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Post-traumatic neck pain. Epidemiological, neuro-radiological and clinical aspects

Thesis for the degree of Philosophiae Doctor

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Post traumatiske nakkesmerter. Epidemiologiske, nevroradiologiske og kliniske aspekter.

Nakkesleng (whiplash) er et akselerasjons/deselerasjonstraume med energi som overføres til nakken, og som oftest oppstår ved trafikkulykker. Enkelte pasienter utvikler kroniske nakkesmerter samt andre symptomer i forløpet. Dette medfører store helsemessige og økonomiske konsekvenser for både pasienter og samfunnet. Det har vært fremsatt ulike hypoteser og det er gjort en rekke studier som så langt ikke har gitt noen endelig avklaring på årsaken til utvikling av kroniske plager. I de senere år har det vært rettet fokus mot strukturelle forandringer i støttestrukturer i nakken som mulig forklaring på hvorfor noen pasienter får kroniske smerter etter whiplash. Utviklingen av avanserte MR teknikker har gjort det mulig å se små leddbånd i overgangen mellom hode og nakke. Resultatene av ulike studier har imidlertid vært sprikende.

Formålet med denne studien var å undersøke forekomst og helseplager hos pasienter med selvrapportert whiplash i Helseundersøkelsen i Nord-Trøndelag fra 1995-1997. Videre var formålet å bruke MR for å se på om det var forskjeller i signalforandringer i alarligamentene hos tre ulike grupper; pasienter med whiplash, pasienter med kroniske nakkesmerter uten nakketraume og en gruppe med friske kontroller. Til slutt ønsket vi å undersøke om det var forskjeller i kliniske karakteristika som smerter, funksjon og psykiske plager relatert til MR funn i de tre gruppene.

Hovedfunnene i avhandlingen:

1. De som rapporterte nakkesleng hadde betydelig mer hodepine og muskel-skjelettplager enn de uten nakkesleng. Nakkeslengpasientene hadde mye nakkesmerter, men smertene var også dominerende i andre deler av muskel-skjelettapparatet som øvre rygg, bryst og mage.
2. Funn av høysignal i alarligamentene på MR var like vanlig i den friske gruppen og i gruppen med kroniske nakkesmerter som i nakkeslenggruppen.
3. Nakkeslenggruppen hadde mer smerter, mer angst og depresjon samt dårligere livskvalitet enn de andre to gruppene, men det var ingen sammenheng mellom smerter, funksjon, psykiske plager og grad av MR funn i de tre gruppene.

Resultatene fra dette arbeidet viser at nakkeslengpasientene er en gruppe med sammensatte plager. MR undersøkelse av ligamentene i øvre del av nakken etter nakkesleng har ikke vist funn som kan forklare symptomer hos pasienter med kroniske nakkesmerter etter whiplash.

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PAPER I - III

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ABBREVIATIONS AND ERRATA

Abbreviations

BAER	Brainstem Auditory Evoked Responses
BPI	Brief Pain Inventory
CI	Confidence interval
CNP	Chronic non-traumatic neck pain
CT	Computer tomography
EEG	Electroencephalography
EMG	Electromyography
EQ 5D	EuroQol 5D
EQ VAS	EuroQol Visual Analog Scale
GAD	Generalised Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HUNT	Helseundersøkelsen i Nord-Trøndelag
MSC	Musculoskeletal complaints
MRI	Magnetic Resonance Imaging
OR	Odds ratio
PTSD	Post Traumatic Stress Syndrome
QTF	Quebec Task Force
SD	Standard deviation
SEP	Somatosensory Evoked Potential
SPSS	Statistical package for the social sciences®
T	Tesla
VAS	Visual Analog Scale
WAD	Whiplash Associated Disorders

Errata

Paper II: page 2015, table 4. For interpreter 2, correct number of WAD patients that were classified as Grade 2 to 3 is 42.4 % and not 57.6%, which is the number of WAD patients classified as Grade 0 to1.

PUBLICATIONS INCLUDED IN THE THESIS

The thesis is based on the following papers, which are referred to in the text by their roman numerals.

I. Myran R, Hagen K, Svebak S, Nygaard ØP, Zwart JA. Headache and musculoskeletal complaints among subjects with self reported neck distortion. The HUNT-study. *Submitted to Injury.*

II. Myran R, Kvistad KA, Nygaard ØP, Andresen H, Folvik M, Zwart JA. Magnetic resonance imaging assessment of the alar ligaments in whiplash injuries. A case-control study. Spine 2008;33: 2012-6.

III. Myran R, Zwart JA, Kvistad KA, Folvik M, Lydersen S, Rø M, Woodhouse A, Nygaard ØP. Clinical characteristics, pain and disability in relation to alar ligament MRI findings. *Resubmitted to Spine.*

1. INTRODUCTION

1.1. Definition and classification

Multiple anatomical structures in the neck have been proposed to be associated with the complaints after whiplash injuries. However, the pathological basis for the clinical features of whiplash associated disease (WAD) is not clear. In addition, the whiplash injury mechanism has been difficult to define because the patients present a wide variety of subjective symptoms and signs. This has lead to a wide range of interpretations and therefore a vague definition of the term whiplash.

In clinical practice whiplash associated injuries are classified according to the International Diagnostic Classification system ICD 10. The ICD 10 classification codes refer to symptoms, location and injury mechanism (1).

A more useful classification was presented in 1995 by the Quebec Task Force (QTF) that introduced the term "whiplash associated disorders" (WAD)(2). The QTF presented the definition:
"Whiplash is an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear-end or side-impact motor vehicle collisions, but can also occur during diving or other mishaps. The impact may result in bony or soft-tissue injuries (whiplash injury), which in turn may lead to a variety of clinical manifestations (whiplash-associated disorders—WAD)" .

The Quebec Task Force proposes a classification of WAD on clinical-anatomical findings (grades 0-4) corresponding to the severity of the injury (Table 1). In the monograph they also take into consideration a time axis. For duration of symptoms patients are categorized as acute if symptom duration is less than four days from the time of injury, chronic if symptoms are persistent after 6 months (2). The latter condition is also known as "late whiplash syndrome".

Table I. The WAD classification system.

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)[a]
3	Neck complaint and neurological sign(s)[b]
4	Neck complaint and fracture or dislocation

[a]Musculoskeletal signs include decreased range of motion and point tenderness.

[b]Neurological signs include decreased or absent deep tendon reflexes, weakness and sensory deficits.

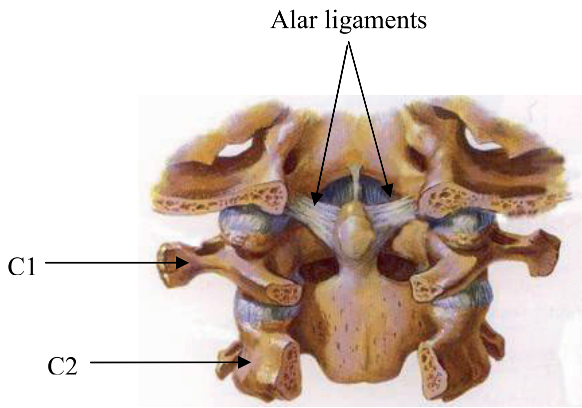
A consensus from a Swedish medical task force finds that distinguishing whiplash trauma and whiplash injury is essential in clarifying the definition of whiplash. They suggest whiplash trauma as an indirect trauma to the cervical spine to better reflect the trauma mechanism. In addition, they proposed deleting grades 0 and 4 in the QTF classification because individuals lacking symptoms and findings do not have a WAD disorder, and because fractures and dislocations are rare in indirect cervical spine trauma (3). The classification and definition of whiplash is carefully discussed in this consensus.

1.2. Background

Whiplash injuries represent the largest proportion of all motor vehicle injuries in the western world. This type of injury has been estimated to be present in between 60%- 85% of all reported traffic accidents (3). Harold Crowe introduced the term "whiplash" in 1928 (4). The first publication about the whiplash accident mechanism was published in Journal of the American Medical Association (JAMA) in 1953 (5). Crowe first used the term to denote the motion of the head and neck induced by forces of acceleration or deceleration. The term gradually became more widely used, and it has since come to signify the injuries induced by this motion. Despite a high number of scientific papers on the subject, there is a lack of controlled studies, and the observers have commonly used methods that are not comparable. In addition, the fact that patients with whiplash injuries are a heterogeneous group with a variety of clinical manifestations makes it difficult to provide consistent figures for whiplash-induced disability. A wide variety of studies have investigated different trauma-related causes of the symptoms and functional impairment, but there is still no general agreement regarding the cause of the late whiplash syndrome.

In recent years the ligaments in the craniocervical junction have been focused on in whiplash injuries. In particular the alar ligaments have been subject for research. This thesis has main focus on the alar ligaments. The normal anatomy of the alar ligament is well described (6).

Figure 1. Ligamenta alaria. Seen from dorsal (Sobotta, Atlas of Human Anatomy,Vol.1, 1982)



The alar ligaments are on both sides, approximately 1 cm in length, elliptical in cross-section and the mean diameter is 3x6 mm. They originate from the posterior-lateral aspect of the dens of C2, and insert on the occipital condyles (C0). In the cervical spine the rotation between C0 and the C1, accounts for only 5% of the total rotation (7). Approximately 50% of the flexion and extension of the cervical spine takes place in this joint. In the next joint, between C1 and C2, 55% of the total rotation occurs. The rest of the rotation is distributed approximately equally among the rest of the cervical joints. With the absence of intervertebral discs between C0-C1 and C1-C2, and the presence of a flat shape of the articulate facets, the alar ligaments may have a key role in stabilizing the C0-C2 complex (7, 8). The axial rotation is primarily limited by ligamentous structures, of which alar ligaments are believed to be the primary restraint. The rotation to the left is limited by the right alar ligament and vice versa. The ligaments are most stretched when the head is both rotated and flexed (6).

1.3. Epidemiology

The reported annual incidence of whiplash injuries varies between different countries, studies and time periods. Due to the use of seatbelts and safer car designs, the fatal vehicle injuries have decreased. However, the reported incidence of minor injuries and whiplash injuries has increased over the past decades (9-11). Published reports from the Confederation of Norwegian Enterprise comprising all the Norwegian insurance companies indicate that the most common cause of whiplash, a rear- end collision, in year 2000 involved 54000 vehicles (12). Half of these were hit from behind. Both chronic neck pain and chronic headache are prevalent in the general population with prevalence estimates of respectively 14% and 2.5 % (13, 14). Accordingly a large estimated numbers of subjects with pre-existing chronic neck pain and headache will be involved in a rear-end collision. Over a 10 year period one can calculate that approximately 270 000, i.e. 6% of the population, will be involved in such a collision and have been exposed to a whiplash mechanism (15). However, the number of people reporting whiplash injuries is much lower. In Sweden the annual incidence of whiplash injuries ranges from 100-420 pr 100.000 (16, 17). In Canada and the USA an incidence of between 100-700 per 100 000 is reported (2, 18). In total whiplash associated disorders (WAD) are estimated to be 300-600 cases per 100,000 in North America and Western Europe (9, 19, 20).

1.4. Pathological anatomy

It is not clear whether chronic pain originates from the acutely injured tissue or whether other physiologic processes account for the persistence of pain (21). In an attempt to provide a pathoanatomic explanation for WAD, the main attention has been directed toward injuries of the cervical muscles, discs, facet joints and ligaments (21, 22). Pathoanatomical explanations of the symptomatology are often based on experimental animal studies, cadaver studies, post-mortem observations and findings at surgery (3, 23) and have proved difficult to confirm by available imaging tools (24-26). The imaging findings may be normal variations that are present to a similar degree in asymptomatic individuals (27-32). Furthermore, there is no indication of neural injury in neurophysiologic studies (e.g. EEG, SEP, BAER, EMG) (33-36). To extrapolate the results of experimental animal and human cadaver studies to the clinical situation is problematic (3). The difference between subjects with respect to anatomical and physiological conditions and the injury mechanism as well, are of importance and complicate the evaluation and application of such findings.

Typically, the whiplash patient has neck pain and headache (37). The common understanding of these symptoms is that they are attributed to a musculoligamentous sprain in the neck in the acute whiplash state (23). From an experimental animal model muscle injuries varied in severity from minor tears of the sternocleidomastoid muscle to more severe tears of the longus colli muscle (38), although later studies could not find evidence of direct injury to muscle (21, 39). In some whiplash patients elevated serum creatine kinase has been observed 24 hours post-injury, but not after 48 hours, despite neck pain extending beyond 3 months (39). This work suggests that direct muscle injury may not be responsible for chronic whiplash pain. The usual expectation after sprain or tears of muscles is that they heal in a matter of weeks forming a scar, but leaving the patient with no residual pain (23). MRI studies support the clinical experience that muscle injuries do not contribute to persistent WAD symptoms (3, 25, 40, 41).

Studies using diagnostic facet joint blocks have demonstrated that the facet joint pain may be a common cause of chronic neck pain after a whiplash injury (42-44). Excessive compression of the facet joints and facet capsule strain have been proposed as likely injury mechanisms (43, 44). A study on healthy volunteers investigating the mechanism of facet joint injury (45), indicated that the lower cervical vertebra is the most likely site of injury.

Clinical evidence suggests that disc injury and degenerative changes are common in whiplash patients (28, 40, 46, 47). A study concluded that degenerative changes occurred significantly more in patients who had sustained soft- tissue injury than in a control population (47). Injuries to the lower cervical ligaments have been observed in experimental studies. Often the ligaments (the anterior and posterior longitudinal ligament, the ligamentum flavum, the supraspinous and interspinous ligament) are at risk for injury due to excessive strain and increased elongation (28, 38, 48-50). However, prospective clinical studies using MRI have not found any lower ligament injuries in the acute stage after whiplash injuries (25, 40, 41).

In a MRI study of ligaments and membranes in the craniocervical junction in the late stage of whiplash injury, Krakenes et al. found significantly more high-grade signal changes in the whiplash group compared to asymptomatic controls for all structures in the region (51-53).

These signal changes were interpreted as injuries to the ligament caused by a whiplash trauma (54). The same group linked the signal changes to specific trauma mechanisms, e.g. head position, and found a significant association between high-grade signal intensity changes in the alar ligaments and rotated head position during the trauma (55).

1.5. Symptoms and pain mechanisms

Patients with the whiplash syndrome present with a variety of symptoms including neck pain, headache, shoulder- and back pain, dizziness, paresthesias, vertigo and cognitive/ psychological symptoms (5, 56-58).

The relation between the acute whiplash injury and late whiplash syndrome is not clear. Both psychological and psychosocial factors have been suggested (59-61). Some authors have taken into consideration both cultural differences and differences between the insurance system to explain long-term symptoms (62-67). Some studies strongly indicate that few or no patients with acute pain develop chronic pain due to the whiplash trauma (70, 72).
It is difficult to find pathophysiological mechanisms for the development of persistent pain specific to whiplash injury, but changes in the pain transmission do occur soon after a whiplash injury (68, 69). The intensity and duration of acute pain in whiplash patients depends to some extent on the degree of tissue injury (3). Other pain mechanisms like peripheral and central sensitization as well as psychological mechanisms have been found to influence both acute and chronic WAD (62, 73-75).

Peripheral sensitisation is a local reaction characterised by the release of pain-producing substances at the site of an injury or inflammation that induce a sensitisation of peripheral receptors (57). Sterling et al. reports that patients with whiplash injury who reported high pain intensity and disability, showed signs of decreased pain thresholds for local pressure as a results of peripheral sensitisation (61).

Central sensitisation is characterised by an increased distribution of the pain with a spread of pain sensations to much wider body areas, distant from the site of injury/inflammation (62). A number of mechanisms may contribute to such sensations (3). In whiplash patients it has been demonstrated increased sensitivity to pain in other parts of the body quite distinct from the originally painful area (61, 70). One study found that a mechanism of generalised central hyperexcitability is involved in the whiplash syndrome (71). In the whiplash patients there was muscular hyperalgesia not only in the neck and shoulder, but also in distant areas where the patient does not normally experience pain.

1.6 Psychological aspects

The psychological symptoms in whiplash patients do not differ from patients with other pain syndromes (72, 73). Post traumatic stress syndrome (PTSD) is defined as stress-related symptoms that last longer than 3 months after a trauma (3). The prevalence of PTSD in whiplash injuries is 10-30%, the same as after a car accident in general (72, 74). Pain catastrophising, reduced function and disability are factors that contribute to persistent PTSD in WAD (75). As in PTSD, cognitive processes prove to play an important role in the development and maintenance of chronic pain. Cognitive dysfunctions like impairment of memory, concentration and attention have been reported both among whiplash patients but also among patients with other conditions like PTSD, depression, sleep impairment and anxiety (76). This coexistence of conditions seems to be a challenge in the treatment of pain syndromes in general, and especially in the chronic whiplash syndrome which often leads to a high degree of medical disability rate (3).

1.7. Prognostic factors

It is not clear which patients are at risk of delayed recovery following whiplash injury (9, 61). Reports on the course of whiplash injuries show highly variable results, probably due to differences in study populations and definitions of outcome (77). Some follow-up studies report as much as 95% recovery within a few months (25, 26). Others report that 70 % recover within a few days up to 2-3 weeks and around 20% have remaining symptoms after 1 year and 5-10 % have complaints that influence work ability or leisure activities (2, 17, 78).

Prospective studies found strong evidence that high initial pain intensity is an important prognostic factor (77, 79). There is also strong evidence that high grades of WAD (grade 2-3) are a warning sign of developing persistent complaints (17, 80). According to Sterner et al., factors like previous neck pain, low educational level and female gender are significantly related to poor prognosis of disability after a whiplash trauma (17). Sterling et al. concluded that the early presence of high levels of pain and disability, older age and post-traumatic stress symptoms predict a poor outcome at 2-3 years post injury (60, 61).

A follow-up study using standard cervical MRI found frequent pre-existing disc degeneration, but this was not related to more intense pain at neither baseline nor follow-up (26). These results were not in line with prior studies that concluded that pre-existing degenerative changes relate to poor prognosis (81, 82).
In a study of the natural evolution of late whiplash syndrome, the risk of chronic neck pain was equally frequent in patients with a history of whiplash and in normal controls (67). The authors suggested that disabling or persisting symptoms do not occur as a result of whiplash, but that the complaints represent symptoms that are prevalent in the normal population, possibly worsened by the expectation of disability and attribution of pre-existing symptoms to the trauma (67). The same group argues that in countries where the condition called late whiplash syndrome is non-existent and where there is no financial compensation for whiplash injuries, the symptoms after such injury are almost always short-term (65). In a population-based study from Canada initial neck pain intensity and depressive symptomatology were associated with poor expectations for recovery in a WAD population (83). The study supports a biopsychosocial model in explaining the expectancies on recovery and their influence on important health outcomes.

A financial compensation system in a state in Canada was changed from a system where payment for pain and suffering was common to a system with no compensation in whiplash injuries. This elimination of compensation caused a 28% reduction in the incidence of whiplash claims and improved prognosis of whiplash injury. The conclusion was that the type of insurance system has profound effect on the frequency and duration of whiplash claims and that claimants recover faster if compensation for pain and suffering is not available (62).

A recent review investigated prognostic factor for the development of chronic symptoms after a whiplash trauma (84). The natural course for those that report symptoms after a whiplash trauma will in most cases be rapid improvement of pain and disability the first three months. Beyond three months there is usually little improvement. Despite a large volume of research, they concluded that there is such diversity in the manner of measuring and reporting prognostic associations that the interpretation of the literature becomes difficult (84).

1.8. Radiological investigations in whiplash

Conventional radiography (plain x-ray and CT) of the cervical spine is indicated to locate fractures or dislocations in whiplash patients with pre-existing risk (as in the case of Bechterew's disease, rheumatoid arthritis and in patients aged 65 and over) of cervical spine fractures after a whiplash injury. This is according to two large prospective studies referred to as NEXUS and the Canadian C-spine Rule on guidelines for the use of cervical spine radiography in patients with trauma (85, 86). For patients with pain and stiffness, but without clinical findings in low-speed accidents, radiological investigation is not indicated. In high-speed traumas, a CT examination is indicated. In patients with neurological deficit or radicular symptoms an additional MRI examination may be justified.

The evidence of injury to the ligaments in the craniocervical junction in whiplash patients is conflicting. Krakenes introduced high resolution proton-weighted MR images in three planes, which give more detailed information of the small ligamentous structures in the craniocervical junction (87). They investigated whether there are structural changes in the alar ligaments in patients that have been exposed to a trauma with whiplash mechanism (52). The study report findings in high-resolution proton density-weighted MRI (1.5 Tesla) for 92 patients who had been involved in an accident with whiplash mechanism 2 to 9 years earlier. The results for these patients were then compared with a control group of 30 age- and gender-matched individuals without preceding head or neck trauma. Findings in the alar ligaments were graded from 0 to 3 based on the ratio between areas of high signal intensity and the total cross sectional area of the alar ligament. The main result was that 45 individuals (49 %) in the whiplash group had alar ligaments graded 2 or 3, whereas not any of the 30 controls had such ligament changes. The same group suggested that the transverse ligaments as well as tectorial and posterior atlantooccipital membranes can be damaged by whiplash injuries (51, 53).

Using functional MRI, Volle included 200 patients in his first study. Among these 200 patients, 15% demonstrated complete or incomplete ruptured alar ligaments (88). Among 420 individuals in a later study, 5% had complete rupture and 12% had incomplete rupture of the alar ligaments (89).

In contrast to Krakenes and Volle, several investigators were not able to find any difference in the appearance of the alar ligaments in WAD patients and in healthy controls. In a Dutch MRI study with 12 whiplash patients and 6 healthy subjects, both asymmetric alar ligaments and signal changes were found in both groups and there was no significant difference between the groups (31). Another MRI study from Switzerland including 50 healthy subjects found signal changes in 20 % of the subjects and asymmetric ligaments in 80% (29). Roy et. al included 15 healthy young individuals in a MRI study and found that 30% had high-signal changes in the alar ligaments (32). In a non-controlled MRI study, 35% of the WAD patients had high signal changes in the alar ligaments and 25% had high signal changes in the transverse ligaments (90). Furthermore, a recent MRI study found high intensity signals in the alar - and transverse ligaments in about 50% both among WAD patients and healthy control subjects (91).

1.9. Management of WAD

The aim of preventing chronic WAD is an important issue both from an individual and socioeconomic point of view (92). The primary goals of treatment are a quick return to normal daily activities and prevention of chronicity.

In the management of acute WAD, several randomized clinical trials recommend active intervention in terms of continuing activity as usual, patient education and stressing the high probability of recovery (93-95). Thus, immobilization and the use of neck collar should be avoided (93, 96).

The management of chronic WAD is supposed to be a more complicated challenge.
Studies on active coping strategies and guidelines for physiotherapy in whiplash patients have been provided. An early active strategy in both modalities is recommended to improve functions, increase activities and prevent chronicity (97, 98).
A multimodal intervention programme on cognitive-behavioural treatment of pain catastrophizing, fear of movement, perceived disability and physical activity reported a significant increase in returning to work after long-standing pain in whiplash injuries (99). However, in a hospital-based multidisciplinary treatment including somatic, psychological and social aspects, doubt was raised about the effectiveness of the rehabilitation programme. The patients in the intervention programme did not recover any faster than those receiving the usual individual primary care (100). In a randomized study on neuromuscular control in chronic whiplash patients, there was no statistical difference in pain, disability, psychological distress and sick leave between traditional physiotherapy and a new sling exercise group with or without home training (101). A recent Cochrane review concluded that there is little

evidence concerning effective therapies for patients with acute, subacute or chronic WAD grade I-II (102).

There are still no general guidelines or scientific documentation to support any single treatment following whiplash injury. The increase of whiplash injuries the last decades reveals a substantial economic burden on the society. Therefore, studies on cost-effective treatments for WAD patients have been proposed (103, 104).

1.10. Surgery for WAD I-II.

It has been suggested that instability in the craniocervical junction can be diagnosed in some patients with chronic WAD by functional MRI (88). Images are taken during flexion and extension as well as by laterally bending and rotating the head. After diagnosing incomplete and complete ruptures in the alar ligaments using an open MRI, a new indication for craniocervical fixation was introduced by Volle and Montazem (89). In the study including 420 individuals, they found 20 patients with complete rupture and 52 patients with incomplete rupture of the alar ligaments. This study did not include a control group. Of these 72 patients, 42 patients were chosen to undergo occipitocervical fixation. The results after surgery were reported as excellent in all of these patients. Up to 2003, the German neurosurgeon Montazem operated 500 patients with chronic WAD (105). There is, however, no scientific evidence to support such a drastic surgical procedure for this condition (106, 107).

2. AIMS OF THE THESIS

One aim of the present thesis was to evaluate the life-time prevalence of self reported neck distortion and the relationship to chronic musculoskeletal complaints (MSCs) and headache in a large unselected adult population.
Another aim was to assess the signal intensity in the alar ligaments using MRI in a case controlled designed study and to evaluate clinical characteristics, pain and disability in relation to these MRI findings.

The aims of the individual studies were:

Paper I: To evaluate the life-time prevalence of self-reported whiplash and the relationship to headache and musculoskeletal complaints.

Paper II: To evaluate MRI as a diagnostic method in assessing signal intensity areas in alar ligaments and to evaluate the difference between a whiplash group, a group with chronic neckpain and a healthy control group.

Paper III: To evaluate the clinical characteristics, pain and disability in relation to alar ligament MRI findings in a whiplash group, in a group with chronic neckpain and in a healthy control group.

3. MATERIAL AND METHODS

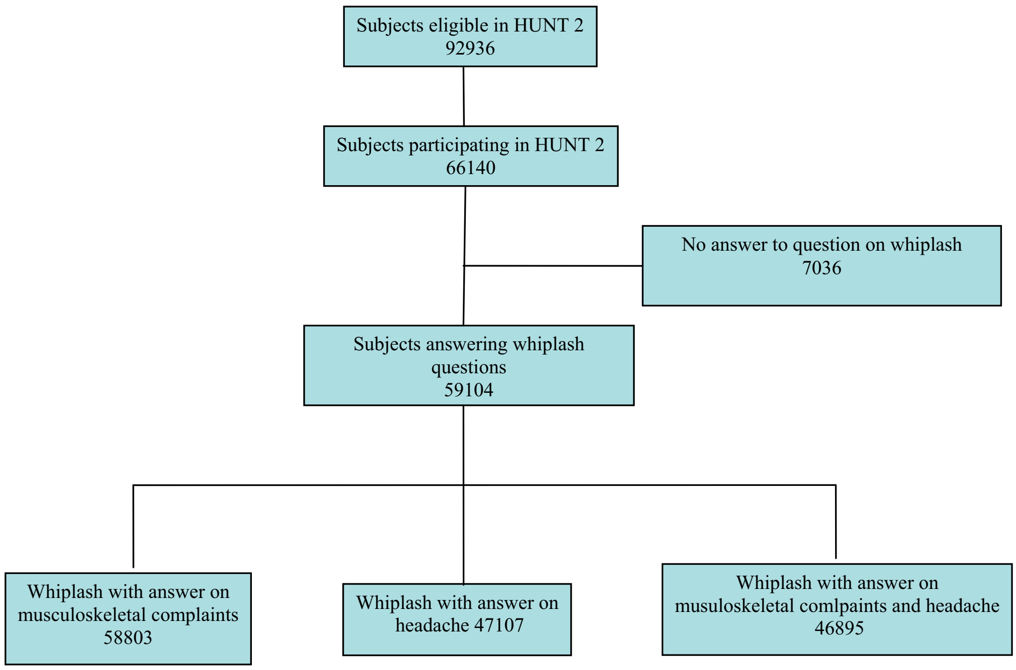
The methods in this thesis are described in detail in each paper. Some general methodological considerations are given below.

3.1. Study populations

3.1.1. Paper I

All inhabitants of the Nord-Trøndelag County aged 20 years and older were invited to the health survey in the two-year period from August 1995 to June 1997. Out of 92,936 eligible for participation, a total of 59,104 individuals (63.6%) answered the question about neck distortion (whiplash) and 58,803 also answered questions related to musculoskeletal complaints and 47,107 to questions related to headache. In total 46,895 (79.3%) participants responded to the questions of both musculoskeletal complaints and headache. A diagram demonstrating the population according to participation in the HUNT 2 study is shown in Figure 2.

Figure 2. The population in the HUNT-2 study according to participation.



3.1.2. Paper II and III

The study population in study II and III consisted of three diagnostic groups; the WAD II group (n=59), the chronic neck pain group (n=57) and the healthy control group (n=57). Study II is a MRI study on the alar ligaments in these diagnostic groups. Study III is a clinical study where pain and disability are related to the MRI findings in the alar ligaments.

The inclusion criteria for each group are listed below.

<u>WAD group</u>

- The patients with whiplash associated disorders (WAD) II were classified according to the Québec Task Force criteria.
- They all suffered from neck pain with or without headache after a car collision where they had either been the driver or a passenger of a motor vehicle.
- A post-injury symptom duration of at least 6 months, but not more than 10 years.
- An onset of symptoms within 48 hours after the accident.

<u>Chronic neck pain group</u>

The chronic pain group consisted of subjects without any previous history of neck trauma or any known systemic disease that could explain their complaints.

- They were recruited from local physiotherapists and primary care doctors.
- Pain duration of at least six months and not more than 10 years
- Alternatively the subjects could have repeated episodes of pain of at least one week duration per three months during the last two years.

<u>Asymptomatic control group</u>

- The control group consisted of subjects without neck pain or previous neck trauma.
- They were recruited from different workplaces and educational institutions in order to secure a wide range of educational and occupational backgrounds.

<u>Exclusion criteria</u>

- Subjects were excluded if they had WAD grades III-IV, severe head injury or previous cervical spine surgery.
- They were also excluded if they had a history of similar symptoms previous to the accident or any known systemic disease that could explain their symptoms. If there were contraindications to MRI examination the subjects were excluded from the study.

3.1.3. Ethics

The HUNT 2 study was approved by the Regional Committee for Medical Research and Ethics, and by the Data Inspectorate of Norway (paper I).

For the MRI study and the clinical study (paper II and III), the patients were given oral and written information before consenting to participate in the study. A written form of consent had to be signed when they attended the clinical examination. The study protocols were approved by the Regional Committee for Medical and Health Research and by the Norwegian Social Science Data Services.

3.2. Statistical analysis

3.2.1. Paper I

Differences between means were tested with unpaired t-tests. P-values < 0.05 were considered statistically significant. Using logistic regression, we estimated prevalence odds ratios (OR) with 95% confidence intervals (CI) for the association between neck distortion and headache as well as chronic MSCs. Potential confounders were adjusted for as described in paper I.

3.2.2. Paper II and III

In study II, Pearson's chi-square, were used to assess between group differences. Kappa-coefficients were used to evaluate pair-wise interobserver agreement and intraobserver agreement. Linear weighted kappa were calculated on basis of all four MRI gradings, and when the groups were dichotomised (grade 0-1 and grade 2-3), ordinary kappa coefficients were calculated in terms of Cohen's kappa.

In study III, Pearson's chi-square test, Kruskall-Wallis test and pair wise comparisons (Dunn procedure), were used to assess between group differences. Spearman's rho was used to assess the correlation between the alar ligament changes and the respective measures for clinical characteristics and disability. In addition regression analyses were performed with BPI intensity and interference score, EQ-5D, EQ VAS, HADS anxiety or depression as dependent variables, and MRI grading as covariate. The analyses were adjusted for potential confounders such as described in paper III.

Statistical analyses were performed using SPSS (Statistical package for the social sciences®).

3.3. Outcome variables and questionnaires

3.3.1. Paper I

Two questionnaires including more than 200 health-related questions were administered to the participants. The included questions about MSCs were adopted from the Standardized Nordic Questionnaire (108). The Standardized Nordic Questionnaire has been evaluated and found to give reliable estimates for low-back pain, and upper limb and neck discomfort (109, 110). Participants who responded “yes” to the question “Have you during the last year continuously for at least three months suffered from pain or stiffness in muscles and joints?” were defined as having chronic MSCs. These individuals were then asked to indicate locations by “yes” or “no” responses to the following areas of the body: neck, shoulders, elbows, wrist/hands, chest/abdomen, upper back, low back, hips, knees, and/or ankles/feet. The prevalence and incidence of these complaints in the current population has been published previously (111).

Subjects who answered 'yes' to the question 'Have you suffered from headache during the last 12 months?' were classified as headache sufferers. Based on data from the subsequent 12 headache questions, they were classified into two groups of either migraine or non-migrainous headache. The diagnoses were mutually exclusive. The classification of the subjects has been described in detail previously, and has been validated by interview diagnoses (112).

Whiplash injuries where investigated with the following question: “Have you ever had neck distortion (whiplash). Out of 92,936 eligible for participation, a total of 59,104 individuals (63.6%) answered the question about neck distortion (whiplash). Among these, 46,895 (79.3%) responded to the questions of MSCs and headache. The subjects were classified into four groups based on the presence of headache and chronic MSC.

3.3.2. Paper II and paper III

All subjects included were asked to fill in questionnaires about pain, health and anxiety/depression in connection with the clinical examination. In addition demographic data were registrated.

Brief Pain Inventory

The Brief Pain Inventory (BPI) is designed to measure two targets; the subjective intensity of pain and the impairment caused by pain. The BPI, which has been validated in Norwegian, consists of 4 questions related to pain severity and 7 questions related to pain interference with function (113). The pain severity items are presented as numeric rating scales, from 0 (no pain) to 10 (pain as bad as you can imagine). The BPI asks the patients to rate their pain at the time of responding to the questionnaire (pain now) and pain at its worst, least, and average for the last 24 hours. In our study III we used a modified BPI asking for an average pain the last 2 weeks. This was done because of the long duration of symptoms in the groups. A pain severity index is calculated by adding the scores on the pain severity items. The 7 items of pain interference with patient function are also presented as numeric rating scales, from 0 (does not interfere) to 10 (interferes completely). The questions about interference relate to how pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life. A function interference index is calculated by adding the scores of the interference items.

EuroQol 5 D

The EuroQol 5 D (EQ-5D) is a generic health-related quality of life instrument. Extensive cultural and language evaluations have been made and a validated Norwegian version was used in the present study (114). EQ-5D evaluates five dimensions: mobility, self-care activities of daily life, pain, anxiety and depression. Each dimension is described by three possible levels (no, mild to moderate and severe)so that there are 3^5 or 243 possible health states (115). For each of these combinations, one can assign health- state utility indices which are based on different value sets. Respondents` answers to different hypothetical choices are translated into a preference based score, yielding an index score based on a scale from 0 (death) to 1.0 (perfect health).

The EuroQol Visual Analog scale (EQ VAS) forms the second part of the EQ-5D questionnaire. The patients rate their health-state by drawing a line from a box marked “Your health state today” to the appropriate point on the 20 cm VAS scale, which ranges from 0-100 (worst to best imaginable health)(115).

The Hospital Anxiety and Depression Rating Scale

The Hospital Anxiety and Depression Rating Scale (HADS) is a two-dimensional, self-rating instrument for anxiety and depression. It consists of 14 items and all items are scored at a 4-

point scale from 0 (not present) to 3 (maximally present), to assess anxiety and depressive symptoms during the last week. The seven depression items (HADS-D) are related to anhedonia, lowered mood, and psychomotor retardation, and assess some of the depressive symptoms that are part of the diagnostic criteria of depression in ICD 10 and DSM IV. The seven anxiety questions (HADS-A) cover some of the criteria of generalized anxiety disorder as described in both these diagnostic manuals. Psychometrics for the Norwegian version of HADS have been reported previously (116).

3.4. MRI protocol

MRI was performed at 1.5 tesla (T) using a Siemens Symphony magnetic resonance system (Siemens Medical, Erlangen Germany). The patients and controls were scanned in the supine position using both the neck coil and the attachable anterior element from the head coil. The scan protocol of the craniocervical junction consisted of proton-weighted fast spin-echo sequences in three planes. In the sagittal plane 16 interleaved, contiguous slices with 2 mm slice thickness were obtained with TR/ TE/ ETL/ NEX/ FoV/ band width/ acquisition time 3290ms/ 13ms/ 13/ 4/ 20cm / 130Hz/pixel/ 7.05min and a matrix of 291x512 giving a pixel size of 0.6x0.4 mm. The sagittal slices covered the area between the occipital condyles including the insertions of the alar ligaments. In the axial plane 17 interleaved contiguous slices with 2 mm slice thickness were obtained with TR/ TE/ ETL/ NEX/ FoV/ band width/acquisition time 3520ms/ 14ms/ 13/ 4/ 20cm/ 130Hz/pixel/ 5.43min and a matrix of 291x512 giving a pixel size of 0.6x0.4 mm. The axial images covered the area from the base of the dens axis to the foramen magnum. In the coronal plane 19 interleaved contiguous slices with 1.5 mm slice thickness were obtained with TR/ TE/ ETL/ NEX/ FoV/ band width/acquisition time 3090ms/ 15ms/ 9/ 5/ 20cm/ 136Hz/pixel/ 7.02min and a matrix of 227x384 giving a pixel size of 0.7x0.5 mm. The coronal images covered the area from the anterior arch of the atlas to the middle part of the spinal canal and the images were angulated parallel to the anterior border of dens axis. Total examination time for all three imaging sequences including localizer scans was approximately 25 min.

3.4.1. Image evaluation.

All MRI examinations were independently evaluated on a radiological work-station by two experienced neuroradiologists (interpreter 1 and interpreter 2). The images from patients and controls where presented in random order and the interpreters were blinded to original evaluation, patient data, history and group allocation. In case of disagreement between the interpreters, those images were re-evaluated and a consensus was reached for the respective study participants (n=88). One of the interpreters (interpreter 1) re-evaluated the MRI from 50 patients and controls after six months and was blinded to the results from the first evaluation. The alar ligaments were evaluated according to a 4-point grading scale proposed by Krakenes et al. (52). In this grading system low signal throughout the entire cross-section area of the alar ligament was graded 0, high signal in less than 1/3 of the cross-section was graded 1, high signal in 1/3-2/3 of the cross-section was graded 2 and high signal in more than 2/3 of the cross-section was graded 3. In some examinations the alar ligaments were overall grey. These ligaments were graded as 2. In the evaluation of the alar ligaments the images in the sagittal plane were most useful since the cross section could easily be evaluated. In the lateral part of the ligament care was taken to avoid misinterpretation of partial volume effects from the fatty bone marrow in the occipital condyle as high signal intensity in the ligaments. Before the final grading the findings in the sagittal images were compared to the coronal images and particularly in the areas close to the dens axis and the occipital condyles this comparison was useful.

4. RESULTS

4.1. Paper I

Headache and musculoskeletal complaints among subjects with self reported neck distortion. The HUNT-study.

We evaluated the life-time prevalence of self reported neck distortion (whiplash) and the relationship to chronic musculoskeletal complaints (MSCs) and headache in a large unselected adult population. The subjects were classified into four groups based on the presence of headache and chronic MSC.

The conclusion is that subjects with self reported neck distortion had significantly more headache and musculoskeletal complaints than those without and may in part be due to selective reporting. The association was not restricted to the neck region, but was also seen in other anatomical sites and was even stronger in some areas other than the neck. Our findings correspond to other cross-sectional studies, which reports a wide range of symptoms in whiplash patients. The life-time prevalence of self-reported whiplash was 2.9%, which was much lower than other strictly comparable studies. It is likely that whiplash traumas were grossly underreported in the present study and that selective reporting among those with complaints may be present.

4.2. Paper II

Magnetic resonance imaging assessment of the alar ligaments in whiplash injuries. A case-control study.

A case-control designed study of 173 subjects included a group with persistent WAD grade II after a car accident (n=59), a group with chronic non-traumatic neck pain (n=57) and a group without neck pain or previous neck trauma (n=57). The MR images were independently evaluated by two experienced neuroradiologists who were blinded to patient history and group allocation. The alar ligaments were seen on both sides in all subjects. Areas of high signal intensity (grade 2-3) were found in at least one alar ligament in 49 % of the patients in the WAD grade II group, in 33 % of the chronic neck pain group and in 40% of the control group (Chi-square, p=0.22).

Our conclusion is that high-signal intensity changes in the alar ligaments are not only seen among whiplash patients, but also with similar frequency in patients with chronic neck pain and in healthy controls. The use of MRI for the evaluation of signal intensity changes in the alar ligaments after whiplash is questionable.

4.3. Paper III

Clinical characteristics, pain and disability in relation to alar ligament MRI findings.

We used the same diagnostic groups, MR imaging protocol and MRI classification system on the alar ligaments as in study II. Pain and disability were assessed by using the Brief Pain Inventory, the EuroQol and the Hospital Anxiety and Depression Rating Scale. With respect to BPI and HADS, the scores were highest in the WAD group, intermediate in the chronic non-traumatic neck pain group, and lowest among controls. EuroQol scores were lowest in the WAD group, intermediate in the chronic non-traumatic neck pain group, and highest among controls ($p<0.001$, Kruskall-Wallis test). There was, however, no significant correlation (Spearman's rho) between the alar ligament changes and measures for pain and disability.

The study shows that the WAD group reports more pain, more anxiety and depression and lower quality of life than the chronic neck pain group and the healthy control group, but there is no association between degree of signal changes in the alar ligaments on MRI with respect to pain and disability.

5. DISCUSSION

Study I is based upon cross-sectional data from the HUNT-2 study, and shows that the prevalence of headache and musculoskeletal complaints is higher among subjects with self-reported neck distortion than those without. The significant association was not restricted to the neck region, but was also seen in all anatomical sites and was even stronger in some areas other than the neck. These results are in accordance with other studies reporting an association between whiplash and a wide variety of symptoms and pain in other areas not restricted to the head and neck region (94, 117-123). The results from this cross-sectional study must be evaluated with caution. Even though the high participating rate in this unselected population and the large sample size decreased the risk of chance findings, the study design cannot address the causal relationship, i.e. whether neck distortion causes MSCs or headache. The wide range of data made it possible to adjust for potential confounding variables, but one cannot rule out that other risk factors or a shared susceptibility causes the associations observed. The use of validated questionnaires reduces the risk for misclassification, but there is a possibility of non-differential misclassification that might weaken real associations, but we think this is a minor problem as the prevalence of headache and MSC in the current population is consistent with data from other population-based studies in the Western countries (124, 125). The higher prevalence of MSCs and headache among those with self-reported neck distortion might be due to recall bias, i.e. that individuals with pain are more likely to remember and report a previous neck trauma than those without complaints (126). In addition studies dealing with subjective complaints like headache and musculoskeletal pain may be influenced by a tendency to answer in a similar way all questions regarding complaints ("reporting bias") (127), which may create strong associations that may reflect personality traits rather than biological mechanisms (128). The life-time prevalence of self reported whiplash in our study was 2.9 %, which is much lower than the 15.9 % reported in another population-based cross-sectional in Canada (19). Based upon the published reports from the Confederation of Norwegian Enterprise the percentage who have sustained on an accident with whiplash mechanism within a relevant time period is probably much higher than the 2.9% who self report a whiplash injury (15). It is very likely that whiplash traumas were grossly underreported in the study, and that selective reporting, e.g. among those with complaints may be present.

In study II and III we compared MRI findings in the alar ligaments, clinical characteristics, pain and disability in three study groups. The results show that high signal intensity changes on MRI are not a specific finding only in WAD patients, but is seen in similar frequency also among patients with chronic neck pain without any known previous neck injury and healthy control subjects. In addition, there was no association between the degree of MRI findings and pain, quality of life and psychological problems measured by BPI, EuroQol and HADS. MRI findings could not explain the high pain score, the high disability score and the low quality of life score in the WAD group.

One strength of the study is that patients with chronic neck-pain without a previous neck trauma were included. In addition, all the MR images were investigated by two experienced radiologists, who where blinded to original evaluation, patient data, history and group allocation. Comparing the alar ligaments in a whiplash group with *two control groups* strengthens our conclusion. Finally, we have used well validated questionnaires like BPI, Euro Qol and HADS.

A symptom duration of at least 6 months was used in the present study, because the QTF classification system includes a time axis; a post-injury symptom duration of 6 months is designated as late whiplash syndrome (2). The upper limit of 10 years symptom duration was chosen in order to compare the results with a previous study that included WAD patients injured up to 9 years earlier (52). The mean duration of the post-injury symptoms was 4.3 years in the present study.

Patients in the chronic neck pain group without any previous neck injury were recruited from local physiotherapists and primary care doctors. Despite the fact that chronic neck pain is a common symptom in the general population (5, 6), the process of recruiting persons in this group was time-consuming and one cannot rule out the possibility of selective participating, i.e. that those with most complaints were more likely to participate.

The healthy controls were recruited from different workplaces and educational institutions in order to secure a wide range of educational and occupational backgrounds. None of them were on sick leave or out of work in the study period. A confounding factor may be that the socioeconomic status is above normal, but as earlier stated, they were from different workplaces, and we suppose they represent the general population. The control group consisted of subjects without neck pain or previous neck trauma.

In the cervical spine standard MRI allows evaluation of at least the anterior and posterior longitudinal ligament, skeletal structures including the uncovertebral and facet joints, the spinal cord and the cervical discs. The tectorial membrane can be evaluated as well on sagittal images as a continuation of the posterior longitudinal ligament toward the clivus. Evaluating the alar ligaments and the other small ligaments in the craniocervical junction requires additional imaging series in several imaging planes with thinner sections (3). The development of a more advanced MRI technology has made it possible to assess morphological changes in ligaments and membranes in that region.

We found high-signal changes both in the WAD group, in the CNP group and in the healthy control group, respectively 49%, 33% and 40% (129). The percentage of high signal changes in the alar ligaments was higher in controls than among subjects with chronic neck pain, respectively 40% and 33%. This finding can not explain the proposal that signal changes could represent adaptive changes in the presence of chronic neck pain (130, 131). If adaptive changes are the explanation of the high-signal changes, there should be no such changes in the healthy control group. Our results suggest that the high-signal changes in the alar ligaments represent normal morphological variation in a population.

In the Krakenes study the findings that were interpreted as lesions in the alar ligaments were graded from 0 to 3 and were based on the ratio between any high signal part and the total cross sectional area of the alar ligament (52). The main result was that 45 individuals (49 %) in the whiplash group had a lesion grade 2 or 3 (27 persons with lesion grade 2 and 18 persons with lesion grade 3) whereas no such lesion were found in any of the 30 controls. These results are in great contrast to previous MRI studies of symptom free individuals. One study reported a wide variation of segmental motion in the upper cervical spine without correlation between segmental rotation and morphological characteristics of the craniocervical joints or ligament structures (132). Furthermore, it has been impossible to demonstrate that lesions of the alar ligaments should be the cause of WAD (31). It is also important to mention that asymmetry of alar ligaments, craniocervical junction and of the facet joints in the neck as well as joint effusions are frequent findings in asymptomatic subjects (29). However we found no asymmetry indicating rupture of the alar ligaments in the study. In addition, Roy et al. found high signal changes in about one third of the asymptomatic controls (32). It is important to consider that these studies used different MRI-protocols and/or different grading systems. In addition to different MRI protocols and different grading systems the magnetic field strength may influence the image quality and is important in the ability to detect small structural changes in the ligaments. In some studies low field magnetic strength (0.2-0.5 T) has been used (31, 89). Other studies have been performed on high field magnetic strength (1.0 -1.5 T) (29, 32, 52, 90, 91).

Three studies used the same MRI protocol and the same grading system as we did (52, 90, 91). Vetti et al. did a prevalence study on 1266 individuals with WAD I-II, and did not include a control group. They found a considerable lower prevalence (35.5%) of high signal changes in the alar ligaments in the WAD patients than Krakenes (49%) (52, 90). Dullerud et al. reported high signal changes in about 50 % both among patients and controls (91), which is in accordance with our results.

In our study the interobserver agreement for both the right and the left alar ligament was moderate, 0.42 and 0.48, respectively. The respective values for weightened kappa indicated better agreement, 0.57 and 0.62, respectively. In the study by Krakenes (52) the inter- and intra observer values were rather similar to those presented in our study. However, the inter- and intraobserver agreement improved in both studies when the groups were dichotomized into low-grade (grade 0-1) and high-grade (grade 2-3). One study noticed significant interobserver disagreement (32), which is in accordance with a recent MRI study that found poor interobserver agreement both for the alar ligament and the transverse ligament (91). Accordingly the use of MRI for the evaluation of signal intensity changes in these ligaments in WAD patients in daily clinical practice is highly questionable, and the Consensus Euro Spine 2008 proposes that MRI examination with special reference to the ligaments in the craniocervical junction should only be performed in clinical research (3).

The questionnaires used in study III are well validated. Both HADS and EuroQol are used in previous whiplash studies (121, 133, 134). In addition we used the well validated BPI in assessing pain and impairment caused by pain (113, 135-137). We did not find that BPI was used in earlier whiplash studies and there was not a neck specified pain question in BPI, but the patient entered the pain localization on a body drawing. To address the neck pain properly, we used a visual analog scale (VAS) asking for an average neck pain the last two weeks. The pain intensity was graded in a 100-mmVAS, end points being no pain and worst imaginable pain. This score corresponded to the BPI intensity score. However, issues concerning on how pain interferes with the patients function in respect to general activity, mood, walking, work, relations with others, sleep and enjoyment of life is addressed in the questionnaire. The EuroQol is a well validated generic quality of life instrument and the questionnaire has been used in a previous whiplash study (134). The findings indicated a lower quality of life in patients with depression and a high pain score after a whiplash injury. Wallin et al. used SF-36 as a quality of life measurement in chronic WAD patients and found quality of life significantly lower in all SF-36 scales, when compared to healthy pain-free subjects (138). Another study is in accordance with our findings, i.e. that WAD patients report lower quality of life than healthy controls (139).

The neck disability index (NDI) is a condition specific instrument (140), but was not linguistically validated in Norwegian until 2007. In addition the reliability and validity of the NDI is still lacking. Furthermore, issues concerning emotional and social functioning are not addressed in the NDI questionnaire, which is important in WAD patients (141). In a previous study NDI was used to assess disability in whiplash patients, and they reported that the NDI score increased significantly with increasing MRI grade (Krakenes classification, grade 0-3) (142). They concluded that subjects with MRI grade 2-3 reported more difficulties in daily living than subjects with grade 0-1 signal changes or normal controls. Furthermore, they reported an increase in NDI with increasing number of structures (all ligaments and membranes) with MRI grade 2-3. This is in great contrast to findings in our paper III. We found no association between the degree of MRI findings and pain, quality of life and psychological problems measured by BPI, EuroQol and HADS. MRI findings could not explain the high pain score, the high disability score and the low quality of life score in the WAD group.

Intervention with craniocervical fixation has been done in over 500 subjects with symptoms after whiplash injury (89, 105). The German neurosurgeon Montazem reported incomplete and complete ruptures in the alar ligaments, and introduced a new indication for craniocervical fixation (89). Craniocervical fixation is major surgery with a moderate level of perioperative complications. There is also a theoretical risk of increasing the degenerative process in the level below the fixation (106, 107). The surgical method of choice is incorporating C3 lateral mass screws, transarticular screws from C1 and C2 and screws in the occipital bone. The screws are connected to rods which fuse occiput to the upper cervical vertebrae. The surgeon uses a bone graft from the iliac crest to fuse the occiput to C1 and C2. The usual indications for craniocervical fixation are serious conditions like instability caused by rheumatic arthritis, tumours and fractures. The scientific evidence for introducing a new indication for craniocervical fixation is lacking, and craniocervical fixation in WAD I – II must be considered experimental surgery (106, 107).

The fact that the outcome of an acute whiplash injury is benign in countries like Litauen, Greece and Germany, and causes epidemic proportions of chronic pain in countries in North America and Europe, has lead to a biopsychosocial approach in the explanation of the late whiplash syndrome (59). The descriptive validity of the WAD classification is questionable (37), because the symptoms reported after a whiplash injury are nonspecific and also highly prevalent in the general population (3, 13, 14, 59, 143). The biopsychosocial model is also supported by the fact that the whiplash syndrome does not have clinical or other findings that are distinct from those of other patients with head and neck pain. Then a reasonable explanation for the complaints may be that the symptoms are caused by other mechanisms than the whiplash injury and that the mechanism for the chronic pain is multifactorial.
In a cross sectional study on symptom-profile in patients with self-reporting whiplash, Wenzel reports a wide range of symptoms in chronic WAD, in fibromyalgia and in rheumatoid arthritis compared to controls (122). The chronic WAD group had a higher prevalence of both psychological and physical symptoms than the controls and a more similar symptom profile to patients with fibromyalgia than to patients with rheumatoid arthritis. This also included symptoms from body parts which should have no relation to the whiplash trauma, e.g. the hips and the gastrointestinal tract and included also other symptoms than pain symptoms. Both in North America and in Scandinavia, there is an expectation of potential symptoms after whiplash, which may lead persons to attribute all their symptoms to a car collision. The patients' behaviour in response to the injury may often be amplified by the circumstances of the collision where paramedics apply a neck collar and tell the person not to move, and the treatment and attention after the injury. This triad of expectation, amplification and attribution seems to be important factors in the explanation of the late whiplash syndrome (59, 83).

The interpretation of signal intensity changes in the alar ligaments is difficult. The increased signal in the ligaments may be due to atrophy of fibres and fat replacement due to the trauma

(52). Fat and connective tissue interspersed between the ligament fibres have higher proton density than the fibres themselves and can cause high signal on MRI (144). If the ligament has high fiber density it will appear hypointense on MRI, whereas a ligament with loose fiber density and interspersed fatty tissue will appear with high signal intensity. Another explanation is that the alar ligaments are surrounded by high-signal epidural fat and partial volume artefacts has been suggested as the cause of alar ligament changes (32). A fat suppression technique is widely used in musckuloskeletal MRI. This technique suppress the fatty tissue and fibrosis, while oedema retain high signal (145). Dullerud et al. used this technique and propose fat-suppressed sequences in future studies of the craniocervical junction due to the reduced abnormalities reported for e.g. the alar ligaments (91). Accordingly, the use of fat-suppression in acute phase studies has to be considered in future studies on WAD.

To improve image quality, the use of 3T MRI systems has been proposed. Our experience is that 3T images do not improve image quality and that 3T images produces artefacts that makes the interpretation difficult.

6. MAIN CONCLUSIONS

1. Subjects with self- reported neck distortion have significantly more headache and musculoskeletal complaints than those without.

2. The association between self reported neck distortion and musculoskeletal pain was not restricted to the neck region, but was also seen in other anatomical sites and was even stronger in some areas other than the neck.

3. The high signal intensity changes in the alar ligaments on MRI are not specific findings only found in WAD patients.

4. The frequency of high signal intensity changes in the alar ligaments are similar in the WAD group, the group with chronic neck pain and in the healthy control group.

5. The WAD group has more pain, more anxiety and depression and lower quality of life than the chronic neck pain group and the healthy control group.

6. There is no association between signal changes in the alar ligaments on MRI and the degree of pain and disability.

7. AIMS OF FUTURE STUDIES

In order to address the causal relationship between a whiplash trauma and the multiple complaints reported among patients with chronic symptoms, it is necessary to use prospective designed case-control or preferable cohort studies. There are, however, several methodological aspects and confounding factors that have to be considered in future studies. The use of MRI in patients with whiplash associated disorders cannot at present be recommended. There is, however, still a need to confirm our findings in future studies with appropriate numbers of patients and controls. In addition there is a further need for prospective designed studies including a thorough clinical assessment combined with MRI to evaluate whether there are detectable changes in these ligaments in the acute phase after injury and during follow up. Beyond this, reliability studies on MRI are needed before MRI findings can be implemented in clinical studies. The reported interrater agreement rates in study II and in previous studies indicate that using a 4 point grading scale is highly questionable in clinical practice. Even the dichotomized inter – and intrarater kappa values did not reach acceptable agreement for this rating scale to be clinically useful. Consequently, a more reliable classification system is needed in future studies.

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Paper I

Headache and musculoskeletal complaints among subjects with self reported neck distortion.

The HUNT Study.

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ABSTRACT

Objective: To evaluate the life-time prevalence of self reported neck distortion and the relationship to chronic musculoskeletal complaints (MSCs) and headache in a large unselected adult population.

Methods: Between 1995 and 1997, all inhabitants 20 years and older in Nord-Trøndelag county in Norway were invited to a comprehensive health survey. Out of 92,936 eligible for participation, a total of 59,104 individuals (63.6%) answered the question about neck distortion (whiplash). Among these, 46,895 (79.3%) responded to the questions of musculoskeletal complaints and headache.

Results: The total life-time prevalence of self reported neck distortion was 2.9%, for women 2.7% and for men 3.0%. There was a significant association between self reported neck distortion and headache (OR = 2.1; 95% CI 1.8-2.4), and chronic MSCs (OR=3.3; 95% CI 2.8-3.8), evident for all ten anatomical sites investigated. The association was most pronounced for those with a combination of headache and chronic MSC for both men (OR = 4.8; 95% CI 3.6-6.2) and women (OR = 5.2; 95% CI 3.7-7.1).

Conclusions: Subjects with self reported neck distortion had significantly more headache and musculoskeletal complaints than those without, and may in part be due to selective reporting. The causal mechanism remains unclear and cannot be addressed in the present study design.

Introduction

Whiplash injury occurs due to an acceleration-deceleration energy transfer to the neck resulting from motor-vehicle collisions, and the term whiplash associated disorders (WAD) was introduced in order to describe the sign and symptoms associated with the injury [32].

The prognosis of whiplash injuries show highly variable results and may be due to differences in study populations and definitions of outcome [29]. Some follow-up studies report as much as 95% recover within a few months [27,38], while others report that 70 % recover within a few days up to 2-3 weeks, but around 20% have remaining symptoms after 1 year and 5-10 % have complaints that influence work ability or leisure activities [32,26,35]. It is not clear which patients are at risk of delayed recovery following whiplash injury [16,34], but a slow or poor recovery seems to be associated with psychological factors, compensation or legal factors and initial self reported symptom severity [5]. The construct validity of the whiplash syndrome is, however, questionable [36] , and several studies report an association between whiplash injury and a wide variety of symptoms and pain in other areas not restricted to the head and neck region [6,8,10,11,15,23,28,33,39,40,41]. Two studies have specifically evaluated the risk factors associated with the occurrence of wide spread bodily pain after motor vehicle collision [15,41], but these studies included insurance claimants and it is therefore not known whether there is an increased prevalence of musculoskeletal complaints (MSCs) among subject with self reported neck distortion in the general population. Thus the main purpose of the present study was to study the relation between self reported neck distortion and chronic MSCs and headache in a large unselected adult population.

Methods

In the years 1995 to 1997, all inhabitants aged 20 years and above in the County of Nord-Trøndelag of Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT-2). Out of 92,936 invited individuals, 66,140 (71.2%) took part in the study. The target population and the description of the participants and non-participants have been published previously [17]. In short, two questionnaires including more than 200 health-related questions were administered to the participants. The first questionnaire (Q1) was enclosed with the invitation letter and delivered when attending the health examination. The second questionnaire (Q2) was filled in after the health examination and returned by mail.

The Q1 included questions about MSCs adopted from the Standardized Nordic Questionnaire [19]. The Standardized Nordic Questionnaire has previously been evaluated and found to give reliable estimates for low-back pain, and upper limb and neck discomfort, in particular for symptoms during the past year [9,22]. In Q1 participants who responded “yes” to the question “Have you during the last year continuously for at least three months suffered from pain or stiffness in muscles and joints?” were defined as having chronic MSCs. These individuals were then asked to indicate locations by “yes” or “no” responses to the following areas of the body: neck, shoulders, elbows, wrist/hands, chest/abdomen, upper back, low back, hips, knees, and/or ankles/feet.

Subjects who answered 'yes' to the question 'Have you suffered from headache during the last 12 months?' were classified as headache sufferers. Based on data from the subsequent 12 headache questions, they were classified into two groups of either migraine or non-migrainous headache. The diagnoses were mutually exclusive. The classification of the subjects has been described in detail previously, and has been validated by interview diagnoses [13].

Whiplash injuries were investigated with the following question: “Have you ever had neck distortion (whiplash). Out of 92,936 eligible for participation, a total of 59,104 individuals (63.6%) answered the question about neck distortion (whiplash) in Q1. Among these, 46,895 (79.3%) responded to the questions of MSCs and headache. The subjects were classified into four groups based on the presence of headache and chronic MSC, as shown in Table 1.

Statistical analysis

Between group differences for continuous and categorical variables were evaluated using parametric and non-parametric tests. P-values < 0.05 were considered statistically significant. Using logistic regression, we estimated prevalence odds ratios (OR) with 95% confidence intervals (CI) for the association between self-reported neck distortion in relation to headache and chronic MSCs. Potential confounders such as gender, age (10 years categories), duration of education (<10, 10-12 and >12 years), anxiety and depression measured by Hospital Anxiety and Depression Scale (HADS), use of pain medication, physical activity, smoking and body mass index were adjusted for. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The HUNT study was approved by the Regional Committee for Medical Research and Ethics, and by the Data Inspectorate of Norway.

Results

The total life-time prevalence of self reported neck distortion was 2.9%, for women 2.7%, and for men 3.0%. As demonstrated in Table 1, there was a significant difference in age between the diagnostic groups (One-way ANOVA, $p<0.0001$) and for all the different categorical variables (Kruskall-Wallis test, $p<0.0001$). This was most pronounced for educational level, smoking, analgesic use, physical activity, anxiety and depression among those with a combination of headache and chronic MSC. Adjustments for all these confounders were made in the final multivariate analyses. There was a significant association between neck distortion and headache (OR = 2.1; 95% CI 1.8-2.4), and chronic MSCs (OR=3.3; 95% CI 2.8-3.8). The association was most pronounced for those with a combination of headache and chronic MSC as shown in Table 2.

The association between self reported neck distortion and chronic MSC was evident for all ten anatomical sites for both men and women (Table 3). Among women the strongest association was found for pain in the chest and/or abdomen (OR=7.1, 95% CI 4.9-10.4), and for both genders the association was not stronger for neck pain than upper back pain (Table 3).

Among those with chronic MSC, 39.3% of the subjects with neck distortion reported that these complaints had a significant impact on their work ability compared to 25.5% of those with chronic MSC but without self reported neck distortion ($p<0.0001$). There was also a significant difference in impact on leisure activities between these two groups (75.4% versus 61.3%, $p<0.0001$). There association between self reported neck distortion and headache was found for both migraine (OR = 2.2; 95% CI 1.8-2.6) and non-migrainous headache (OR =2.1; CI 1.7-2.4) for both genders (data not shown).

Discussion

In this large population-based, cross-sectional study, self-reported neck distortion was associated with increased prevalence of headache and chronic MSCs, which was evident for all anatomical sites. Individuals with a combination of headache and chronic MSC were five times more likely to report neck distortion than those without any complaints.

The results from the present cross-sectional study must be evaluated with caution. Firstly, it cannot be determined whether neck distortion causes neither MSCs nor headache, or whether other risk factors or a shared susceptibility causes these associations. Secondly, since both headache, chronic MSCs and neck distortion are based on self-report, individuals with neck pain and other pain are more likely to remember and report a previous neck trauma than those without complaints, i.e. differential information (recall bias) [18]. Thirdly, in studies dealing with subjective complaints like headache, musculoskeletal pain and psychiatric symptoms the results may be influenced by a tendency to answer in a similar way all questions regarding complaints ("reporting bias") [25]. This may create strong associations that may reflect personality traits rather than biological mechanisms [20]. Headache, neck pain and other subjective complaints are common in the general population [7,12,14,37], and both headache and neck pain are equally frequent in patients with and without a history of whiplash [30]. One population-based prospective study reported that the symptoms after a whiplash injury were usually mild and disappeared in most cases after a few days [21], which is supported by findings from experimental studies [2,3]. The occurrence of frequent neck pain and headache is also common among untraumatised subjects [21] and the course of WAD is very similar to the course of neck pain in the general population [4,5].

Even though the use of validated questionnaires reduces the risk for misclassification, the questionnaire-based diagnoses are not optimal when compared to interview diagnoses. There is a possibility of non-differential misclassification of diagnosis that might weaken real associations, but we think this is a minor problem as the prevalence of headache and MSC in the current population is consistent with data from other population-based studies in the Western countries [1,24,37]. In addition the large and unselected population and the high participating rate, reduces the risk of selection bias. Selective participation was unlikely, since neither headache, neck-distortion nor chronic MSCs were the main objectives. The impact of non-participants has been discussed in more detail previously [17], but the large sample size decreased the risk of chance findings and the wide range of data made it possible to adjust for potential confounding variables.

The life-time prevalence, however, of having sustained a whiplash traumas in our study was 2.9 % and is much lower than the 15.9% reported in a population-based cross-sectional study among the Saskatchewan population [6]. Published reports from the Confederation of Norwegian Enterprise comprising all the Norwegian government insurance companies indicate that the most common cause of whiplash, a rear end collision, in year 2000 involved 54000 vehicles and half of these were hit from behind, i.e. 27000 people. Over a 10 year period one can calculate that approximately 270 000, i.e. 6% of the population, will be involved in such collision. In addition comes all other traffic- and sport accidents. This means that the percentage who have sustained on an accident with whiplash mechanism within a relevant time period is probably much higher than the 2.9% who self report a whiplash accident [31]. It is therefore very likely that whiplash traumas were grossly underreported in the present study, and that selective reporting, e.g. among those with complaints may be present.

Conclusions: Subjects with self reported neck distortion had significantly more headache and musculoskeletal complaints than those without, and may in part be due to selective reporting. The causal mechanism remains unclear and cannot be addressed in the present study design.

Table 1 Demographic data

	No MSC or HA	HA-no MSC	MSC-no HA	MSC and HA
Total number	17524	8096	11195	10080
Age (mean, SD)	48.7 (17.6)	40.8 (13.7)	56.0 (15.6)	47.6 (14.0)
Gender, female %	44.3	63.3	48.6	67.1
Years of education > 12 years (%)	23.7	27.4	15.4	18.3
Current smokers (%)	24.6	28.1	28.3	33.8
Analgesic use (%)*	1.4	5.3	11.7	22.1
HADS anxiety score >8 (%)	4.6	9.6	9.6	19.9
HADS depression score >8 (%)	3.7	4.8	8.1	11.5
Alcohol abstainers (%)	11.0	8.2	13.3	11.7
BMI > 25 (%)	57.9	52.6	66.1	60.8
High physical activity (%)**	14.6	11.7	10.3	9.6

HA=Headache, MSC= Musculoskeletal complaints

*Analagesic use daily or almost daily

**≥ 3 hours/week with hard physical activity.

Table 2 Prevalence odds ratio (OR) of self reported neck distortion in relation to diagnostic groups.

	Men			Women		
		Neck-distortion			Neck-distortion	
	Total no	%	OR (95% CI)	Total no	%	OR (95% CI)
MSC - / HA -	9761	1.4	1.0 (ref)	7763	0.8	1.0 (ref)
MSC - / HA +	2969	2.2	1.6 (1.1-2.2)	5127	1.6	1.3 (0.9-1.9)
MSC + / HA -	5758	3.5	2.2 (1.7-2.9)	5437	2.5	2.8 (2.0-4.2)
MSC + / HA +	3315	8.1	4.8 (3.6-6.2)	6765	6.0	5.2 (3.7-7.1)

HA=Headache, MSC= Musculoskeletal complaints

Analyses adjusted for all variables in Table 1.

Table 3 Prevalence odds ratio (OR) of self reported neck distortion related to musculoskeletal complaints.

	Men			Women		
Location of MSCs		Neck-distortion			Neck-distortion	
	Total no*	No (%)**	OR (95% CI)	Total no	No (%)	OR (95% CI)
Neck	4347	384 (57.2)	5.4 (4.4-6.8)	7136	458 (66.9)	6.2 (4.9-7.9)
Shoulders	4957	326 (48.6)	3.7 (2.9-4.6)	7675	425 (62.0)	5.6 (4.4-7.2)
Elbows	1679	113 (16.8)	3.8 (2.8-5.1)	2515	140 (20.4)	5.1 (3.7-7.2)
Wrist/hands	2202	146 (21.8)	3.9 (3.0-5.1)	4577	251 (36.6)	4.9 (3.7-6.4)
Chest/abdomen	972	68 (10.1)	3.6 (2.4-5.2)	1543	107 (15.6)	7.1 (4.9-10.4)
Upper back	1421	125 (18.6)	5.0 (3.7-6.7)	3361	235 (34.3)	5.9 (4.4-7.8)
Low back	4476	255 (38.0)	3.1 (2.4-3.9)	6399	326 (47.6)	4.8 (3.8-6.3)
Hips	2693	155 (23.1)	2.9 (2.2-3.9)	5554	260 (38.0)	4.8 (3.6-6.3)
Knees	2979	170 (25.3)	3.2 (2.5-4.2)	4686	219 (32.0)	4.7 (3.5-6.3)
Ankles/feet	2179	115 (17.1)	3.0 (2.3-4.1)	3881	209 (30.5)	5.3 (3.9-7.1)

HA=Headache, MSC= Musculoskeletal complaints. Analyses adjusted for all variables in Table 1.
*Total number of subjects with complaints in the population.
**Total number and percentage of subjects with compliants among those with self reported neck-distortion

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77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.

135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.

164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.

194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.

219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS

247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
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