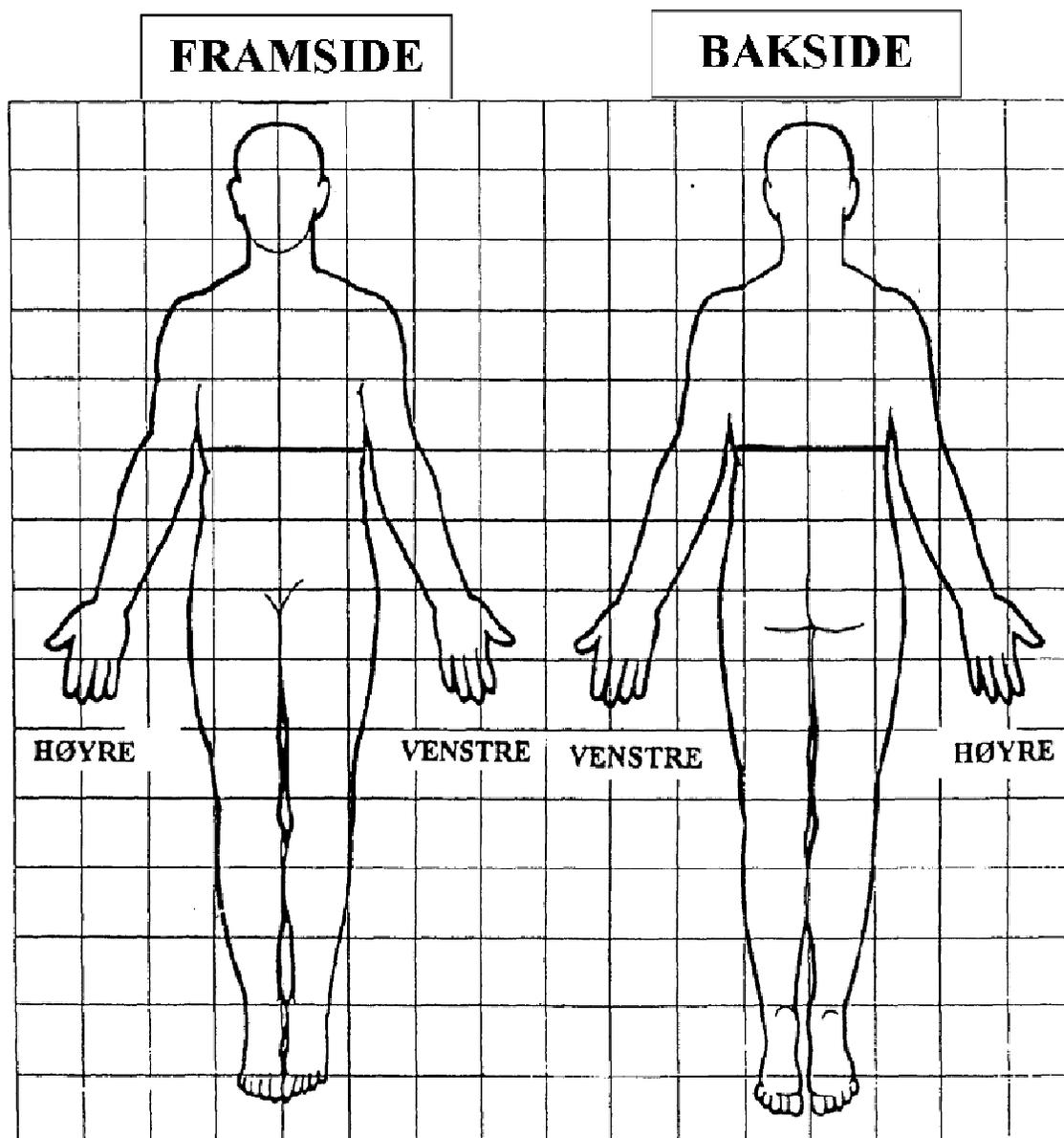
## SPØRSMÅL OM SMERTER

3. Har du hatt smerter i løpet av den siste uken? (sett kryss)

- Ja  
 Nei

Hvis "Nei": Gå til neste side.

Hvis "Ja": Skraver de områder på kroppen hvor du har hatt smerter den siste uken.



## SPØRSMÅL OM EVENTUELLE NAKKESMERTER

Nå følger en del spørsmål om nakkesmarter. Prøv å besvare alle disse spørsmålene enten du har hatt nakkesmarter eller ikke. Det finnes alltid et svar som passer for din situasjon.

4. Har du hatt nakkesmarter i løpet av den siste uken? (sett kryss)

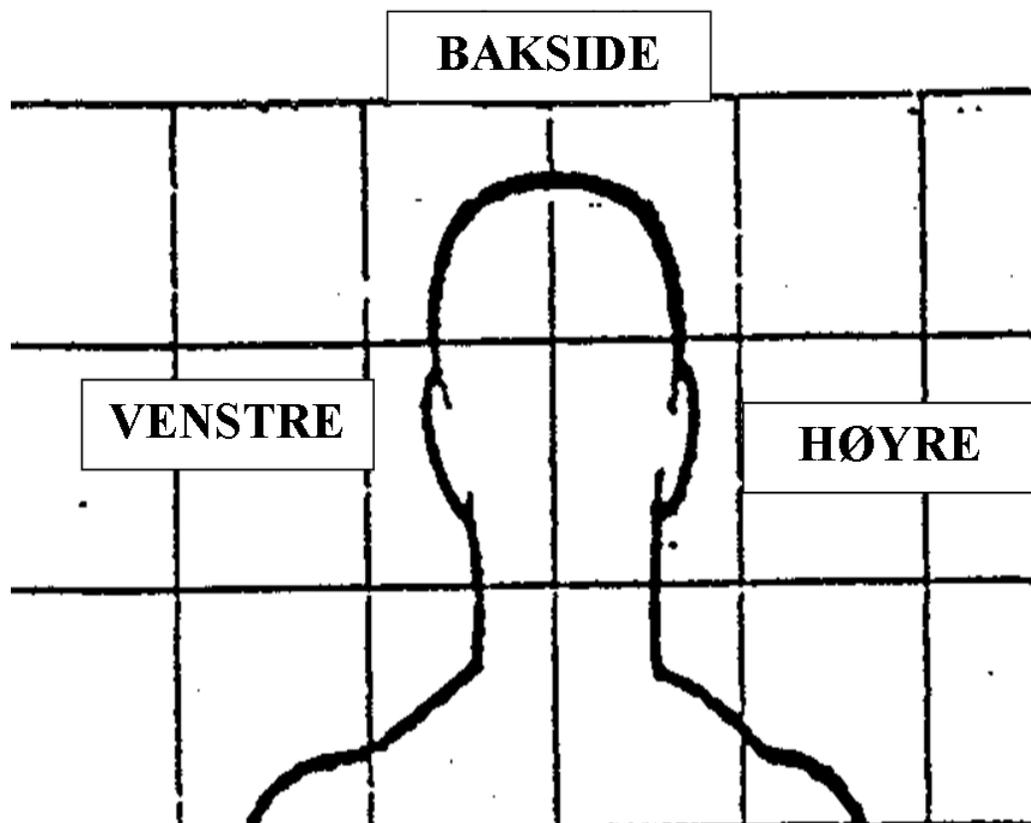
- Ja  
 Nei

Hvis "Nei": gå til spørsmål 5 på neste side.

Hvis "Ja":

a) Skraver på tegningen nedenfor de områder hvor du har hatt smerter den siste uken.

b) Sett så ett X på det punktet der du har følt mest intense smerter den siste uken.





## 10. Nakkefunksjonsindeks

Dette skjemaet er utformet for å gi oss informasjon om hvordan dine eventuelle nakkesmerter har påvirket din evne til å klare deg i hverdagen. Vennligst besvar hver del, og sett kryss i den ENE rubrikken innenfor hver del som passer for deg.

Vi er oppmerksomme på at du kan mene at to av utsagnene i enkelte deler kan gjelde deg, men vennligst kryss av i den rubrikken som best beskriver ditt problem eller din situasjon.

<p><b>Del 1: Intensitet av nakkesmerter</b></p> <p><input type="checkbox"/> 0. Jeg har ingen smerter i nakken nå.</p> <p><input type="checkbox"/> 1. Nakkesmertene er milde nå.</p> <p><input type="checkbox"/> 2. Nakkesmertene er moderate nå.</p> <p><input type="checkbox"/> 3. Nakkesmertene er ganske sterke nå.</p> <p><input type="checkbox"/> 4. Nakkesmertene er meget sterke nå.</p> <p><input type="checkbox"/> 5. Nakkesmertene er de verst tenkelige nå.</p>
<p><b>Del 2: Personlig stell (vask, påkledning etc.)</b></p> <p><input type="checkbox"/> 0. Jeg kan stelle meg selv som vanlig uten at det medfører ekstra nakkesmerter.</p> <p><input type="checkbox"/> 1. Jeg kan stelle meg selv som vanlig, men det medfører ekstra nakkesmerter.</p> <p><input type="checkbox"/> 2. Det er smertefullt i nakken når jeg steller meg selv, det tar lang tid og jeg må være forsiktig.</p> <p><input type="checkbox"/> 3. På grunn av nakkesmerter trenger jeg noe hjelp, men klarer det meste av mitt personlige stell.</p> <p><input type="checkbox"/> 4. På grunn av nakkesmerter trenger jeg daglig hjelp til det meste av mitt personlige stell.</p> <p><input type="checkbox"/> 5. På grunn av nakkesmerter klarer jeg ikke å vaske og kle meg selv, og jeg holder sengen.</p> <p><input type="checkbox"/> Ingen av påstandene over passer for meg.</p>
<p><b>Del 3: Løfting</b></p> <p><input type="checkbox"/> 0. Jeg kan løfte tunge ting uten at det medfører ekstra nakkesmerter.</p> <p><input type="checkbox"/> 1. Jeg kan løfte tunge ting, men det medfører ekstra nakkesmerter.</p> <p><input type="checkbox"/> 2. Nakkesmerter hindrer meg fra å løfte tunge ting fra gulvet, men jeg klarer det hvis de er plassert lett tilgjengelig, for eksempel på et bord.</p> <p><input type="checkbox"/> 3. Nakkesmerter hindrer meg fra å løfte tunge ting, men jeg kan løfte lette til middels tunge ting hvis de er lett tilgjengelig plassert.</p> <p><input type="checkbox"/> 4. På grunn av nakkesmerter klarer jeg kun å løfte lette ting.</p> <p><input type="checkbox"/> 5. På grunn av nakkesmerter klarer jeg ikke å løfte eller bære noe i det hele tatt.</p> <p><input type="checkbox"/> Ingen av påstandene over passer for meg.</p>
<p><b>Del 4: Lesing</b></p> <p><input type="checkbox"/> 0. Jeg kan lese så mye jeg vil/ønsker uten smerter i nakken.</p> <p><input type="checkbox"/> 1. Jeg kan lese så mye jeg vil, men med lette smerter i nakken.</p> <p><input type="checkbox"/> 2. Jeg kan lese så mye jeg vil, men med moderate smerter i nakken.</p> <p><input type="checkbox"/> 3. Jeg kan ikke lese så mye jeg vil, på grunn av moderate smerter i nakken.</p> <p><input type="checkbox"/> 4. Jeg kan nesten ikke lese, på grunn av sterke smerter i nakken.</p> <p><input type="checkbox"/> 5. Jeg klarer ikke å lese i det hele tatt, på grunn av sterke smerter i nakken.</p> <p><input type="checkbox"/> Ingen av påstandene over passer for meg.</p>
<p><b>Del 5: Hodepine</b></p> <p><input type="checkbox"/> 0. Jeg har aldri hodepine.</p> <p><input type="checkbox"/> 1. Jeg får av og til lett hodepine.</p> <p><input type="checkbox"/> 2. Jeg får av og til moderat hodepine.</p> <p><input type="checkbox"/> 3. Jeg får ofte moderat hodepine.</p> <p><input type="checkbox"/> 4. Jeg får ofte sterk hodepine.</p> <p><input type="checkbox"/> 5. Jeg har hodepine nesten hele tiden.</p>

**Del 6: Konsentrasjon**

- 0. Jeg kan konsentrere meg fullt ut når jeg vil uten nakkesmerter.
- 1. Jeg kan konsentrere meg fullt ut når jeg vil, men med lette nakkesmerter.
- 2. Jeg har litt vanskeligheter med å konsentrere meg når jeg vil, på grunn av nakkesmerter.
- 3. Jeg har store vanskeligheter med å konsentrere meg når jeg vil, på grunn av nakkesmerter.
- 4. Jeg har veldig store vanskeligheter med å konsentrere meg når jeg vil, pga nakkesmerter.
- 5. Jeg klarer ikke å konsentrere meg i det hele tatt, på grunn av nakkesmerter.
- Ingen av påstandene over passer for meg.

**Del 7: Arbeid**

- 0. Jeg kan arbeide så mye jeg vil /ønsker.
- 1. Jeg klarer å utføre mitt vanlige arbeid, men ikke mer enn det, på grunn av nakkesmerter.
- 2. Jeg klarer å utføre det meste av mitt vanlige arbeid, men ikke mer, på grunn av nakkesmerter.
- 3. Jeg klarer ikke å utføre mitt vanlige arbeid, på grunn av nakkesmerter.
- 4. Jeg klarer nesten ikke å utføre noe arbeid, på grunn av nakkesmerter .
- 5. Jeg klarer ikke å utføre noe arbeid i det hele tatt, på grunn av nakkesmerter.
- Ingen av påstandene over passer for meg.

**Del 8: Bilkjøring**

- 0. Jeg kan kjøre bil uten smerter i nakken.
- 1. Jeg kan kjøre bil så lenge jeg vil/ønsker, men med lette smerter i nakken.
- 2. Jeg kan kjøre bil så lenge jeg vil, men med moderate smerter i nakken.
- 3. Jeg kan ikke kjøre bil så lenge jeg vil, på grunn av moderate smerter i nakken.
- 4. Jeg klarer nesten ikke å kjøre bil, på grunn av sterke smerter i nakken.
- 5. Jeg klarer ikke å kjøre bil i det hele tatt, på grunn av nakkesmerter.
- Ingen av påstandene over passer for meg.

**Del 9: Søvn**

- 0. Jeg har ingen problemer med å sove.
- 1. Min søvn er minimalt forstyrret av nakkesmerter (mindre enn 1 times søvnløshet).
- 2. Min søvn er noe forstyrret på grunn av nakkesmerter (1-2 timers søvnløshet).
- 3. Min søvn er moderat forstyrret på grunn av nakkesmerter (2-3 timers søvnløshet).
- 4. Min søvn er veldig forstyrret på grunn av nakkesmerter (3-5 timers søvnløshet).
- 5. Min søvn er fullstendig forstyrret på grunn av nakkesmerter (5-7 timers søvnløshet).
- Ingen av påstandene over passer for meg.

**Del 10: Fritid**

- 0. Jeg kan delta i alle mine vanlige fritidsaktiviteter uten smerter i nakken.
- 1. Jeg kan delta i alle mine vanlige fritidsaktiviteter, men med noe smerter i nakken.
- 2. Jeg kan delta i de fleste, men ikke i alle mine vanlige fritidsaktiviteter, pga smerter i nakken.
- 3. Jeg kan kun delta i noen få av mine vanlige fritidsaktiviteter, på grunn av smerter i nakken.
- 4. Jeg kan nesten ikke delta i noen fritidsaktivitet, på grunn av nakkesmerter.
- 5. Jeg klarer ikke å delta i noen fritidsaktivitet i det hele tatt, på grunn av nakkesmerter.
- Ingen av påstandene over passer for meg.

Original: Vernon and Mior: The Neck Disability Index  
Canadian Memorial College, Toronto, Canada 1991  
Toveis oversetting til norsk ved Vigdis Underland

Modifisert av Nils Vetti etter Ackelman and Lindgren J Rehabil Med 2002;34:284-287

## **12. Papers I-IV**



# Paper I



# MRI of the alar and transverse ligaments in whiplash-associated disorders (WAD) grades 1–2: high-signal changes by age, gender, event and time since trauma

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## Abstract

**Introduction** This study describes the prevalence of high-signal changes at magnetic resonance imaging (MRI) of the alar and transverse ligaments in whiplash-associated disorders (WAD) grades 1–2 in relation to age, gender, spinal degeneration, type of trauma event and time since trauma. **Materials and methods** In 1,266 consecutive WAD1–2 patients (779 women, 487 men; mean age 42 years) referred from clinicians, high-signal changes in the alar and transverse ligaments at high-resolution proton-weighted MRI were prospectively graded 0–3 based on a previously reported, reliable grading system. Type of event according

to The International Statistical Classification of Diseases and Related Health Problems and time of trauma were obtained from referral letters.

**Results** MRI showed grades 2–3 alar ligament changes in 449 (35.5%; 95% confidence interval (CI), 32.8 to 38.1%) and grades 2–3 transverse ligament changes in 311 (24.6%; 95% CI, 22.2% to 26.9%) of the 1,266 patients. Grades 2–3 changes were more common in men than women, odds ratio 1.9 (95% CI, 1.5 to 2.5) for alar and 1.5 (95% CI, 1.1 to 2.0) for transverse ligament changes. High-signal changes were not related to age, spinal degeneration, type of trauma event or time since trauma (median 5 years). Unilateral changes were more often left- than right-sided.

**Conclusions** High-signal changes of the alar and transverse ligaments are common in WAD1-2 and unlikely to represent age-dependent degeneration. Their male and left-side preponderance cannot be explained by variation in ligament stretching or image artefacts. Further studies are needed to clarify whether such changes are caused by trauma.

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**Keywords** Alar ligament · Transverse ligament · Whiplash-associated disorder (WAD) · Magnetic resonance imaging · Prevalence

## Introduction

The alar and transverse ligaments are important stabilisers at the cranio-vertebral junction [1–5] and can be injured during neck trauma [6–9]. Both ligaments can be visualised using magnetic resonance imaging (MRI) [10–12]. Up to now, MRI studies of these ligaments have included selected patients with whiplash-associated disorders (WAD) [13] and groups of non-injured individuals [11, 12, 14–19]. At high-resolution proton-weighted MRI, high signal within

the ligaments was frequent in WAD patients but rare in non-injured controls [17, 18] and was related to impact direction and head position at the instant of collision [20]. However, high signal has been reported to be common also in non-injured individuals [11, 15, 19]. Age-dependent degeneration and fat tissue interspersed among fibres are known to cause high-signal MRI changes in tendons and ligaments [21–24].

Thus, the nature and clinical relevance of high-signal changes at MRI of the alar and transverse ligaments are not clear, and the prevalence of these changes has not been documented in an unselected sample of WAD patients. This study concerned patients with WAD1 or WAD2, i.e. neck complaints but no fractures or neurological signs [13]. The aim of the study was to describe the prevalence of high-signal changes at MRI of the alar and transverse ligaments in WAD1–2 in relation to patient age and gender, cervical spine degeneration, type of trauma event and time since trauma. We hypothesised that such changes are injury-related rather than degenerative and thus should not be more frequent in older age groups. We expected more neck ligament changes in women, who have generally weaker neck muscles [25, 26].

## Materials and methods

### Patients and clinical data

This cross-sectional study included consecutive, clinically referred patients undergoing MRI of the cranio-vertebral ligaments from 1 January 2005 to 31 May 2006 at the institution performing the majority of such examinations in Norway (Capio Røntgen Bergen, Bergen). Clinical data were obtained from the referral letters only. The inclusion criteria, met by 1,304 patients, were a history of neck trauma combined with neck complaints of pain, stiffness, or tenderness, without (WAD1) or with musculoskeletal signs (WAD2) [13] (Table 1). We excluded patients with reported neurological signs (WAD3;  $n=0$ ), neck fracture reported or seen at MRI (WAD4;  $n=6$ ), incomplete MRI examination/ marked image artefacts ( $n=13$ ), neck mass/tumour at MRI ( $n=5$ ), a history of previous neck operation ( $n=14$ ) or rheumatoid arthritis ( $n=0$ ). The remaining 1,266 patients were eligible for analyses; 1,121 (88.5%) were referred from general practitioners. The Regional Committee for Medical Research Ethics, Western-Norway approved the study.

The neck trauma event was classified according to the International Statistical Classification of Diseases and Related Health Problems [27]. If more than one event was reported in the referral letter, the first one was registered. The exact date of trauma was noted if reported, but otherwise defined as the 15th of any given month and 1

July of any given year. Time since trauma was calculated as the time from the date of the trauma to the date of MRI.

### Imaging protocol

All patients underwent MRI with the same 1.5 T scanner (Symphony Mastroclass, Siemens Medical System, Erlangen, Germany) using a standard receive-only head coil, with head and neck in a neutral position. To visualise the delicate cranio-vertebral ligaments with high spatial resolution while maintaining adequate imaging contrast and a reasonable high signal to noise ratio, an established MRI protocol was used, which included proton-density-weighted fast spin echo (FSE) sequences in three orthogonal planes (Table 2) [16]. A sagittal  $T_2$ -weighted FSE sequence covering the whole cervical spine was also applied. The total imaging time was 21 min 42 s.

The sagittal  $T_2$  sequence was taken in one concatenation and 13 slices with 3,360 ms/103 ms repetition time/echo time, 17 echo train length, three acquisitions, 191 Hz/pixel receiver bandwidth, head to feet phase-encoding direction and 50% phase oversampling. Using a 256×512 matrix, 280×280-mm field of view, 3 mm slice thickness and 0.3 mm inter-slice gap, the voxel size was 1.1×0.5×3.0 mm. Anterior saturation pulses were applied, and the acquisition time was 3 min 57 s.

### Image interpretation

Using a previously reported classification system [10, 17], high signal in the alar and transverse ligaments was graded on the image with the largest cross-sectional area of high signal. No high signal was graded 0, high signal in one third or less of the total cross-section of the ligament was graded 1, high signal in one third to two thirds of the total cross-section was graded 2, and high signal in two thirds or more of the total cross-section was graded 3. The right

**Table 1** Classification of whiplash-associated disorders (WAD) according to the Quebec Task Force.

Grade	Clinical presentation
0	No complaint about the neck. No physical sign(s)
1	Neck complaint of pain, stiffness or tenderness only No physical sign(s)
2	Neck complaint and musculoskeletal sign(s) <sup>a</sup>
3	Neck complaint and neurological sign(s) <sup>b</sup>
4	Neck complaint and fracture or dislocation

<sup>a</sup> Musculoskeletal signs include decreased range of motion and point tenderness

<sup>b</sup> Neurological signs include decreased or absent deep tendon reflexes, weakness and sensory deficits

**Table 2** Magnetic resonance imaging (1.5 T) parameters for proton-density-weighted sequences of the cranio-vertebral junction in three orthogonal planes.

	Axial	Coronal	Sagittal
Repetition time (TR)	2,660 ms	2,870 ms	2,150 ms
Echo time (TE)	15 ms	15 ms	15 ms
Echo train length (ETL)	13	13	13
Number of acquisitions	5	5	4
Number of concatenations	1	1	2
Number of slices	12	13	20
Matrix	291×512	271×512	246×512
Field of view (FOV)	175×200 mm	200×200 mm	175×200 mm
Slice thickness	1.5 mm, inter-leaved	1.5 mm, inter-leaved	1.5 mm, inter-leaved
Inter-slice gap	0	0	0.3 mm
Voxel size	0.6×0.4×1.5 mm	0.7×0.4×1.5 mm	0.7×0.4×1.5 mm
Receiver bandwidth	136 Hz/pixel	136 Hz/pixel	136 Hz/pixel
Phase-encode direction	Right to left	Right to left	Head to feet
Saturation pulses	None	Left, right, superior	Anterior, superior
Acquisition time	5 min 23 s	5 min 06 s	7 min 16 s
Coverage	Below foramen magnum to base of <i>dens axis</i>	Anterior arch of atlas to halfway through spinal canal	Right to left occipital condyle

and left sides were graded separately, using sagittal sections of the alar ligaments and coronal or sagittal sections of the transverse ligament, depending on the sharpness of its curvature around the *dens axis*. Any high signal had to be seen in at least two imaging planes to be graded 1–3; otherwise, it was graded 0 (no high signal).

One neuroradiologist (with 25 years experience)—who had a previously documented good intra-observer agreement on such grading (weighted kappa with linear weights 0.67 to 0.69) [17, 18]—prospectively graded all images with clinical data available but prior to the formation of the study hypotheses. The results of this grading were used in the analyses. To evaluate inter-observer agreement, another radiologist (with 5 years experience), blinded to clinical data, independently graded a random sub-sample of 100 examinations. Inter-observer agreement was moderate or good (weighted kappa with linear weights 0.54 to 0.62). In the analyses below, ligament changes grade 2 and 3 were combined. The two radiologists did not report significantly different prevalence of combined grades 2–3 changes ( $p>0.05$ , McNemar's test).

The whole cervical spine was also assessed by one observer (the most experienced of the two radiologists). The number of cervical levels (0, 1, 2 or more) with degeneration (e.g. disc bulge/herniation, low disc height, narrow facet joint, osteophytes) was noted.

#### Statistical analyses

Fisher's exact test was used to compare proportions with grades 2–3 changes between groups of age, gender, cervical spine degeneration, event of trauma and time since trauma.

Mantel–Haenszel's exact chi-square test for trend (linear-by-linear association) was applied to assess linear trends in frequency of grades 2–3 changes between ordered groups of age, cervical spine degeneration and time since trauma. Differences in frequency of right- and left-sided ligament changes were analysed by McNemar's test.

Age as a continuous variable was normally distributed, so an unpaired independent *t* test was applied to compare mean age between patients with and without grades 2–3 ligament changes. Differences in mean time since trauma were analysed by the Mann–Whitney *U* test as this continuous variable clearly deviated from a normal distribution.

Stepwise backward binary logistic regression was performed with grades 2–3 ligament changes as outcome variable and mutual adjustments for continuous variables (age, time since trauma) and categorical variables (gender, degeneration, type of event) using likelihood-ratio tests. SPSS 14.0 was used to analyse data.  $p\leq 0.05$  indicated statistical significance.

## Results

### Patient characteristics

The 1,266 WAD1–2 patients consisted of 779 (61.5%) women aged 13 to 84 (mean 41.7) years and 487 (38.5%) men aged 11 to 72 (mean 41.3) years. Based on the referral letters, 707 (55.8%) patients had headache, dizziness, memory loss, tinnitus, deafness, visual disorder

der, dysphagia and/or temporomandibular joint pain in addition to their neck complaints. The event of trauma, specified for 1,048 patients, was transport accidents in 738 (70.4%), other causes of accidental injury in 277 (26.4%), assault or intentional self-harm in 27 (2.6%) and complication of medical or surgical care in six (0.6%). In 218 patients, neck trauma was reported, but the exact type of event was not specified. A lower proportion of males than females had experienced transport accidents: 64.2%, 262 of 408 vs. 74.4%, 476 of 640 ( $p=0.001$ , Fisher's exact test). Time since trauma, reported for 1,097 patients, was 39 days to 59 years (median 5.0 years).

#### Prevalence of ligament changes

The prevalence of grades 2–3 high-signal changes on MRI was 35.5% for the alar ligament (95% confidence interval

(CI), 32.8% to 38.1%) and 24.6% for the transverse ligament (95% CI, 22.2% to 26.9%). Of the 1,266 patients, 637 (50.3%) had no grades 2–3 ligament changes, 318 (25.1%) had isolated alar changes, 180 (14.2%) had isolated transverse changes and 131 (10.4%) had concomitant alar and transverse changes.

#### Ligament changes by age and gender

The prevalence of grades 2–3 changes did not differ between age groups (Table 3) and was not related to age as a continuous variable ( $p=0.36$  for alar ligament,  $p=0.27$  for transverse ligament). Significantly more males than females had grades 2–3 ligament changes (Table 3). Age-adjusted Mantel–Haenszel test of conditional independence showed  $p$  value  $<0.001$  for alar ligament and 0.010 for transverse ligament. The male preponderance did not vary across age groups (Breslow–Day's test for

**Table 3** MRI in WAD1–2: high-signal ligament changes by age, gender, cervical spine degeneration, type of trauma event and time since trauma.

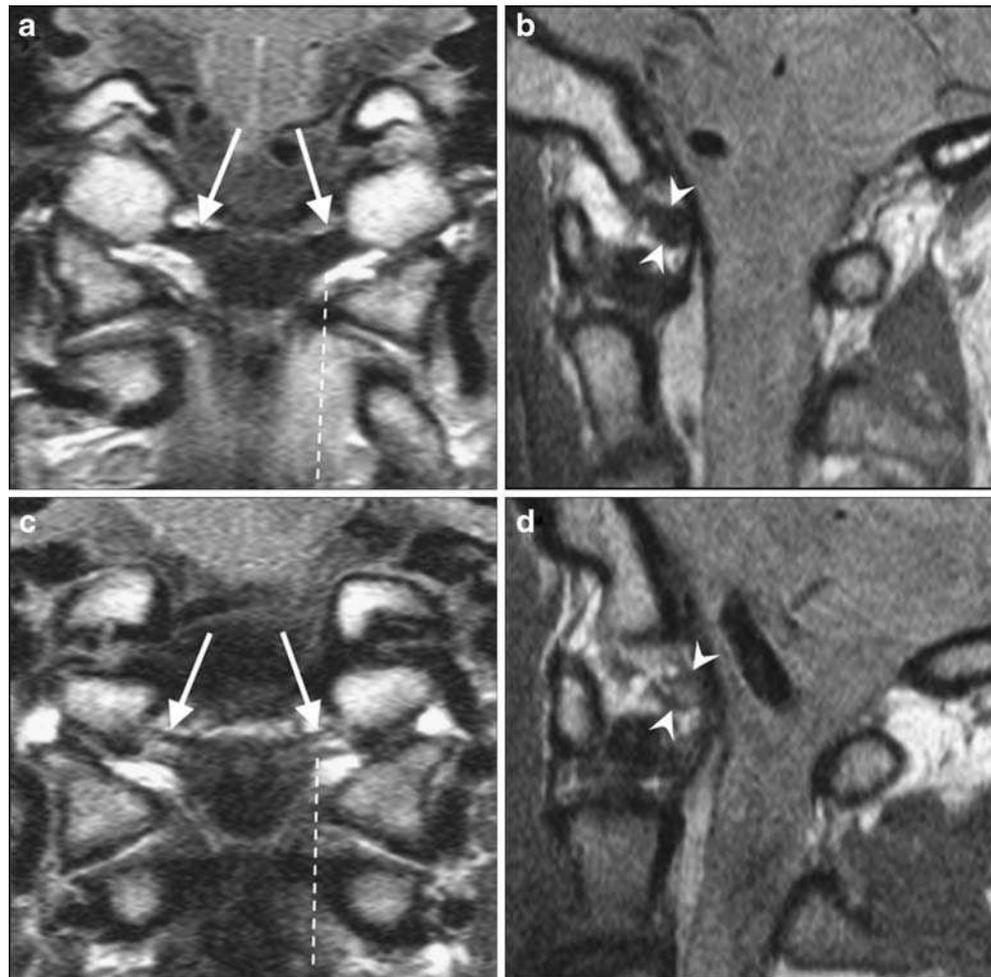
	Total	Alar ligament changes grades 2–3 <sup>a</sup>			Transverse ligament changes grades 2–3 <sup>a</sup>		
	<i>N</i>	<i>n</i>	%	<i>p</i> value <sup>b</sup>	<i>n</i>	%	<i>p</i> value <sup>b</sup>
Age, years				0.87			0.20
<20	52	21	40.4	(0.50)	19	36.5	(0.61)
20–29	162	55	34.0		32	19.8	
30–39	358	134	37.5		83	23.2	
40–49	366	125	34.2		92	25.1	
50–59	249	88	35.3		62	24.9	
≥60	79	26	32.9		23	29.1	
Gender				<0.001			0.007
Female	779	231	29.7		171	22.0	
Male	487	218	44.8		140	28.7	
Spinal degeneration				0.66			0.75
No	718	256	35.7	(0.62)	179	24.9	(0.58)
At 1 level	264	284	37.1		67	25.4	
At >1 level	284	95	33.5		65	22.9	
Type of event				0.52			0.64
Transport accident	738	256	34.7		175	23.7	
Other event	310	101	32.6		78	25.2	
Not specified	218						
Time since trauma				0.43			0.67
<3 months	17	7	41.2	(0.73)	3	17.6	(0.43)
3–6 months	41	12	29.3		12	29.3	
6–12 months	105	35	33.3		24	22.9	
1–3 years	235	80	34.0		63	26.8	
3–9 years	349	140	40.1		89	25.5	
9–18 years	214	68	31.8		54	25.2	
>18 years	136	50	36.8		26	19.1	
Not specified	169						
Total	1,266	449	35.5		311	24.6	

MRI magnetic resonance imaging, WAD1–2 whiplash-associated disorders grades 1 and 2

<sup>a</sup>Highest assigned grade if different between right and left side

<sup>b</sup> $p$  values are based on Fisher's exact test, except  $p$  values in parentheses which are based on Mantel–Haenszel's exact chi-square test for linear trend

**Fig. 1 a–d** Normal (a, b) and grade 3 high-signal (c, d) changes bilaterally at coronal (a, c) and sagittal (b, d) proton-weighted MRI sections of alar ligaments (arrows/arrowheads). Broken lines mark the sagittal plane



homogeneity:  $p=0.38$  for alar ligament and 0.47 for transverse ligament).

#### Ligament changes in relation to cervical spine degeneration

In contrast to the ligament changes, cervical spine degeneration (yes/no) increased by age as a continuous variable ( $p<0.001$ ,  $t$  test). MRI showed no degeneration in 718 (56.7%) of 1,266 patients, degeneration at one cervical level in 264 (20.9%) and multilevel degeneration in 284 (22.4%). Patients in these three groups of cervical spine degeneration did not differ regarding the frequency of grades 2–3 ligament changes (Table 3).

#### Ligament changes by event and time since trauma

The frequency of grades 2–3 ligament changes was similar after transport accidents and after all other specified events of trauma grouped together (Table 3). This frequency was not related to time since trauma as a categorical variable (Table 3) or as a continuous variable (alar changes:  $p=0.65$ ; transverse changes:  $p=0.60$ ).

#### Right- and left-sided ligament changes

The changes were bilateral in 53.0% (238 of 449) of patients with grades 2–3 changes in the alar ligament(s) (Fig. 1) and 52.7% (164 of 311) of patients with grades 2–3 changes in the transverse ligament (Fig. 2). Unilateral grades 2–3 changes were more often left- than right-sided in the alar ligaments (134 left/77 right,  $p<0.001$ ) but especially in the transverse ligament (125 left/22 right,  $p<0.001$ ). This left-side predominance was found in males (alar changes 60/35,  $p=0.013$ ; transverse changes 49/5,  $p<0.001$ ) as well as in females (alar 74/42,  $p=0.004$ ; transverse 76/17  $p<0.001$ ) and both after transport accidents (alar 73/43,  $p=0.007$ ; transverse 64/11,  $p<0.001$ ) and after all other specified events grouped together (alar 34/19,  $p=0.053$ ; transverse 37/6,  $p<0.001$ ).

#### Results of multiple logistic regression analysis

In the multiple logistic regression analysis, gender had a significant effect on grades 2–3 ligament changes with odds ratio (males/females) of 1.9 (95% CI, 1.5 to 2.5;  $p<0.001$ )

for alar and 1.5 (95% CI, 1.1 to 2.0;  $p=0.012$ ) for transverse ligament changes. The other exposure variables had no significant effect (alar ligament:  $p>0.33$  for all variables; transverse ligament:  $p=0.089$  for time since trauma, 0.094 for age, 0.17 for spinal degeneration and 0.38 for type of event). No significant interactions between the exposure variables were found.

## Discussion

In the present study of consecutive patients with a history of neck trauma and clinical complaints, high-signal MRI changes in the alar and transverse ligaments were more common in men and showed left-side predominance. About one third of patients had alar changes, and one fourth had transverse ligament changes.

### Strengths and limitations

Among the strengths of this study are a large and consecutive sample and the prospective grading of ligament changes prior to the formation of the study hypotheses. Differences in prevalence of ligament changes were not due to observer variation since the same observer, with proven good intra-observer agreement [17, 18], graded all images. This observer had access to clinical data, which may affect grading of images. However, the data used in this study (age, gender, type of trauma event and time since trauma) probably had little influence on the grading. Inter-observer agreement in a random sub-sample of images indicated reliable grading and unbiased prevalence estimates.

Our study did not include non-trauma controls. A comparison of high-signal changes between WAD patients and controls would have been of interest. Clinical data were obtained from referral letters and therefore reflect a combination of patient information to the clinician and information in the clinician's file. Although such data may be imprecise, the report of WAD1–2 was quite certain. The referral letters were unlikely to lack crucial data on neurological signs or neck fracture (WAD3–4) or to falsely report neck complaints in WAD0. The exact type of trauma event was detailed in 83% (1,048 of 1,266) of the referral letters. In about one third of the letters, the month of trauma was lacking. For more recent traumas, where this can cause relevant bias, the time was specified; it had to be estimated in only three of 231 patients sustaining traumas during the last 18 months before their MRI. Our results do not necessarily apply to WAD1–2 patients who are not referred for MRI. Such patients may differ in trauma severity or symptoms and maybe in ligament changes.

### Comparison with other studies

To our knowledge, this is the first study to examine the prevalence of ligament changes at MRI in an unselected sample of WAD1–2 patients referred from clinicians and the first to explore the relations between such changes and age, gender, degeneration, event and time since trauma. About two thirds of the patients were females, which reflects a higher prevalence of reported WAD among females [13, 25, 28–30]. The majority of the patients (56%) in this study were reported with associated symptoms in addition to their neck complaints, as in other studies of WAD [13, 31].

Grades 2–3 ligament changes on MRI were less prevalent in our study than in a previous study of 92 WAD patients [25]. Those patients' neck trauma may have been more severe as they were front-seat drivers/passengers fulfilling the WAD2 criteria both in the acute phase and 12–16 weeks later. Grades 2–3 alar ligament changes were also less prevalent in our study than in a recent study of 59 car drivers/passengers with WAD1–2 for 6 months to 10 years [19].

In contrast to many studies on WAD [19, 20, 32–34], the present study was not restricted to patients who had experienced a transport accident. Nearly one third of our patients had experienced other events. These patients had similar prevalence of ligament changes as did those experiencing transport accidents.

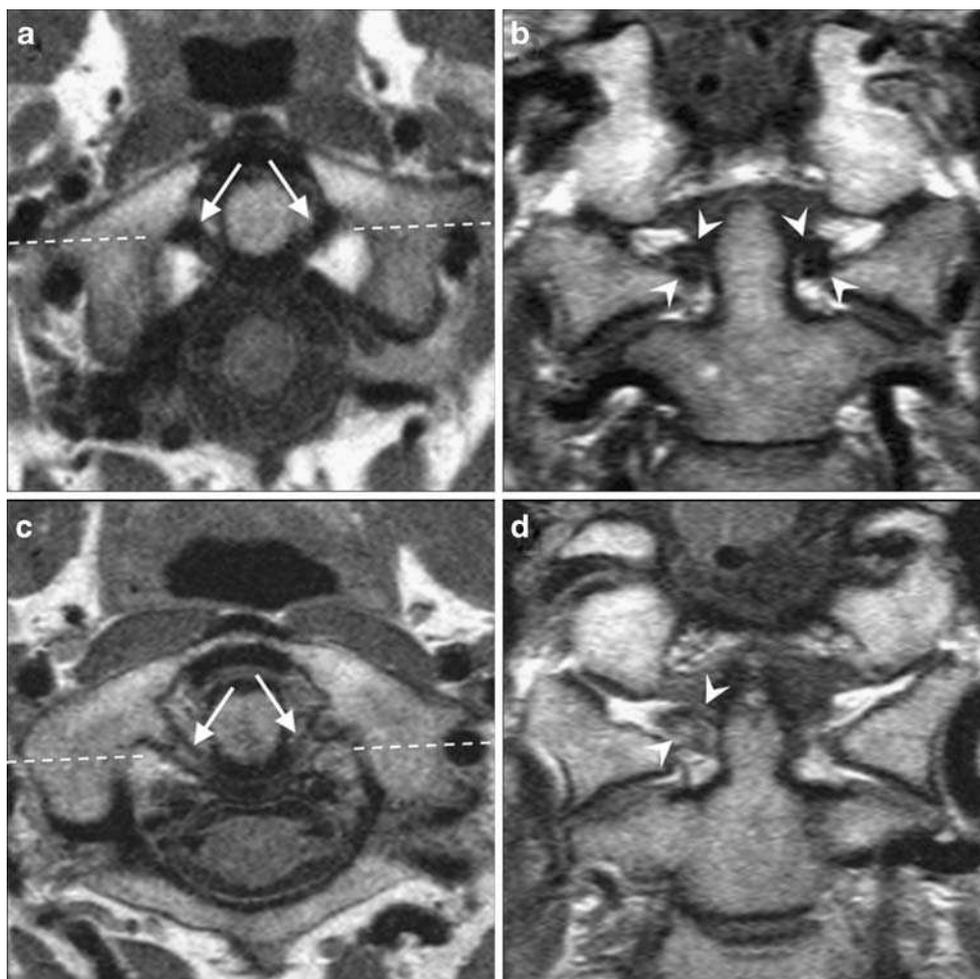
Two previous studies of non-trauma controls used the same MRI protocol and grading system as we did. One found much lower prevalence of grades 2–3 changes in controls than in WAD patients [17, 18]. The other, concerning alar changes only, found similar prevalence in controls with and without neck pain and in WAD patients (33%, 40% and 49%, respectively) [19]. Non-comparable studies using different MRI protocols and/or different grading systems have reported high-signal changes in one fifth to one third of asymptomatic controls [11, 14, 15].

### Discussion of findings

The histopathological correlation of the high-signal changes found at MRI of the alar and transverse ligaments is unknown. Degenerative changes can cause high signal from ligaments and tendons at MRI [22–24] and increase with age [24, 35]. In our study, the frequency of alar and transverse ligament changes did not increase with age, nor were we able to demonstrate an association between such changes and age-dependent cervical spine degeneration.

Fat interspersed between ligament fibres can also cause high signal at MRI [22] and might represent normal variation in ligament structure. This could account for reported high-signal changes among non-injured controls. However,

**Fig. 2 a–d** Normal (a, b) and grade 3 high-signal (c, d) changes bilaterally at axial (a, c) and coronal (b, d) proton-weighted MRI sections of transverse ligament (arrows/arrowheads). Broken lines mark the coronal plane



physiological variants with excessive amount of fat tissue were not reported in a histological study of the alar and transverse ligaments [5] and would be unlikely to explain the left-side preponderance of MRI signal changes found in the current study. Fat suppression techniques such as Short Tau Inversion Recovery may help to evaluate the presence of fat tissue but were not included in our imaging protocol.

It has been hypothesised that females' generally weaker neck muscles make their neck structures more vulnerable to abrupt strain forces [25, 26]. Unexpectedly, we found more ligament changes among males. As we had no data on trauma severity, we do not know if this male preponderance is related to this aspect. In general, males are more often involved in high-energy accidents, especially transport accidents [36–40]. However, in our study population, a lower proportion of males than females had sustained transport accidents, and such accidents did not imply more ligament changes than other events. It has been reported that males are less likely than women to seek medical attention after neck injury [29, 31]. One might speculate whether males who are referred for MRI have

experienced more severe trauma than women who are referred for MRI.

We found no relation between the time since trauma (median 5 years) and the frequency of high signal at MRI of the alar and transverse ligaments. This fits well with the suggestion that high signal in these ligaments represents chronic and stable structural changes [20].

Stretching alters the MRI signal of ligaments and tendons, and loose ligaments show a higher signal [41]. This cannot explain the increased frequency of left-sided high-signal changes, as all our patients were imaged with their head and neck in a neutral position.

In a previous study, alar high-signal changes were more frequent among those who had their head rotated at the time of the impact [20]. The left alar ligament may be more vulnerable when tightened by rotating the head towards the right [1, 5, 20]. A potential explanation for more frequent changes in the left alar ligament in our study might thus be that drivers in a right-hand driving country more often have their head turned right on impact. However, this explanation is unlikely since the left-side predominance was found

after both transport accidents and non-transport events. It was also present in the transverse ligament, where no significant association between head position and MRI changes has been found [20].

Image artefacts could be a possible explanation for the observed left-side predominance. Both the alar and transverse ligaments are surrounded by high-signal epidural fat, and partial volume artefacts have been suggested as the cause of alar ligament changes [15]. These artefacts become more pronounced in thin structures running obliquely to the imaging plane. However, rather similar average thickness and obliquity on the left and right side have been reported for both alar and transverse ligaments [1, 42, 43].

On proton-weighted images, the magic angle effect can cause high signal from ligaments running close to 55° to the main magnet field (B0) [44, 45]. In a standard MRI scanner, B0 is in the cranio-caudal direction of a supine patient. Considering the direction of the ligaments at the cranio-vertebral junction [16, 43], an angle close to 55° between the alar or transverse ligaments and B0 is rare, especially for the transverse ligament, and is unlikely to occur more often on the left side.

Chemical shift artefacts are also unlikely to explain the observed side differences. Chemical shift appears in the frequency direction [46, 47]. Only if a left to right (or right to left) frequency direction had been used could a chemical shift artefact have been a plausible explanation for the side differences. This frequency direction was not used in our MRI protocol.

## Conclusion

This non-controlled study has provided prevalence data from a large and relatively unselected patient sample. MRI showed grades 2–3 alar ligament changes in 35.5% of WAD1–2 patients and grades 2–3 transverse ligament changes in 24.6%. Such changes were more common in men and on the left side but were not related to patient age or time since trauma. These findings can hardly be explained by age-dependent degeneration, by the stretching of ligament fibres or by image artefacts. The finding of no relation with age, time since trauma or type of event would be compatible also with normal variation in ligament structure, but the male and left side preponderance fits less well with this theory. It is unknown whether the male and left side dominance of these changes at MRI is related to differences in the severity or mechanics of the trauma. Further studies are needed to clarify whether the changes are caused by trauma.

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**Conflict of interest statement** The MRI examinations used in this study were performed at a private institution. The MRI method applied is not generally accepted as a diagnostic tool in the investigation of WAD I–II patients.

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## **Paper II**



# MRI of the transverse and alar ligaments in rheumatoid arthritis: feasibility and relations to atlantoaxial subluxation and disease activity

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## Abstract

**Introduction** Dysfunctional transverse and alar craniovertebral ligaments can cause instability and osseous destruction in rheumatoid arthritis (RA). This study examined (1) the feasibility of high-resolution magnetic resonance imaging (MRI) of these ligaments in RA and (2) the relation between ligament high-signal changes and atlantoaxial subluxation and RA duration/severity.

**Methods** Consecutive RA patients ( $n=46$ ) underwent clinical examination, functional radiography, and high-resolution MRI. Two blinded radiologists rated MRI image quality,

graded ligament high-signal changes 0–3 on proton-weighted sequences using an existing grading system, and assessed cervical spine rheumatic changes on short tau inversion recovery images. Agreement was analyzed using kappa and relations using multiple logistic regression.

**Results** MRI images had good quality in 42 (91.3%) of 46 patients and were interpretable in 44 (32 women and 12 men, median age/disease duration 60.4/9.1 years). MRI grades 2–3 changes of the transverse and alar ligaments showed moderate and good interobserver agreement (kappa 0.59 and 0.78), respectively, and prevalence 31.8% and 34.1%. Such ligament changes were more frequent with increasing anterior atlantoaxial subluxation ( $p=0.012$  transverse,  $p=0.028$  alar), higher erythrocyte sedimentation rate ( $p=0.003$  transverse), positive rheumatoid factor ( $p=0.002$  alar), and neck pain ( $p=0.004$  alar).

**Conclusion** This first study of high-resolution MRI of these ligaments in RA showed high feasibility and relations with atlantoaxial subluxation, RA disease activity, and neck pain. The clinical usefulness of such MRI needs further evaluation.

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Radiography

## Introduction

The transverse and alar ligaments stabilize the craniovertebral junction (CVJ) [1–4] and prevent atlantoaxial instability [5–9]. Rheumatoid arthritis (RA) often affects these ligaments, and atlantoaxial subluxation is reported on functional radiography in 23–86% of adult RA patients [10]. Both

ligaments contain fibrocartilage, and fibrocartilage epitopes are targeted by the autoimmune reaction in RA [11–13]. Structural changes in these ligaments could therefore be an early sign of cervical RA. The transverse and alar ligaments should also be regarded as important to prevent osseous destruction at the CVJ in chronic RA, since mechanical instability due to ligament dysfunction can cause destruction even in the absence of active synovitis [14].

These ligaments are not accessible for biopsy or during surgery, and no non-invasive method has been established to study their structure in cervical RA. Magnetic resonance imaging (MRI) was applied in one small study from 1991 [15] to examine the transverse ligaments of four RA patients. More recently, high-resolution MRI has been used to visualize the detailed structure of the transverse and alar ligaments in patients with previous neck trauma and in non-injured volunteers [16–20] but not in RA patients, where joint dislocations and pain can make such time-demanding MRI a challenge.

The aim of this study was to examine the feasibility of high-resolution MRI of the transverse and alar ligaments in different stages of adult RA and to explore whether high-signal ligament changes are related to other imaging and clinical features. We hypothesized that such changes are related to increasing atlantoaxial subluxation and increasing severity and duration of RA.

## Methods

### Patients

Consecutive patients with adult RA were prospectively recruited from the Department of Rheumatology, Haukeland University Hospital, from October 2006 to May 2007. The inclusion criteria, met by 84 patients, were confirmed RA according to the American College of Rheumatology criteria [21], age 18–80 years, and no surgery during the last 4 weeks (to avoid influence of surgery on serological laboratory test results). We excluded patients with reported neck injury ( $n=4$ ), severe head injury ( $n=1$ ), prior cervical spine operation ( $n=2$ ), current cancer ( $n=2$ ), other serious somatic ( $n=5$ ) or psychiatric diseases ( $n=3$ ), known cervical nerve root syndrome ( $n=0$ ) or myelopathy ( $n=0$ ), contraindications to MRI ( $n=1$ ), those declining to participate ( $n=14$ ), and non-Norwegian speaking ( $n=2$ ). This left 50 patients eligible for the study; all gave their written informed consent to participate, but four did not complete the MRI due to claustrophobic discomfort. The remaining 46 patients underwent MRI and constitute the study sample. The Regional Committee for Medical Research Ethics, Western-Norway approved the study.

### Clinical evaluation

An experienced rheumatologist (R.A.) performed a clinical examination including a 28-joint count [22]. The same day, the patient filled out a questionnaire including the Modified Health Assessment Questionnaire (MHAQ) [23] and visual analog scale (VAS) scores of the last 7 days' RA disease activity and neck pain. Further clinical data were obtained from their hospital medical journals. Serological laboratory tests, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were taken within 6 days before or after the clinical examination. Immunological laboratory tests, rheumatoid factor, and anti-cyclic citrullinated peptide (CCP) were ordered if not taken within 6 months before admission. A disease activity score in 28 joints (DAS28 score) was calculated [22].

### Radiography protocol

Lateral cervical spine radiographs in both flexion and extension and an anterior–posterior open-mouth view were taken with tube distance 1.50 and 1.00–1.15 m, respectively. Patients were imaged in upright position while sitting or standing. The radiographs were taken 0–33 (median 2) days after the clinical examination.

### Radiographic evaluation

One radiologist (N.V.) blinded to clinical data and MRI findings interpreted all radiographs in random order. The anterior atlantodental interval (AADI) was measured on the lateral views in both flexion and extension. AADI represents the midline distance between the posterior part of the anterior tubercle of atlas and the anterior surface of the odontoid process [24–26]. AADI > 3 mm indicated anterior atlantoaxial subluxation. Vertical dislocation was evaluated on the lateral radiographs according to Kauppi [27]. Vertical subluxation was defined as present when the sclerotic ring of C2 reached the inferior line of the atlas.

### MRI protocol

Within 0–32 (median 2) days after the clinical evaluation, all patients underwent MRI with the same 1.5 T scanner (Symphony Mastroclass, Siemens Medical System, Erlangen, Germany), using a standard one-channel receive-only head coil, with head and neck in a neutral position. To visualize the delicate craniovertebral ligaments with high spatial resolution while maintaining adequate imaging contrast and signal-to-noise ratio, an established MRI protocol was used [20]. It included proton-density-weighted fast spin echo (FSE) sequences in three orthogonal planes, axial, coronal, and sagittal: repetition time (TR)/echo time (TE) 2,150–2,660/

15 ms, slice thickness 1.5 mm, interslice gap 0–0.3 mm, field of view (FOV) 175×200 mm or 200×200 mm, voxel size 0.6–0.7×0.4×1.5 mm<sup>3</sup> and echo train length (ETL) 13.

A focused sagittal short tau inversion recovery (STIR) sequence with the same FOV, slice number, slice thickness, and interslice gap as the sagittal proton sequence was added to assess inflammatory changes at the craniovertebral junction: TR/TE 6,990/88 ms, inversion time (TI) 150 ms, flip angle 160°, voxel size 1.0×0.5×1.5 mm<sup>3</sup>, and ETL 13. This allowed coupling of sagittal STIR and proton images to ensure adequate anatomic delineation when reading the STIR images, which showed fewer anatomic details due to a lower signal-to-noise ratio resulting from the suppression of fat signal.

To evaluate the whole cervical spine, we also included a sagittal STIR sequence with a larger FOV, covering through the apophyseal joints on both sides: TR/TE 5,680/51 ms, TI 160 ms, flip angle 160°, slice thickness 3.0 mm, interslice gap 0.3 mm, number of slices 19, FOV 180×180 mm<sup>2</sup>, voxel size 0.8×0.6×3.0 mm<sup>3</sup>, and ETL 13. The summarized acquisition time for the five sequences was 31 min 5 s.

#### MRI evaluation

Using a previously reported classification system, the alar and transverse ligaments were graded 0–3 on the proton sequences based on the ratio between any high-signal part and the total cross section area of the ligament [16, 20, 28]. No high signal was graded 0, high signal in one third or less of the total cross section was graded 1, high signal in one third to two thirds of the total cross section was graded 2, and high signal in two thirds or more of the total cross section was graded 3. The right and left sides were graded separately. The image with the largest cross-sectional area of high signal was used for grading. Any high signal had to be seen in at least two imaging planes to be graded 1–3; otherwise, it was graded 0 (no high signal). Homogenous gray ligaments were graded 2. On the focused STIR sequence, the intensity of any high signal from these ligaments was compared to the signal from adjacent craniovertebral bone marrow and cerebrospinal fluid (CSF).

The whole cervical spine was assessed for rheumatic changes on MRI. AADI was measured on the mid-sagittal proton image with the patient's neck in neutral position. Odontoid lateral mass interval (OLMI) was measured on coronal or axial sequences as the smallest distance between the medial part of the lateral mass of C1 and the lateral surface of the odontoid process [29, 30]. If OLMI on one side exceeded OLMI on the opposite side by 2 mm or more, lateral atlantoaxial subluxation (LAAS) was recorded [29]. Erosion was defined as a bone defect with sharp margins visible in at least two planes, synovitis as intermediate to high-signal intensity on STIR images of a

thickness greater than the width of the joint capsule, and bone edema as a poorly defined area within the trabecular bone with high-signal intensity on STIR consistent with increased water content [31, 32]. Absent CSF signal in both anterior and posterior subarachnoid spaces on sagittal STIR images was regarded as stenosis at the spinal cord or brain stem level. Decreased cord/brainstem diameter at the stenotic level indicated cord/brainstem compression [31]. Signal changes within the cord and brainstem were evaluated on STIR sequences.

Two independent radiologists (6 and 26 years experience) who were blinded to clinical data and radiography findings interpreted all MRI images, which were completely de-identified and presented in random order interspersed between similar images of individuals without RA. They thereafter solved all disagreements in consensus by joint reinterpretation of images. This consensus grading was used in all analyses except observer agreement analyses. To prevent RA suspicion from findings on the STIR sequences, the proton sequences were graded before the STIR sequences were made available. Both radiologists, in consensus only, evaluated the image quality as good, reduced (but images interpretable), or poor (images not interpretable) based on ligament visualization and artifacts, noise, and contrast.

#### Statistical analyses

Weighted kappa (linear weights) was applied to assess interobserver agreement on grading of high-signal ligament changes, using all four grades. In all further analyses, we dichotomized this grading system by combining grades 0 and 1 and grades 2 and 3, as was also done in most previous comparable studies [16, 19, 20]. Kappa was calculated for interobserver agreement on the presence or not of grades 2–3 changes. Fisher's exact test was used to compare proportions between patients with and without grades 2–3 ligament changes. To compare means, we used the Mann–Whitney *U* test as normality could not be assumed. Stepwise, backward, binary logistic regression was performed with grades 2–3 ligament changes as outcome variable and mutual adjustments done for continuous and categorical variables, using likelihood-ratio tests. The regression model included all variables with  $p < 0.2$  in the univariate analysis. SPSS 16.0 was used to analyze data.  $p \leq 0.05$  indicated statistical significance.

## Results

#### MRI image quality and patient characteristics

The image quality was good in 42 (91.3%) of the 46 patients, reduced for proton sequences in one patient

(2.2%), and reduced for the focused STIR sequence in one (2.2%). Two patients (4.3%) had non-interpretable proton sequences, leaving 44 patients eligible for analysis.

Table 1 shows clinical and imaging characteristics of these 44 RA patients; 32 (72.7%) were women, median age was 60.4 years and median RA disease duration 9.1 years. Neck pain during the last week was reported by 23 (52.3%). AADI was larger on flexion radiography than on neutral position MRI: median 2.0 (range 1.0–8.5) mm versus 1.2 (range 0.0–4.3) mm ( $p < 0.001$ , Wilcoxon signed ranks test). On MRI, three (6.8%) patients had dens erosion. No patient had compression or signal changes of the cord or brainstem.

### Ligament changes on MRI

MRI showed grades 2–3 transverse ligament changes (Fig. 1) in 14 (31.8%; 95% confidence interval (CI), 17.5% to 46.1%) and grades 2–3 alar ligament changes (Fig. 2) in 15 (34.1%; 95% CI, 19.5% to 48.7%) of the 44

RA patients. Interobserver agreement on ligament changes was moderate (weighted kappa 0.57 for the transverse ligament and 0.52 for the alar ligaments) and moderate to good for grades 2–3 versus grades 0–1 changes (kappa 0.59 for the transverse and 0.78 for the alar ligaments).

Table 2 depicts clinical and imaging characteristics of RA patients with and without grades 2–3 high-signal ligament changes. Patients with transverse ligament changes had higher ESR, larger AADI on radiography, and more often dens erosion on MRI. Patients with alar changes had higher ESR and CRP, more often dens erosion and were more likely men. Other clinical and imaging characteristics given in Table 1 did not differ significantly between patients with and without grades 2–3 ligament changes; Table 2 shows all characteristics with  $p < 0.2$ .

The mutually adjusted multiple logistic regression analysis (Table 3) confirmed that grades 2–3 transverse ligament changes were related to ESR ( $p = 0.003$ ) and AADI on radiography ( $p = 0.012$ ). Grades 2–3 alar ligament changes were related to gender ( $p = 0.001$ ), neck pain

**Table 1** Clinical and imaging characteristics of the 44 analyzed RA patients.

	N (%)	Median (range)
Clinical characteristics		
Women	32 (72.7)	
Age (years)		60.4 (19.8–79.6)
RA duration (years)		9.1 (0.0–34.6)
DAS28 score		5.3 (2.9–7.9)
MHAQ score (possible scores 1.0 to 4.0)		1.5 (1.0–3.4)
Last week neck pain intensity, VAS score (0 to 10)		3.0 (0.0–10.0)
ESR (mm/h)		29.0 (7.0–107.0)
CRP (mg/l)		9.5 (1.0–67.0)
Positive rheumatoid factor	25 (56.8)	
Positive anti-CCP	35 (79.5)	
Methotrexate treatment	24 (54.4)	
TNF inhibitor treatment	9 (20.5)	
Radiographic findings		
Anterior atlantoaxial subluxation (flexion)	11 (25.0)	
Anterior atlantodental interval (flexion), mm		2.0 (1.0–8.5)
Vertical subluxation	5 (11.4)	
MRI findings C0–C2		
Lateral atlantoaxial subluxation (LAAS)	8 (18.2)	
Dens erosion	3 (6.8)	
Peridental synovitis	8 (18.2)	
Bone edema	7 (15.9)	
Atlantooccipital joint erosion/synovitis	2 (4.5)	
Lateral atlantoaxial joint erosion/synovitis	7 (15.9)	
Spinal or brainstem stenosis	0	
MRI findings C3–C7		
Bone edema	7 (15.9)	
Erosion/synovitis at endplate and/or apophyseal joint	6 (13.6)	
Spinal stenosis	2 (4.5)	

DAS 28 disease activity score in 28 joints, MHAQ Modified Health Assessment Questionnaire, VAS visual analog scale, ESR erythrocyte sedimentation rate, CRP C-reactive protein, anti-CCP anti-cyclic citrullinated peptide, TNF tumor necrosis factor, MRI magnetic resonance imaging

**Fig. 1 a–d.** Grade 3 high-signal changes bilaterally (**a**) and normal (**b**) transverse ligament at axial proton-weighted MRI sections of transverse ligaments in two different RA patients (*arrows*), flexion lateral radiography (**c**) with increased anterior atlantoaxial interval, AADI, (*double arrow*) and mid-sagittal STIR MRI section (**d**) indicating anterior and posterior peridental synovitis (*arrowheads*) in same RA patient as in **a** and **c**



intensity ( $p=0.004$ ), rheumatoid factor ( $p=0.002$ ), and AADI on radiography ( $p=0.028$ ). Dens erosion could not be included in the regression models (all patients with erosion had grades 2–3 changes) but was nearly significant in further unadjusted analyses using Cytel Studio8, StatXact ( $p=0.055$  for transverse and  $p=0.069$  for alar changes).

On the focused STIR sequence, only one transverse ligament and no alar ligament had signal intensity higher than bone marrow. No ligament had STIR signal as intense as CSF.

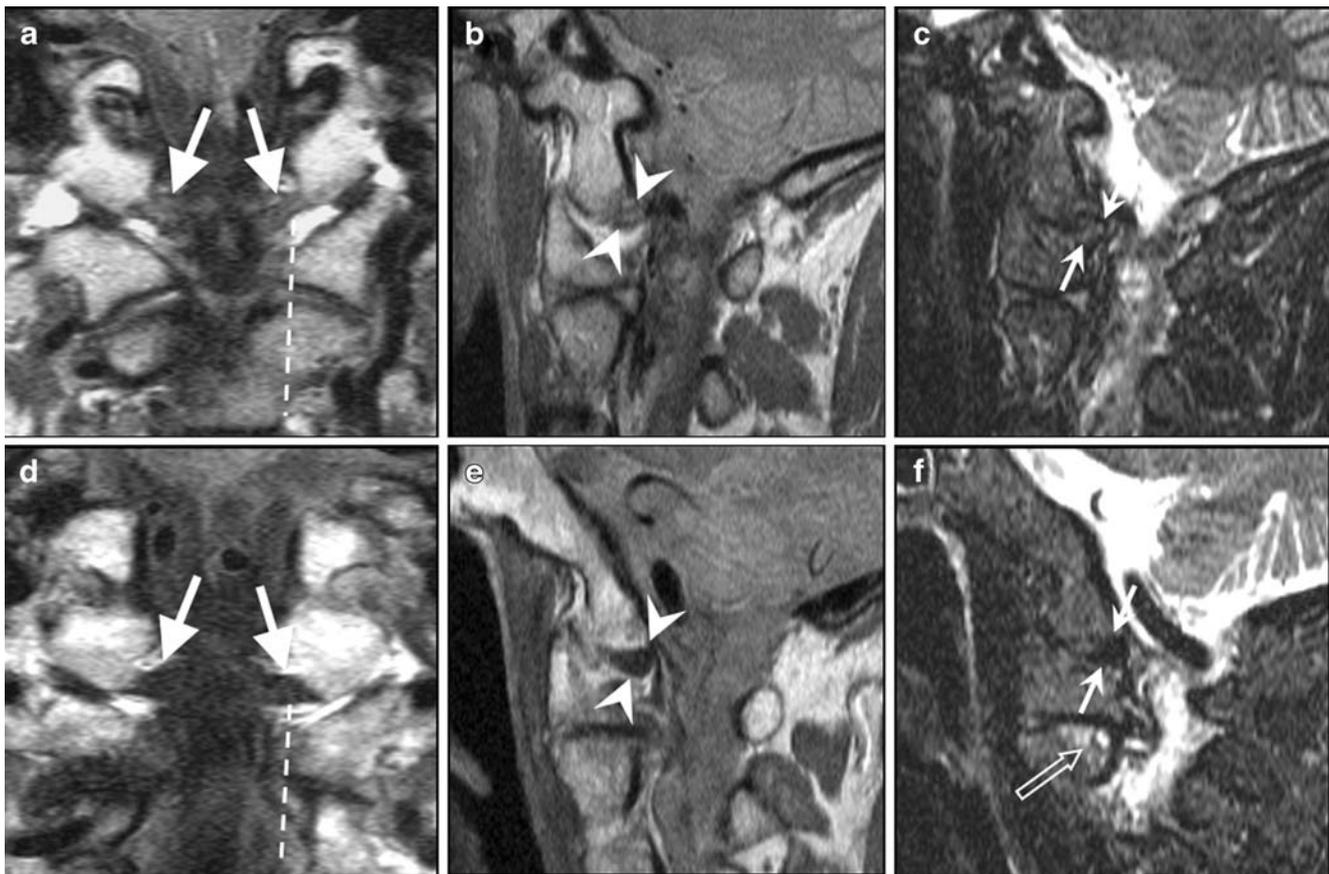
## Discussion

In this study, for the first time a high-resolution MRI technique for assessing high-signal changes of craniovertebral ligaments has been applied on RA patients. High-resolution MRI provided high-quality images and reliable evaluation of the transverse and alar ligaments in different stages of adult RA disease. MRI ligament changes were related to atlantoaxial subluxation, neck pain, and markers of disease activity: elevated ESR and rheumatoid factor.

The MRI sequences used in the current study are possible to perform and interpret in most adult RA patients. The patients in our study accepted the long acquisition times despite the fact that they had more severe RA (higher DAS28 scores) than patients in a general RA population [33]. Their ligaments were graded with similar interobserver reliability as reported for non-RA subjects [16, 19, 20] and for many radiological examinations in daily use [34–36].

The present high-resolution FSE sequences with 1.5 mm slice thickness allow a more detailed evaluation of the ligament structure than the 3-mm gradient-echo slices that were applied on four RA patients in the study by Dickman et al. [15]. They reported alterations of the transverse ligament but did not describe the signal characteristics.

Having examined feasibility and reliability, a next step in evaluating a new imaging method is to explore relations between imaging findings and clinical variables. To ensure valid results for such relations, our prospective study included nonselected RA patients, the same experienced rheumatologist examined all patients, and the radiologists graded the ligaments blinded to presence/severity of RA



**Fig. 2** a–f Grade 3 high-signal changes (a, b) and normal (d, e) alar ligaments (arrows/arrowheads) at coronal (a, d) and sagittal (b, e) proton-weighted MRI sections of alar ligaments in two different RA patients. Respective sagittal STIR MRI sections (c, f) show signal

intensity similar (c) and lower (f) compared to adjacent bone marrow (small arrows). Broken lines mark the sagittal plane. Note bone edema (open arrow) at the left lateral atlantoaxial joint (f)

and subluxation. Short time from clinical assessment to MRI further enhanced the validity of the relations found between clinical variables and ligament changes on MRI. We tested a priori hypotheses and found statistically significant relations despite the small sample.

Grades 2–3 ligament changes were related to larger AADI on flexion radiography, but which came first is not clear from this cross-sectional study. Longitudinal studies are needed to test the hypothesis that MRI ligament changes increase the risk of larger AADI and later subluxation. If so, MRI ligament changes can justify early RA treatment to prevent subluxation. Transverse ligament changes could be particularly relevant as this ligament is the most important structure preventing anterior dislocation of atlas on axis; a functionally intact transverse ligament usually prevents AADI from exceeding 3 mm [2, 5, 7, 9].

LAAS was not related to grades 2–3 alar ligament changes, despite the fact that it has been postulated that dysfunctional alar ligaments can cause LAAS in RA patients [30]. However, the role of the alar ligaments in the development of LAAS is not clear since the odontoid

process can deviate laterally on MRI also in asymptomatic non-RA individuals [37].

Our findings suggest that MRI ligament changes are related both to general and local RA disease activity. Patients with transverse changes had higher ESR, patients with alar changes were more often rheumatoid factor positive, and both groups tended to have more dens erosions. However, MRI ligament changes were not significantly related to DAS 28, anti-CCP, or disease duration. In DAS 28, the subcategories patients' peripheral joint status and assessment of global health to a lesser degree reflect cervical RA activity, and most (79.5%) of the RA patients were anti-CCP positive, making a relation with ligament changes hard to prove statistically. Rheumatic cervical spine changes usually appear within 2 years of RA disease onset [38]. Most of our patients had longer disease duration (median 9.1 years), making a relationship with ligament changes less likely.

High-signal alar ligament changes were associated to neck pain but were also found in RA patients without neck pain. Thus, such changes are not always symptomatic, as

**Table 2** Characteristics of RA patients with and without MRI ligament changes grades 2–3.

	With	Without	<i>p</i> <sup>b</sup>
Transverse ligament (14 patients with grades 2–3 MRI changes <sup>a</sup> and 30 without)			
Neck pain intensity, median VAS score	4.5	1.0	0.054
ESR, median (mm/h)	47.0	28.5	0.003
CRP, median (mg/l)	18.5	7.0	0.123
AADI on radiography (flexion), median (mm)	3.6	2.1	0.003
Dens erosion on MRI, <i>n</i> (%)	3 (21.4)	0 (0.0)	0.027
Peridental synovitis on MRI, <i>n</i> (%)	5 (31.8)	3 (10.0)	0.087
Lateral atlantoaxial joint erosion/synovitis on MRI, <i>n</i> (%)	4 (28.6)	3 (10.0)	0.184
Alar ligaments (15 patients with grades 2–3 MRI changes <sup>a</sup> and 29 without)			
Men, <i>n</i> (%)	8 (53.3)	4 (13.8)	0.011
Neck pain intensity, median VAS score	4.0	2.0	0.113
ESR, median (mm/h)	38.0	24.0	0.001
CRP, median (mg/l)	19.0	7.0	0.020
Positive rheumatoid factor, <i>n</i> (%)	11 (73.3)	14 (48.3)	0.199
AADI on radiography (flexion), median (mm)	3.1	2.3	0.060
LAAS on MRI, <i>n</i> (%)	5 (33.3)	3 (10.3)	0.099
Dens erosion on MRI, <i>n</i> (%)	3 (20.0)	0 (0.0)	0.034

Only characteristics with  $p < 0.2$  are given

*MRI* magnetic resonance imaging, *VAS* visual analog scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AADI* anterior atlantodental interval, *LAAS* lateral atlantoaxial subluxation

<sup>a</sup>Highest assigned grade if different between right and left side

<sup>b</sup>*p* values are based on Fisher's exact test or Mann–Whitney *U* test

**Table 3** Logistic regression of MRI grades 2–3 transverse and alar ligament changes on potential explanatory variables.

	Unadjusted		Final model <sup>a</sup>		
	OR	<i>p</i> <sup>b</sup>	OR	95% CI	<i>p</i> <sup>b</sup>
Transverse ligament					
Neck pain intensity, VAS score (0 to 10)	1.29	0.032			0.708 <sup>c</sup>
ESR (per 10 mm/h)	1.63	0.001	1.69	(1.10,2.59)	0.003
CRP (per 10 mg/l)	1.28	0.198			0.457 <sup>c</sup>
AADI on radiography (flexion) (mm)	1.93	0.005	1.81	(1.08,3.04)	0.012
Peridental synovitis on MRI (yes vs. no)	5.00	0.046			0.217 <sup>c</sup>
Lateral atlantoaxial joint erosion/synovitis on MRI (yes vs. no)	3.60	0.129			0.825 <sup>c</sup>
Alar ligaments					
Gender (men vs. women)	7.14	0.006	24.84	(2.69,229.91)	0.001
Neck pain intensity, VAS score (0 to 10)	1.23	0.072	1.68	(1.09,2.61)	0.004
ESR (per 10 mm/h)	1.61	0.002			0.112 <sup>c</sup>
CRP (per 10 mg/l)	1.33	0.130			0.610 <sup>c</sup>
Positive rheumatoid factor (yes vs. no)	2.95	0.106	29.87	(2.00,445.64)	0.002
AADI on radiography (flexion) (mm)	1.32	0.162	1.87	(1.03,3.41)	0.028
LAAS on MRI (yes vs. no)	4.33	0.074			0.327 <sup>c</sup>

Only variables with  $p < 0.2$  from the univariate analysis were included in the model

*MRI* magnetic resonance imaging, *OR* odds ratio, *CI* confidence interval, *VAS* visual analog scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AADI* anterior atlantodental interval, *LAAS* lateral atlantoaxial subluxation

<sup>a</sup>Stepwise backward by using likelihood-ratio tests

<sup>b</sup>*p* values are based on likelihood-ratio tests

<sup>c</sup>Not in the final model, *p* value for adding term to final model

confirmed for other upper cervical spine findings in RA as well [39, 40]. Alar high-signal changes also exist in asymptomatic non-RA subjects [19, 37]. Data on high-signal transverse ligament changes in asymptomatic subjects are sparse [41]. High-signal alar ligament changes may thus not necessarily represent pathologic tissue, and the histological correlate of MRI changes in the transverse and alar ligaments is not known.

The STIR images shed new light on the morphology underlying high-signal changes in the transverse and alar ligaments. Both ligaments consist almost exclusively of collagen fibers [2, 3], and are expected to show low signal on proton-weighted MRI sequences [42]. Inflammation or edema can cause high signal from ligaments on proton sequences and especially on STIR sequences, which suppress the high signal from fat [43]. Only one single ligament in our study had higher signal intensity than bone marrow on STIR. Thus, such changes more likely represent fat or fibrosis than inflammation. Postmortem and postoperative histopathological studies of bone and soft tissue specimen from the upper cervical spine in chronic RA have revealed predominantly fibrous tissue with little or no evidence of active inflammation [14, 44]. Similarly, MRI of the peridental area in chronic RA suggests fibrous tissue consistency rather than ongoing inflammation [45].

Our MRI protocol was primarily intended for optimal visualization of the ligaments, and to limit the examination time it did not include T1 sequences without/with gadolinium contrast enhancement, which are needed for ideal assessment of rheumatic MRI features [32]. Although synovitis and bone edema can be evaluated at STIR sequences alone [31, 46], the lack of gadolinium-enhanced T1 sequences probably diminished the sensitivity to such features, especially synovitis. MRI during cervical flexion, which tightens the transverse ligament [2], could have added further information on the nature of the high-signal changes since loose ligaments might show a higher MRI signal and tightening might reduce the signal [47].

To conclude, the successful and detailed visualization of the transverse and alar ligaments on high-resolution MRI provides new opportunities for research on these important structures in patients with RA. In this initial study, MRI ligament changes were related to atlantoaxial subluxation, markers of RA disease activity, and neck pain. Further studies with larger samples, longitudinal design, and control groups are needed to clarify if high-resolution MRI of transverse and alar ligaments can predict, diagnose, and help to treat cervical RA disease.

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**Conflict of interest statement** We declare that we have no conflict of interest.

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## **Paper III**



## **MRI of the alar and transverse ligaments in acute whiplash-associated disorders 1-2 – a cross-sectional controlled study**

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The Regional Committee for Medical Research Ethics, Western-Norway approved this study.

## **Abstract**

**Study Design:** Cross-sectional.

**Objective:** To describe alar and transverse ligament MRI high-signal changes in acute whiplash-associated disorders (WAD) grades 1-2 in relation to the severity and mechanics of trauma, and to compare with controls.

**Summary of Background Data:** The alar and transverse ligaments are important stabilizers at the craniovertebral junction. Acute injury of these ligaments should be detected as high-signal changes on high-resolution MRI.

**Methods:** 114 consecutive acute WAD1-2 patients and 157 non-injured controls underwent upper neck high-resolution MRI using proton-weighted sequences and Short Tau Inversion Recovery (STIR). Two blinded radiologists independently graded high-signal changes 0-3 on proton images and assessed ligament high-signal intensity on STIR. Image quality was evaluated as good, reduced or poor (not interpretable). Multiple logistic regression was used for both within and between groups analysis.

**Results:** All proton and STIR images were interpretable. Interobserver agreement for grades 2-3 versus grades 0-1 changes was moderate to good (kappa 0.71 alar, 0.54 transverse). MRI showed grades 2-3 alar ligament changes in 40 (35.1%) and grades 2-3 transverse ligament changes in 27 (23.7 %) of the patients. Such changes were related to contemporary head injury ( $p = 0.041$  alar), neck pain ( $p = 0.042$  transverse) and gender ( $p = 0.033$  transverse), but did not differ between patients and controls ( $p = 0.433$  alar,  $p = 0.254$  transverse). STIR ligament signal intensity higher than bone marrow was found in only 3 patients and 1 control.

**Conclusions:** This first study on high-resolution MRI of craniovertebral ligaments in acute WAD1-2 indicates that such trauma does not induce high-signal changes. Follow up studies are needed to find out if pre-traumatic high-signal changes imply reduced ligament strength and can predict chronic WAD.

**Key Words:** Alar ligament, transverse ligament, acute whiplash-associated disorder (WAD), magnetic resonance imaging.

**Key Points:**

- Acute injury of the alar and transverse craniovertebral ligaments should be detected as high-signal changes on high-resolution MRI.
- Such high-signal ligament changes were equally common in 114 acute WAD1-2 patients and 157 non-trauma controls without previous neck injury.
- These changes in acute WAD1-2 patients are not caused by the trauma, but further studies should clarify their effect on ligament strength and prognosis.

**Mini Abstract**

Acute injury of the alar and transverse craniovertebral ligaments could be detected as high-signal on high-resolution MRI. Such high-signal did not differ in frequency between 114 acute WAD1-2 patients and 157 controls without previous neck injury and was therefore hardly caused by the trauma.

## Introduction

Biomechanical and postmortem studies have shown that the alar and transverse ligaments, important stabilizers at the craniovertebral junction,<sup>1-5</sup> can be injured during neck trauma.<sup>6-10</sup> No imaging method has been established to diagnose such acute injuries. However, these ligaments can be visualized on magnetic resonance imaging (MRI)<sup>11-14</sup> and particularly using recently developed high-resolution MRI techniques.<sup>15-21</sup> Bleeding and/or edema following sprain or rupture can cause MRI high signal from ligaments.<sup>22-25</sup> Acute alar and transverse ligament injuries could therefore show high signal on high-resolution MRI.

In chronic whiplash-associated disorders (WAD), high-resolution MRI has shown high-signal alar changes in 36-66 % of patients<sup>18,21,26</sup> and high-signal transverse ligament changes in 25-40%.<sup>21,26</sup> It is not clear if such changes are injury related, and their prevalence in non-injured controls varies.<sup>18-20,26</sup>

This study included patients with acute WAD grade 1 or 2 (acute neck complaints after trauma but no fractures, dislocations or neurological signs)<sup>27</sup> and a control group of non-trauma volunteers. The aim was to describe alar and transverse ligament high-signal changes in relation to clinical and accident related factors. We hypothesized that such high-signal changes are related to trauma and should be more frequent in patients than controls.

## Materials and Methods

This cross-sectional study included 271 subjects without prior neck injury or neck complaints: 114 acute WAD1-2 car accident victims and a control group of 157 non-injured volunteers. The Regional Committee for Medical Research Ethics, Western-Norway approved the study. All subjects gave their written consent to participate.

### *Acute WAD1-2 group*

We consecutively and prospectively included Norwegian speaking drivers or passengers, 18-80 years, sustaining a car accident during the last 7 days, reporting onset of neck pain within 48 hours of the accident, without neurological signs or clinical or radiological signs of neck fracture or dislocation. From May 2007 until Mars 2009 we recruited 143 patients from persons attending Bergen Accident and Emergency Department and 111 patients from

Haukeland University Hospital remitted for acute conventional radiography and/or computed tomography of their cervical spine. At interview, 131 of these 254 patients were excluded according to our study protocol. This was due to prior neck injury or whiplash trauma (n = 77), prior severe head injury (n = 3), previous cervical spine surgery (n = 1), reported treatment for neck problems during the last 10 years or prior neck pain of more than 30 days (n = 44), rheumatic disease (n = 2), cancer or other serious somatic or psychiatric conditions (n = 2), and pregnancy (n = 2). Seven patients did not show up for MRI, one aborted MRI due to claustrophobic discomfort, and one had images obscured by dental implant artifacts. This left 114 acute WAD1-2 patients eligible for analysis.

#### *Clinical data*

Within 0 - 13 (median 4) days after their accident all patients filled out a questionnaire including an 11-point numeric rating scale (NRS-11) of average neck pain since injury, pain drawing<sup>28</sup> for indicating the localization of maximum neck pain, questions regarding accident-related factors, and a modified version of The Neck Disability Index (NDI).<sup>29,30</sup> The NDI was calculated only when at least 8 of 10 items were answered and then given as a percentage of highest achievable score.<sup>29,31</sup>

#### *Control group*

A control group was recruited from 224 responders to a letter inviting volunteers without neck problems to participate. The letter was sent to 1125 random persons aged 18 to 80 years in the National Population Register of Bergen, Norway. First author interviewed all responders and excluded 59 using the above criteria: prior neck injury or whiplash trauma (n = 18), prior severe head injury (n = 5), previous cervical spine surgery (n = 0), reported treatment for neck problems during the last 10 years or prior neck pain of more than 30 days (n = 31), neck pain at time of interview (n = 1), rheumatic disease (n = 1), pregnancy (n = 1) and MRI incompatibility (n = 2). Six responders did not meet for MRI and two aborted MRI due to claustrophobic discomfort. The remaining 157 responders completed MRI and constitute the control group.

#### *MRI protocol*

Patients were imaged within 0 - 13 (median 5) days after the car accident, and all patients and controls underwent MRI with the same 1.5 T scanner (Symphony Mastroclass, Siemens Medical System, Erlangen, Germany), using a standard one-channel receive-only head coil,

with head and neck in a neutral position. To visualize the alar and transverse ligaments with high spatial resolution while maintaining adequate imaging contrast and signal to noise ratio, a preexisting MRI protocol was used.<sup>15,21</sup> It included proton-density-weighted fast spin echo (FSE) sequences in three orthogonal planes, axial, coronal and sagittal: repetition time (TR) / echo time (TE) 2150-2660/15 ms, slice thickness 1.5 mm, interslice gap 0.0 mm or 0.3 mm (sagittal), field of view (FOV) 175 mm x 200 mm or 200 mm x 200 mm (coronal), voxel size 0.6-0.7 x 0.4 x 1.5 mm<sup>3</sup> and echo train length (ETL) 13.

To suppress the signal from fat and more easily detect traumatic changes like bleeding or edema, we added a focused sagittal Short Tau Inversion Recovery (STIR) sequence of the upper neck in all but two subjects: TR / TE 6990 / 88 ms, inversion time (TI) 150 ms, flip angle 160 degrees, voxel size 1.0 x 0.5 x 1.5 mm<sup>3</sup> and ETL 13. By using the same FOV, slice number, slice thickness and interslice gap, sagittal STIR and proton images could be coupled to ensure adequate anatomic depiction when interpreting the STIR images, which showed fewer anatomic details. A sagittal STIR sequence of the whole cervical spine was also added but not used in the present study. The summarized acquisition time for the 5 sequences was 31 min 5 s.

### *MRI evaluation*

The alar and transverse ligaments were graded 0-3 on the proton sequences based on the ratio between any high-signal part and the total cross section area of the ligament.<sup>16,21,32</sup> No high signal was graded 0, high signal in 1/3 or less of the total cross section was graded 1, high signal in 1/3 to 2/3 of the total cross section was graded 2, and high signal in 2/3 or more of the total cross section was graded 3. The right and left sides were graded separately. The image with the largest cross-sectional area of high signal was used for grading, alar ligaments on sagittal sections and transverse ligaments on sagittal or coronal sections. Any high signal had to be seen in at least two imaging planes to be graded 1-3; otherwise it was graded 0 (no high signal). Homogenous grey ligaments were graded 2. On the focused STIR sequence, the intensity of any high signal from the ligaments was compared to the signal from adjacent craniovertebral bone marrow and cerebrospinal fluid (CSF).

Two radiologists (6 and 26 years experience) who were blinded to clinical data and group allocation independently graded all proton images, which were completely de-identified and randomized. They solved all disagreements in consensus by joint reinterpretation of images.

Their consensus grading was used in the analysis, where grade 2 and 3 high-signal changes were combined. Disagreement on the presence of grades 2-3 changes in a given subject concerned 32 (11.8%) subjects for alar and 49 (18.1%) subjects for transverse changes. The proton sequences were graded before the STIR images were made available. With the consensus proton ligament grading available, the first radiologist interpreted all STIR images. This interpretation was used in the analysis. To assess interobserver agreement, the second radiologist independently interpreted the STIR images of 45 unselected subjects. The overall image quality for visualization of the ligaments was evaluated by the first radiologist and classified as good, reduced (interpretable images) or poor (non-interpretable images).

### *Statistical analyses*

Kappa was calculated for interobserver agreement on the presence of grades 2-3 changes and of STIR signal intensity higher than craniovertebral bone marrow. Fisher's exact test was used to compare proportions between groups. To compare means, we used the Mann-Whitney U test as normality could not be assumed. Stepwise, backward, binary logistic regression was performed with grades 2-3 ligament changes as outcome variable and mutual adjustments done for continuous and categorical variables, using likelihood-ratio tests. SPSS 16.0 was used to analyze data.  $P \leq 0.05$  indicated statistical significance.

## **Results**

Table 1 shows characteristics of the WAD1-2 patients. Their median age was 29.3 years and 57.0% were women. Controls were older (45.9 years,  $p < 0.001$ ), and 47.8% (75/157) were women. The image quality was rated as good in 94.5% (256/271) of subjects for the proton sequences and in 85.9% (231/269) for the STIR sequence. The remaining images were interpretable but had reduced quality. Patients and controls had similar image quality ( $p = 0.106$  proton,  $p = 0.596$  STIR). Interobserver agreement was moderate to good for grades 2-3 vs. grades 0-1 (kappa 0.71 for the alar ligaments and 0.54 for the transverse ligament). In the subsample of 45 subjects, both observers reported STIR signal intensity higher than bone marrow from only one (same) alar ligament and no transverse ligament (100% agreement).

*MRI ligament changes - acute WAD1-2*

MRI grades 2-3 alar changes were found in 40 (35.1%; 95% confidence interval (CI): 26.2 to 44.0%) and grades 2-3 transverse changes in 27 (23.7 %; 95% CI: 15.8 to 31.6%) of the 114 acute WAD1-2 patients. None of the clinical and accident related characteristic in Table 1 differed significantly between patients with and without grades 2-3 ligament changes.

All characteristics with  $p < 0.2$  were included in a regression analysis (Table 2). In the adjusted analysis, grades 2-3 alar changes were related to contemporary head injury (odds ratio (OR) 3.40, 95% CI: 1.03 to 11.22;  $p = 0.041$ ), and grades 2-3 transverse ligament changes related to neck pain and gender (OR 1.28, 95% CI: 1.00 to 1.63;  $p = 0.042$  and OR 2.79, 95% CI: 1.06 to 7.35;  $p = 0.033$ , respectively).

Unilateral grades 2-3 changes were more often left- than right-sided in the transverse ligament (17 left /2 right,  $p = 0.001$ ) but not in the alar ligaments (11 left /12 right,  $p = 1.000$ , McNemar's Test). In rear end collisions the proportions reporting their head turned right or left at impact did not differ between patients with vs. without right sided ( $p = 0.603$  alar,  $p = 1.000$  transverse) or left sided ( $p = 0.228$  alar,  $p = 1.000$  transverse) changes.

STIR signal intensity higher than craniovertebral bone marrow was found in alar ligaments of three patients (2.7%, 3/112). Such STIR signal intensity was not found in the transverse ligament, and no patient had ligament STIR signal intensity as high as CSF.

*MRI ligament changes - acute WAD1-2 vs. controls*

No difference in frequency of grades 2-3 alar (Figure 1) or transverse changes (Figure 2) between WAD1-2 patients and controls was found in the unadjusted analysis ( $p = 0.434$  alar,  $p = 0.272$  transverse, Table 3) or in a logistic regression analysis adjusted for age and gender ( $p = 0.433$  alar,  $p = 0.254$  transverse). The frequency of alar ligament STIR signal intensity higher than bone marrow did not differ between the groups ( $p = 0.311$ ), but numbers were low.

MRI showed grades 2-3 alar changes in 48 (30.6%; 95% CI: 23.3 to 37.9%) and transverse changes in 47 (29.9%; 95% CI: 22.7 to 37.2%) of the controls (Table 3). Controls with vs. without grades 2-3 changes did not differ in gender ( $p = 0.225$  alar,  $p = 0.486$  transverse) or age ( $p = 0.888$  alar,  $p = 0.176$  transverse). As in the patient group, unilateral grades 2-3

changes were significantly more frequent on the left side in the transverse (13 left / 4 right,  $p = 0.049$ ) but not in the alar ligaments (16 left / 8 right,  $p = 0.152$ , McNemar's Test). On STIR, only one control (1/157, 0.6%) had signal intensity higher than craniovertebral bone marrow (but lower than CSF) in the alar ligaments and none in the transverse ligament.

## Discussion

High-resolution proton-weighted MRI provided high-quality images and reliable evaluation of the alar and transverse ligaments in acute WAD1-2. Grades 2-3 high-signal ligament changes had similar frequency in patients and controls and were only weakly related to trauma factors. Our findings do not support the hypothesis that MRI high-signal changes in craniovertebral ligaments are related to acute trauma in WAD1-2.

### *Discussion of material and methods*

We did not include patients without neck pain (WAD0) or with neck fracture or dislocation (WAD4) and/or neurological signs (WAD3). Thus, the diagnosis of WAD1-2 should be valid. Prospective, consecutive patient recruitment both from a primary ward and a hospital clinic ensured a relevant range of trauma severity. Time from accident to MRI was 7 days or less in 87 % of our patients, and delay did not influence the frequency of high-signal ligament changes (Table 2). It is therefore unlikely that we have missed such changes due to delayed MRI examination.

Controls and patients were recruited from the same geographic area and were interviewed by the same researcher using the same strict exclusion criteria to reduce any effect of prior neck traumas or prior neck conditions on MRI findings. Their images were graded in the same blinded way and with similar interobserver reproducibility as reported for other comparable groups<sup>18,21,32</sup> and for many radiological examinations in daily use.<sup>33-35</sup> Our study included enough patients and controls to detect relevant differences in MRI findings. Since we used logistic regression and did not match patients and controls for age and gender, we could also study potential effects of age and gender on grades 2-3 ligament findings. In chronic WAD1-2, such findings may be more frequent in men.<sup>21</sup>

### *Discussion of findings*

The similar frequency of ligament changes in patients and controls, all declining prior neck injury/ neck complaints, indicates that these changes were not due to the trauma and were not necessarily symptomatic. So does the low and similar frequency of ligament signal intensity higher than bone marrow on STIR.

Alar changes were related to contemporary head injury, and head contact may suggest more severe trauma and higher load on the craniovertebral structures.<sup>36</sup> However, alar changes were not associated to other trauma factors or neck pain, and unilateral alar changes were not related to having the head rotated at impact, which stretches the opposite side's alar ligament and may make it more vulnerable.<sup>1,2</sup> In a previous MRI study of selected chronic WAD2 patients, right-sided alar changes were related to opposite side head rotation.<sup>26</sup>

The left side predominance of transverse ligament changes in both patients and controls was hardly trauma related, despite a similar predominance in chronic WAD1-2.<sup>21</sup> More transverse changes in male patients might be due to trauma, since men more likely experience high energy accidents.<sup>37,38</sup> However, in our WAD1-2 group men and women reported similar speed at impact ( $p = 0.171$  own car and  $p = 0.625$  second involved vehicle). Furthermore, transverse ligament changes were not related to speed or other trauma factors and were only weakly related to neck pain.

Our 157 non-injured controls had similar frequency of MRI grades 2-3 alar ligament changes (30.6%) as 57 comparable non-injured controls in a previous study (31.6%).<sup>18</sup> A lower frequency (6.7%) was reported in 30 non-injured controls with and without neck pain.<sup>26</sup> This difference is hard to explain, since the same proton-weighted sequences and grading system were applied. We found similar frequency of transverse ligament changes in non-trauma volunteers (29.6%) as reported in a previous study (20.0%).<sup>32</sup> Based on the present data, high-signal changes are common both in alar and transverse ligaments in non-injured persons.

The findings from our fat suppression STIR series indicate that these MRI changes may partly represent fat tissue. Physiological variants with loose connective tissue and fat interspersed between fibers can cause high-signal changes from ligaments.<sup>39,40</sup> Histological studies of the alar and transverse ligaments have primarily demonstrated dense collagen structures without evidence of such variants,<sup>1</sup> but have been performed on only a few cadavers. In our study,

only one single control subject with grades 2-3 high-signal changes in the alar or transverse ligaments on proton sequences showed signal intensity higher than bone marrow on STIR. This could be due to the suppression of signal from fat on STIR. Compared to STIR, a coupled proton sequence with chemical fat suppression would have been more appropriate for demonstrating fat tissue, but such a sequence has poor signal to noise ratio at high resolutions.<sup>15</sup> Until MRI-findings and histopathology are compared, the morphologic background of these ligament high-signal changes remains unsettled.

If ligaments in our study were injured during the trauma, the acute morphologic changes could not be detected as high-signal changes neither on proton nor on STIR sequences. An eventual subsequent repair process with fibrosis and scarring could nevertheless cause high-signal changes at a later stage after the injury. Also, if high-signal changes represent physiological variants with loose connective tissue and/or fat, affected ligaments can have reduced strength and increased vulnerability during neck trauma. Our patients are followed to see if those with high-signal changes are more likely to develop chronic WAD.

### *Conclusion*

In this first study on high-resolution MRI of the alar and transverse ligaments in acute WAD1-2, ligament high-signal changes had similar frequency in patients and controls and were only weakly related to trauma factors. The results did not support our a priori hypothesis that such changes can be caused by the actual trauma. More likely they represent physiological ligament variants with loose connective tissue and fat interspersed between fibers. Follow up studies should clarify whether such MRI changes can influence the prognosis in WAD1-2.

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**Table 1. Clinical and accident related characteristics of 114 acute WAD1-2 patients**

	n	%	Median (range)
<b>Clinical characteristics</b>			
Women	65	57.0	
Age, years			29.3 (18.1-69.2)
Neck pain intensity, NRS-11 score			4.0 (1.0-9.0)
Time accident – onset neck pain, hours			0.5 (0.0-48.0)
Pain maximum localized in upper neck (n = 107)	43	40.2	
Neck Disability Index, % (n = 113)			20.0 (0.0-73.3)
Head injury at accident	13	11.4	
Hospitalized	11	9.6	
Recruited from primary ward (vs. hospital clinic)	76	66.7	
Time accident - MRI, days			5.0 (0.0-13.0)
<b>Accident related factors</b>			
Rear end collision	69	60.5	
Face turned at impact (n = 95)	30	31.6	
Seatbelt at impact	107	93.9	
Headrest at impact (n = 110)	96	87.3	
Airbag release at impact (n = 113)	15	13.3	
Patient car speed at impact, km/h (n = 112)			0.0 (0.0-75.0)
Other vehicle speed at impact, km/h (n = 77)			40.0 (0.0-95.0)

WAD = whiplash-associated disorders; NRS-11 = 11-point numeric rating scale (0 to 10);

MRI = magnetic resonance imaging.

**Table 2. Logistic regression of MRI grades 2-3 alar and transverse ligament changes on potential explanatory variables in acute WAD1-2 patients**

	Unadjusted		Adjusted*		
	OR	p†	OR	95% CI	p†
<b>Alar ligaments</b>					
Neck pain intensity, NRS-11 score	1.19	0.090			0.148‡
Neck Disability Index, %	1.04	0.119			0.392‡
Head injury at accident (yes vs. no)	3.45	0.042	3.40	1.03,11.22	0.041
Time accident - MRI, days	1.16	0.066			0.084‡
<b>Transverse ligament</b>					
Gender (men vs. women)	1.95	0.134	2.79	1.06,7.35	0.033
Age, years	0.97	0.217			0.430‡
Neck pain intensity, NRS-11 score	1.23	0.072	1.28	1.00,1.63	0.042
Neck Disability Index, %	1.03	0.231			0.993‡
Headrest at impact (no vs. yes)	2.68	0.097			0.179‡
Airbag release at impact (no vs. yes)	4.80	0.139			0.106‡

Only variables with  $p < 0.2$  from the crude analysis were included in the regression analysis.

MRI = magnetic resonance imaging; WAD = whiplash-associated disorders; OR = Odds ratio; CI = confidence interval; NRS-11 = 11-point numeric rating scale (0 to 10).

\* Final stepwise backward model by using likelihood-ratio tests.

† P values are based on likelihood-ratio tests.

‡ Not in the final model, p-value for adding term to final model.

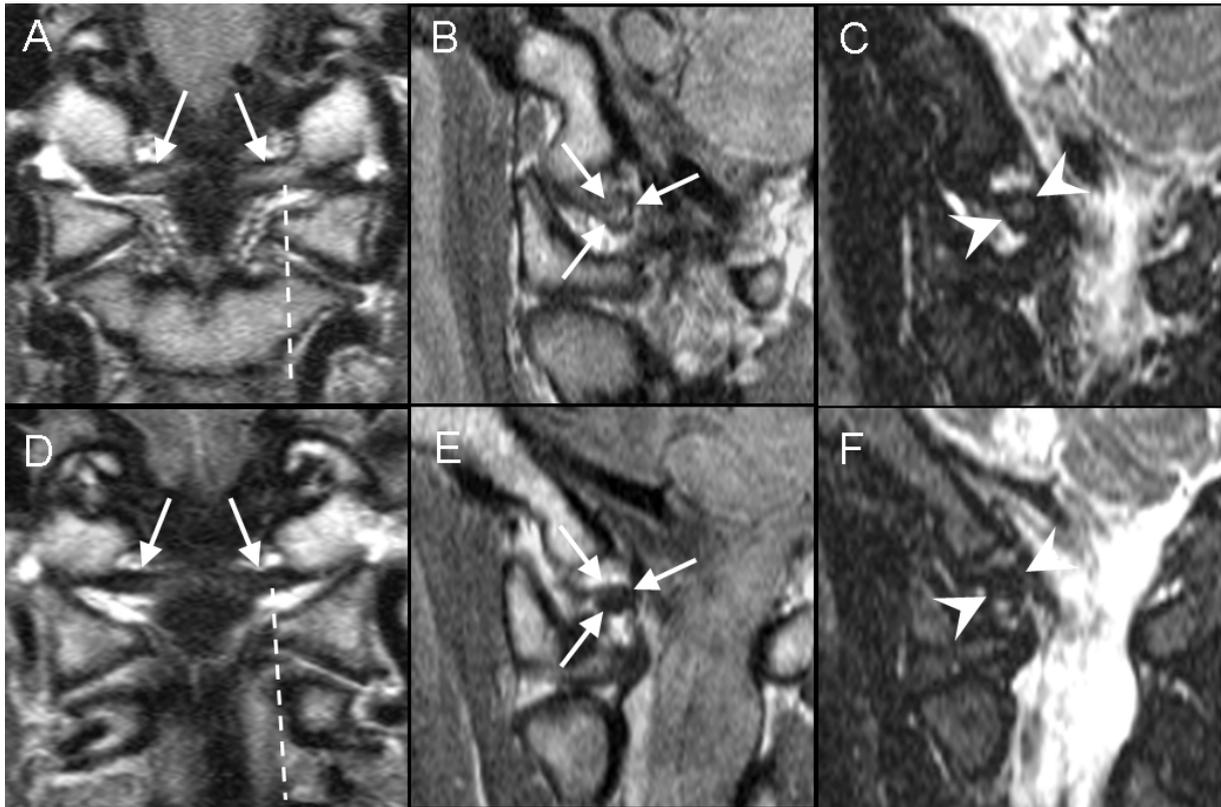
**Table 3. MRI grades 2-3 alar and transverse ligament high-signal changes in 114 acute WAD1-2 patients and 157 controls**

	Patients	Controls	p*
Alar ligament changes†, n (%)	40 (35.1)	48 (30.6)	0.434
Transverse ligament changes†, n (%)	27 (23.7)	47 (29.9)	0.272

MRI = magnetic resonance imaging; WAD = whiplash-associated disorders.

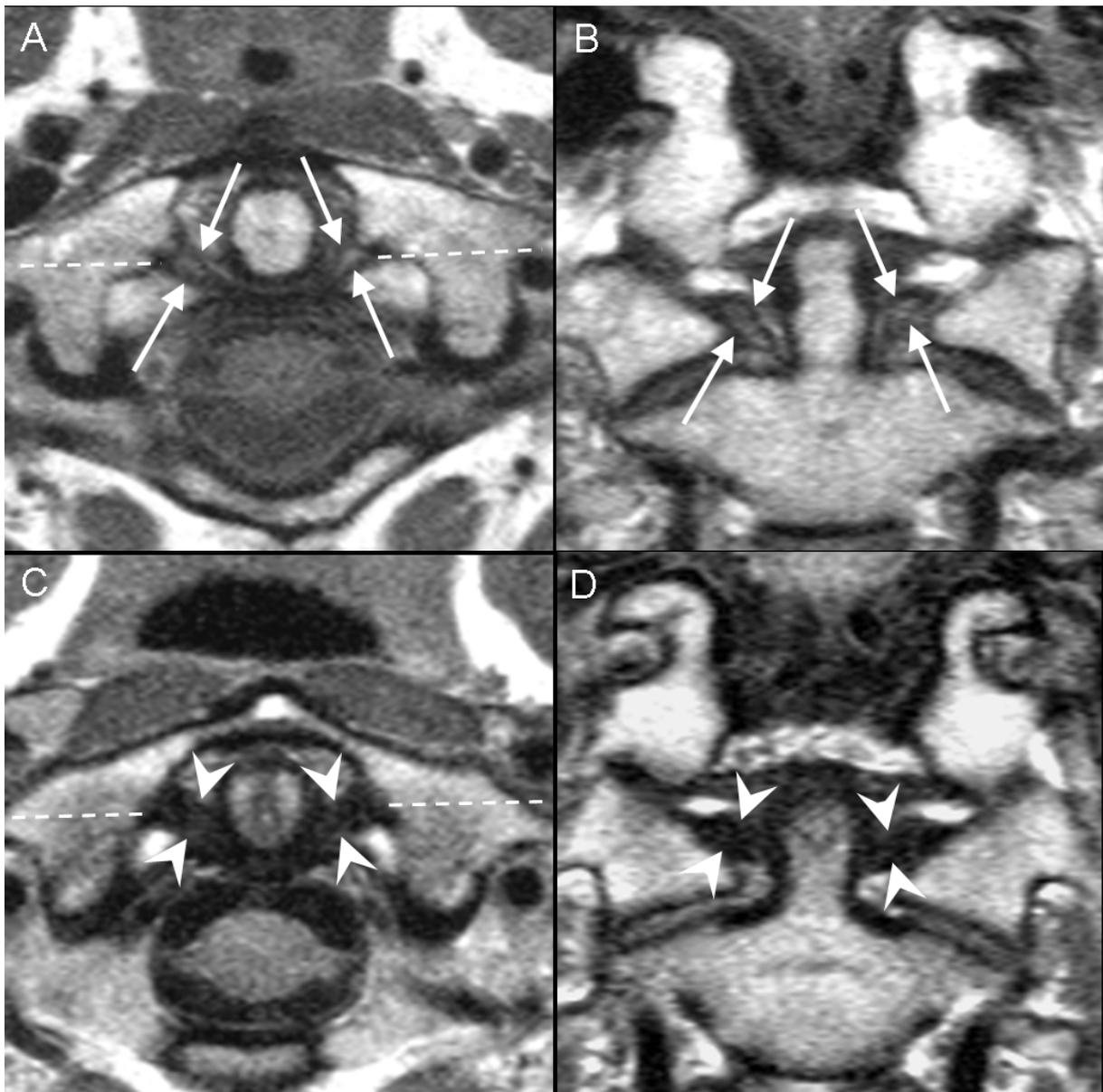
\* P values are based on Fisher's exact test.

† Highest assigned grade if different between right and left side.



**Figure 1.**

**A-C:** Alar ligament grade 3 high-signal (arrows) on coronal (A) and sagittal (B) proton-weighted MRI sections and signal intensity (arrowheads) slightly higher than bone marrow on sagittal STIR (C) in an acute WAD1-2 patient. **D-F:** Grade 0 alar ligaments (arrows/arrowheads) in a control for comparison. Broken lines mark sagittal plane.



**Figure 2.**

Transverse ligament grade 2 high-signal (arrows) at axial (A) and coronal (B) proton-weighted MRI-sections in a non-injured control. Grade 0 transverse ligament (arrowheads) in another control for comparison (C, D). Broken lines mark coronal plane.



## **Paper IV**



## **Acute whiplash-associated disorders (WAD) grades 1-2: Are MRI high-signal changes of alar and transverse ligaments related to outcome?**

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The Regional Committee for Medical Research Ethics, Western Norway Health Region approved this study.

## **Abstract**

**Study Design:** Prospective follow-up study.

**Objective:** To examine if alar and transverse ligament high-signal changes on magnetic resonance imaging (MRI) at injury are related to outcome after 12 months for patients with acute whiplash-associated disorders (WAD) grades 1-2.

**Summary of Background Data:** Upper neck ligament high-signal changes have been found in WAD patients but also in controls. The clinical relevance of such changes is controversial. Their prognostic role has never been evaluated.

**Methods:** Within 13 days after injury, 114 consecutive acute WAD1-2 patients without prior neck injury or prior neck complaints underwent upper neck high-resolution proton-weighted MRI. High-signal changes of the alar and transverse ligaments were graded 0-3. At 12 months follow-up, 111 (97.4 %) patients reported Neck Disability Index (NDI) (primary outcome) and last-week neck pain measured on an 11-point numeric rating scale (NRS-11). Factors potentially related to these outcomes were assessed using multiple logistic regression analyses.

**Results:** Among the 111 responders (median age 29.8 years; 63 women), 38 (34.2%) had grades 2-3 alar ligament changes and 25 (22.5%) had grades 2-3 transverse ligament changes at injury. At 12 months follow-up, 49 (44.1%) reported disability (NDI > 8) and 23 (20.7%) neck pain (NRS-11 > 4). Grades 2-3 ligament changes in the acute phase were not related to disability or neck pain at 12 months. More severe posttraumatic stress response and low expectations of recovery increased the odds for disability; odds ratio: 1.46 ( $p = 0.007$ ) and 4.67 ( $p = 0.005$ ), respectively.

**Conclusions:** High-signal changes of the alar and transverse ligaments close after injury did not affect outcome for acute WAD1-2 patients without previous neck complaints. High-resolution upper neck MRI has limited value for the initial treatment and follow-up of such patients.

**Key Words:** Alar ligaments, transverse ligament, whiplash-associated disorder (WAD), follow-up, outcome, magnetic resonance imaging.

**Key Points:**

- MRI high-signal changes of the alar and transverse ligaments in acute WAD1-2 patients were not related to disability or pain at 12 months follow-up.
- More severe posttraumatic stress response and low expectations of recovery in the acute phase of injury were associated with disability at 12 months.
- MRI of upper neck ligaments in acute WAD1-2 is of little value.

**Mini Abstract**

Among 111 acute WAD1-2 patients without prior neck complaints or neck injury, MRI high-signal changes of the alar and transverse ligaments at injury were not related to disability or neck pain at 12 months follow-up. More severe posttraumatic stress response and low expectations of recovery were associated with disability.

## Introduction

The alar and transverse ligaments are important stabilizers at the craniovertebral junction<sup>1-5</sup> and can be injured during neck trauma.<sup>6-10</sup> These ligaments can be visualized on magnetic resonance imaging (MRI).<sup>11-16</sup> High-signal changes of upper neck ligaments on high-resolution MRI have been reported in chronic whiplash-associated disorders (WAD)<sup>17-20</sup> but also in asymptomatic and symptomatic non-injured controls.<sup>14,17,19,21</sup> Such changes have unclear cause and clinical relevance. They might be traumatic in some cases but might also represent pre-traumatic morphologic variants with loose connective tissue or fat interspersed between fibers.<sup>17,19,20</sup> If such variants affect ligament strength and prognosis after neck trauma these MRI findings could represent a target for interventions to improve patients' recovery.

In prior MRI studies, traumatic findings in the acute phase of whiplash injury were rare<sup>22-26</sup> and did not affect recovery.<sup>22,23,26,27</sup> However, due to the magnetic field strength and MRI protocols chosen, the alar and transverse ligaments could not be assessed. Data on the prognostic role of MRI high-signal changes of these ligaments in acute WAD have been requested.<sup>23</sup>

This prospective follow-up study included patients with acute WAD grade 1 or 2, that is acute neck complaints after trauma but no fractures, dislocations or neurological signs.<sup>28</sup> All patients were examined with a dedicated high-resolution upper neck MRI protocol. The aim was to evaluate if high-signal changes of the alar and transverse ligaments in the acute phase of whiplash injury are related to outcome after 12 months.

## Materials and Methods

The Regional Committee for Medical Research Ethics, Western Norway Health Region approved this study. Written informed consent was obtained from all study participants.

### *Patients*

From May 2007 until March 2009 114 acute WAD1-2 patients were recruited consecutively from a primary ward (Bergen Accident and Emergency Department) (n = 76) and a hospital clinic (Haukeland University Hospital) (n = 38). All patients underwent MRI of their upper

neck ligaments. MRI findings in relation to clinical characteristics in the acute phase of injury of this inception cohort are reported elsewhere.<sup>29</sup>

To be included, patients should be Norwegian-speaking drivers or passengers, aged 18-80 years, sustaining a car accident during the last 7 days, reporting onset of neck pain within 48 hours after the accident, and without any neurological signs or clinical or radiological signs of neck fracture or dislocation. The exclusion criteria were prior neck injury or whiplash trauma, prior neck complaints, prior severe head injury, previous cervical spine surgery, rheumatic disease, cancer or any other serious somatic or psychiatric conditions, and pregnancy.

All participants were asked to complete a follow-up questionnaire 12 months after the accident. Three did not respond despite reminders and were excluded from the study, 111 (97.4%) responded and form the current study sample.

#### *Clinical data - acute phase*

Within 0 - 13 (median 4) days after their accident all patients filled in a questionnaire containing items regarding potential risk factors for developing chronic disability or pain in acute WAD1-2. It included an 11-point numeric rating scale (NRS-11) of average neck pain since injury (initial neck pain); 0 = no pain and 10 = worst possible pain,<sup>30,31</sup> a pain drawing for the localization of maximum neck pain,<sup>32</sup> and questions regarding accident-related factors and education. Patients' subjective reports of concomitant head injury were registered. Post traumatic stress response was evaluated by the impact of event scale (IES, theoretic range 0-75),<sup>33</sup> which has been validated in WAD.<sup>34-36</sup> The result was dichotomized into IES  $\geq$  26 and IES < 26.<sup>35,36</sup> The mean value of completed questions replaced any missing items when calculating the total IES score. Patients also answered to what extent (little, some, great) they expected to get rid of their pain after the accident. These expectations of recovery were dichotomized into high (great extent) and low (little / some extent).

#### *MRI protocol*

MRI was performed within 0 - 13 (median 5) days after the car accident (within 7 days in 96 patients, 86.5%) in an 1.5 T scanner (Symphony Mastroclass, Siemens Medical System, Erlangen, Germany), using a standard one-channel receive-only head coil. Patients' head and neck were in a neutral position. To visualize the alar and transverse ligaments with high spatial resolution while maintaining adequate imaging contrast and signal to noise ratio, a

preexisting MRI protocol was used.<sup>20,37</sup> It included proton-density-weighted fast spin echo (FSE) sequences in three orthogonal planes, axial, coronal and sagittal: repetition time (TR) / echo time (TE) 2150-2660/15 ms, slice thickness 1.5 mm, interslice gap 0.0 mm or 0.3 mm (sagittal), field of view (FOV) 175 mm × 200 mm or 200 mm × 200 mm (coronal), voxel size 0.6-0.7 × 0.4 × 1.5 mm<sup>3</sup> and echo train length (ETL) 13. Two sagittal STIR sequences followed but these were not used in the present study. The summarized acquisition time for the 5 sequences was 31 min 5 s.

#### *MRI evaluation*

The alar and transverse ligaments were graded 0-3 on the proton sequences based on the ratio between any high-signal part and the total cross section area of the ligament.<sup>18,20,38</sup> No high signal was graded 0, high signal in 1/3 or less of the total cross section was graded 1, high signal in 1/3 to 2/3 of the total cross section was graded 2, and high signal in 2/3 or more of the total cross section was graded 3. The right and left sides were graded separately. The image with the largest cross-sectional area of high signal was used for grading, alar ligaments on sagittal sections and transverse ligaments on sagittal or coronal sections. Any high signal had to be seen in at least two imaging planes to be graded 1-3; otherwise it was graded 0 (no high signal). Homogenous grey ligaments were graded 2.

Two radiologists (6 and 26 years experience) who were blinded to clinical data independently graded all proton images, which were de-identified and presented in a random order interspersed between images of non-injured individuals. Both radiologists thereafter solved all disagreements by consensus reading of images. Their consensus grading was used in the analysis, where grades 2 and 3 were combined into one category. Disagreement on the presence of grades 2-3 changes per patient concerned 13 (11.7%) patients for the alar ligaments and 19 (17.1%) patients for the transverse ligament. Kappa for interobserver agreement on presence of grades 2-3 changes was 0.73 for the alar ligaments and 0.52 for the transverse ligament.

#### *Clinical outcome data*

Uninformed of their MRI results, patients filled in the follow-up questionnaire 51-56 (median 52) weeks after the accident. Primary outcome was neck disability as measured by a modified version of the Neck Disability Index (NDI).<sup>39-41</sup> NDI should be calculated only when at least 8 of 10 items are answered and was given as a percentage of the highest achievable score.<sup>39</sup>

According to previously validated cut off values, NDI was dichotomized into  $NDI \leq 8\%$  or  $NDI > 8\%$ .<sup>41-43</sup> Neck pain during the preceding week was registered on an NRS-11 and categorized into NRS-11 0-4 or NRS-11 5-10.<sup>23,30</sup> All 111 patients returned valid data for both NDI and neck pain.

### *Statistical analyses*

Fisher's exact test was used to compare proportions between groups. To compare means the Mann-Whitney U test was used as normality could not be assumed. Multiple logistic regression analyses (stepwise backward, using likelihood-ratio tests) were performed with respectively NDI and neck pain NRS-11 as binary outcome variables. In these regression analyses mutual adjustments were done for age and gender and for all factors potentially related to outcome with  $p < 0.2$  in the crude analysis. Interaction between variables significantly related to outcome was looked for. SPSS 16.0 was used to analyze data.  $P \leq 0.05$  indicated statistical significance.

## **Results**

### *Patient characteristics - acute phase*

Median age of the 111 patients was 29.8 years, and 63 patients (56.8 %) were women (table 1). Fifty patients (45.0%) had initial neck pain NRS-11  $> 4$ , and 36 patients (32.4%) had IES score  $\geq 26$ . MRI in the acute phase of injury showed grades 2-3 alar ligament changes in 38 (34.2%) of the 111 patients and grades 2-3 transverse ligament changes in 25 (22.5 %) (Figure 1).

### *Unadjusted outcome analyses*

At 12 months follow-up, 49 (44.1%) patients had  $NDI > 8\%$  and 23 (20.7%) had neck pain NRS-11  $> 4$ . In unadjusted analyses (Table 2), these outcomes were not significantly related to MRI grades 2-3 changes of alar ( $p = 0.14-0.23$ ) or transverse ligaments ( $p = 0.49-0.59$ ) in the acute phase.

The risk of disability ( $NDI > 8\%$ ) increased with initial neck pain NRS-11  $> 4$  ( $p = 0.034$ ), post traumatic stress response IES score  $\geq 26$  ( $p = 0.015$ ), and low expectations of recovery ( $p = 0.001$ ). Also when treating continuous explanatory variables uncategorized, the risk of

disability increased with initial neck pain NRS-11 scores ( $p = 0.011$ ) and IES scores ( $p = 0.002$ ). Risk factors for neck pain (NRS-11  $> 4$ ) were the same as for disability but in addition included female gender ( $p = 0.032$ ) (Table 2). No other clinical or accident-related characteristic given in table 1 was related to disability or neck pain at follow-up with  $p < 0.2$ .

#### *Adjusted outcome analyses*

In the adjusted logistic regression analysis (Table 3) higher IES scores (odds ratio (OR) per 10 IES points: 1.46) and low expectations of recovery (OR: 4.66) in the acute phase of injury were related to NDI  $> 8\%$  at 12 months. No interaction between these two explanatory variables was found. Female gender (OR: 3.25), higher IES scores (OR per 10 IES points: 1.93), and low expectations of recovery (OR: 21.56) were related to neck pain NRS-11  $> 4$  (Table 3). In this model an interaction between expectations of recovery and posttraumatic stress was found. Post traumatic stress increased the risk of neck pain NRS-11  $> 4$  for patients with high expectations of recovery (OR: 1.93 per 10 IES points) but not for patients with low expectations (OR:  $1.93 \times 0.51 = 0.98$  per 10 IES points).

When included into these logistic regression models, MRI grades 2-3 ligament changes in the acute phase of injury were not related to NDI  $> 8\%$  (alar:  $p = 0.76$ , transverse:  $p = 0.76$ ) or neck pain NRS-11  $> 4$  (alar:  $p = 0.51$ , table 3; transverse:  $p = 0.42$ ) at follow-up.

## **Discussion**

In this first study on the prognostic value of upper neck ligament MRI findings, high-signal changes of the alar and transverse ligaments at injury were not related to outcome 12 months after whiplash injury. This result was highly robust and remained after adjustments for factors that may influence outcome. We hardly missed relevant high-signal changes, since every patient underwent dedicated MRI within 13 days (86.5% within 7 days) after the accident. The ligament grading had adequate reliability, was performed blinded to outcomes, and was not conveyed to any patient, since information *per se* on MRI results can affect prognosis.<sup>44</sup>

The finding that ligament high-signal changes in acute WAD1-2 were not related to outcome has important implications. First, due to this lack of prognostic value, such changes are unlikely to represent a target for treatment, regardless of whether they are traumatic or

represent morphologic ligament variants. Second, routine use of high-resolution upper neck MRI is not warranted in acute WAD1-2. Third, the high-signal changes are unlikely to be injury-induced. If they were due to the acute, mechanic incident, we would expect at least some prognostic effect. The ligament changes more likely reflect normal variants, also because they were not related to trauma factors and were equally frequent in non-injured controls, as previously reported.<sup>29</sup> Imaging artifacts or age dependent degeneration can not explain such high-signal changes.<sup>20</sup> Further data on the underlying morphology could provide insight into MRI evaluation of ligaments, but are unlikely to aid clinical decisions in acute WAD1-2.

The present study showed that female gender, more severe post traumatic stress response, and reduced expectations of recovery are associated with poor outcome in WAD, in line with previous reports<sup>34,35,45-47</sup>. An independent effect of degree of initial pain<sup>36,45,48,49</sup> was not confirmed, probably because pain just after the accident may be intense but temporary. Impact direction, head turned at impact or speed at impact did not affect outcomes, similar to previous findings on collision factors.<sup>45,48,49</sup>

In this prospective study of unselected WAD1-2 patients without previous neck problems we found better outcomes than in two previous studies; one Australian study<sup>36</sup> reporting NDI > 8% in 60% at 24 months and one Danish study<sup>23</sup> reporting NRS-11 score > 4 in 44% at 12 months. This may be explained by their inclusion of patients at higher risk due to neurological signs<sup>36</sup> (WAD3) or more severe initial symptoms.<sup>23</sup> Patients with previous neck problems probably have poorer prognosis,<sup>48,50,51</sup> and the prognosis after isolated whiplash trauma can not be ascertained in cohorts including such patients.

A major strength of our study is the prospective design and the high proportion of responders at follow-up (97%, 111/114) which prevented selection bias. Our sample of patients both from a primary ward and a hospital clinic should be representative of WAD1-2 patients without previous neck problems who seek medical care shortly after a car accident. We had insufficient data to discriminate between WAD1 and WAD2. However, the effect of WAD grades on outcome is controversial.<sup>51-53</sup> Neither did we include data on anxiety, depression or cervical range of movement.<sup>36,54</sup> We had to limit and prioritize between possible risk factors according to sample size and distribution of outcome variables. Potential residual confounders

could not have changed our results for prognostic value of MRI high-signal ligament changes unless they were unequally distributed between patients with and without such changes.

In contrast to previous examinations of acute WAD1-2 patients, our MRI protocol was intended to visualize craniovertebral ligaments. These previous studies focused on fracture or dislocation, traumatic disc or endplate changes, soft tissue bleeding/edema, posterior or anterior longitudinal ligament rupture and spinal cord injuries.<sup>22-27</sup> As no relation to prognosis was found, cervical spine MRI has not been recommended as a standard procedure in these patients<sup>22-24</sup>. Our results show that adding MRI sequences capable of visualizing craniovertebral ligaments does not change these recommendations.

In this study of acute WAD1-2 patients without previous neck problems, MRI high-signal changes of the alar and transverse ligaments in the acute phase were not related to disability or neck pain 12 months after injury. Female gender, more severe post traumatic stress response, and low expectations of recovery were associated with poor outcome at 12 months. Upper neck MRI is of limited value in the initial treatment and follow-up of WAD1-2 patients, and is not recommended for routine use.

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**Table 1. Clinical data and MRI ligament findings at injury of 111 WAD1-2 patients**

	n	%	Median (range)
<b>Clinical characteristics</b>			
Women	63	56.8	
Age, years			29.8 (18.1-69.2)
Higher education (> 12 years)	50	45.0	
Initial neck pain intensity, NRS-11 score (0 to 10)			4.0 (1.0 - 9.0)
Time accident – onset neck pain, hours			0.5 (0.0-48.0)
Pain maximum in upper neck (n = 105)	41	39.0	
Post traumatic stress, IES score (0 to 75)			19.0 (0.0-67.0)
High expectation of recovery (vs. low)	90	81.1	
Time accident - MRI, days			5.0 (0.0-13.0)
<b>Accident-related factors</b>			
Rear end collision (vs. all other directions)	69	62.2	
Face turned at impact (n = 93)	29	31.2	
Head injury at accident	13	11.7	
Seatbelt at impact	105	94.6	
Headrest at impact (n = 107)	94	87.9	
Airbag release at impact (n = 110)	15	13.6	
Patient car speed at impact, km/h (n = 109)			0.0 (0.0 - 75.0)
Relative car speed* at impact, km/h (n = 84)			45.0 (10.0-150.0)
<b>MRI ligament findings</b>			
Grades 2-3 alar ligament changes†	38	34.2	
Grades 2-3 transverse ligament changes†	25	22.5	

MRI = magnetic resonance imaging; WAD = whiplash-associated disorders; NRS-11 = 11-point numeric rating scale.

\*Difference between vehicle speed if rear end collision, otherwise sum of vehicle speed.

† Highest assigned grade if different between right and left side.

**Table 2. Disability and pain outcomes for 111 WAD1-2 patients at 12 months follow-up according to clinical characteristics and MRI ligament changes at injury**

	NDI score > 8%		NRS-11 neck pain score > 4	
	%	p*	%	p*
Gender		0.125		0.032
Women	50.8		28.6	
Men	35.4		10.4	
Age, years		0.286		0.759
< 20	50.0		14.3	
20-30	38.6		22.7	
30-40	34.8		13.0	
40-50	63.6		27.3	
>50	37.5		25.0	
Initial pain		0.034		<0.001
NRS-11 score ≤ 4	34.4		8.2	
NRS-11 score > 4	56.0		36.0	
Post traumatic stress		0.015		0.011
IES score < 26	36.0		13.3	
IES score ≥ 26	61.1		36.1	
Expectations of recovery		0.001		0.013
High	36.7		15.6	
Low	76.2		42.9	
Grades 2-3 alar ligament changes†		0.229		0.143
No	39.7		16.4	
Yes	52.6		28.9	
Grades 2-3 transverse ligament changes†		0.493		0.588
No	41.9		22.1	
Yes	52.0		16.0	

MRI = magnetic resonance imaging; WAD = whiplash-associated disorders; NDI = neck disability index; NRS-11 = 11-point numeric rating scale; IES = impact of event scale.

\* P values are based on Fisher's exact test.

† Highest assigned grade if different between right and left side.

**Table 3. Logistic regression analysis using NDI score > 8% and neck pain NRS-11 score > 4 as 12 months outcome for 111 acute WAD1-2 patients**

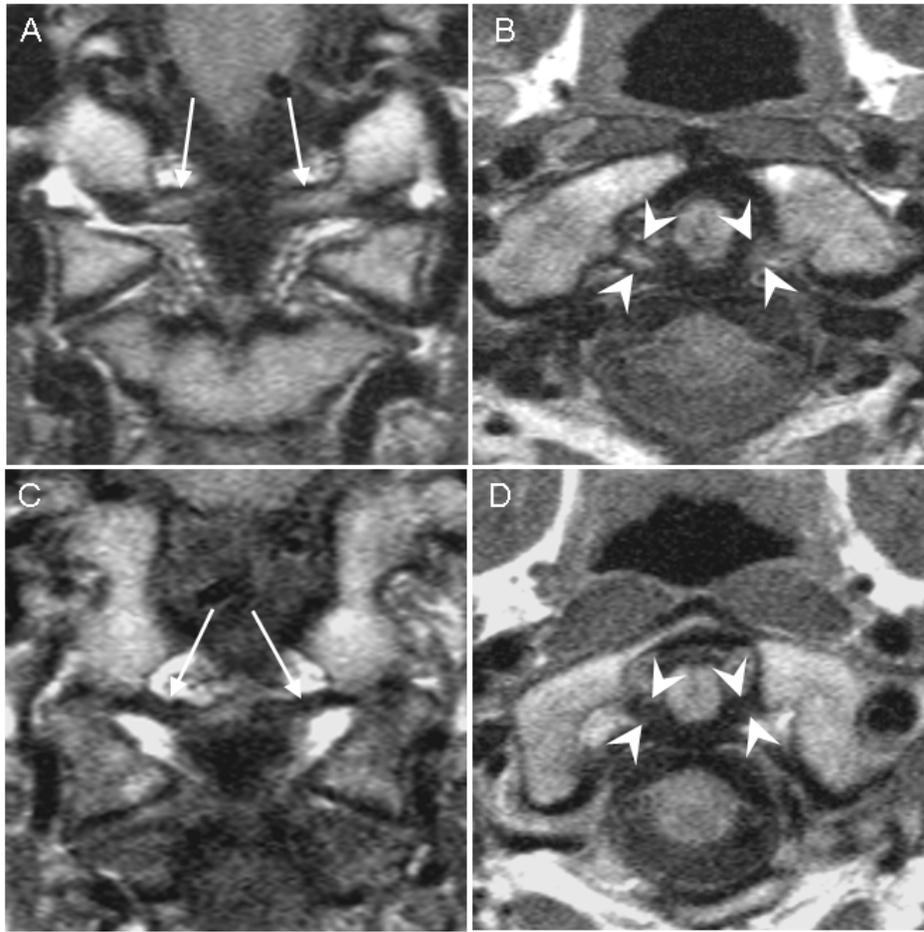
Explanatory variables	NDI score > 8%					NRS-11 neck pain score > 4				
	Unadjusted		Adjusted			Unadjusted		Adjusted		
	OR	p*	OR	95% CI	p*	OR	p*	OR	95% CI	p*
Gender (females vs. males)	1.88	0.105			0.210†	3.44	0.016	3.25	(1.00,10.50)	0.038
Age, years	1.02	0.343			0.093†	1.02	0.310			0.070†
Initial pain, NRS-11 score	1.27	0.016			0.699†	1.50	0.001			0.267†
Posttraumatic stress, per 10 IES points	1.53	0.001	1.46	(1.10,1.94)	0.007	1.65	0.001	1.93	(1.24,3.00)	0.001
Expectation of recovery (low vs. high)	5.53	0.001	4.66	(1.50,14.47)	0.005	4.07	0.009	21.56	(2.52,184.16)	0.006
Expectation of recovery × posttraumatic stress						1.23	0.160	0.51	(0.26,1.00)	0.048
Grades 2-3 alar ligament changes on MRI‡ (yes vs. no)						2.07	0.123			0.369†

NDI = neck disability index; NRS-11 = 11-point numeric rating scale; WAD = whiplash-associated disorders; OR = odds ratio; CI = confidence interval; IES = impact of event scale; MRI = magnetic resonance imaging.

\* P values are based on likelihood-ratio test.

† Not in the final model, p-value for adding term to final model.

‡ Highest assigned grade if different between right and left side.



**Figure 1.**

**A-B:** Grade 3 alar (arrows, coronal section) and grade 2 transverse (arrowheads, axial section) ligament high-signal changes on proton-weighted MRI in patients recovered ( $\text{NDI} \leq 8\%$ ) at follow-up. **C-D:** Grade 0 ligaments (arrows / arrowheads) in two different patients reporting disability ( $\text{NDI} > 8\%$ ) at follow-up for comparison.

