31.10.2008

WHAT ARE THE CAUSES OF CERVICAL SPINAL DEGENERATION?

A systematic critical literature review

by

Svend Lings, Jonas Winkel Holm and Charlotte Leboeuf-Yde

Arbejdsmiljøforskningsfonden udbyder udredningsprojekter i form af referencedokumenter om erhvervssygdomme. I juli 2007 indkaldtes ansøgninger om støtte til udredninger inden for fire temaer, hvoraf det ene var *"Sammenhænge mellem påvirkninger på arbejdet og degenerative sygdomme i halshvirvelsøjlen, herunder gigtiske forandringer og diskusprolaps."* Denne rapport omhandler dette tema og er udarbejdet med støtte fra fonden.

Contents

Recommendations

On the basis of the results of this systematic critical literature review, we want to emphasize the following statements.

The type and number of studies failed to reflect the needs of occupational health practitioners and authorities. It is highly desirable that research funds should be allocated to relevant areas for studies using suitable scientific methods.

At the present time, the significance of degenerative changes for human suffering is uncertain. The primary question is whether such changes are to be considered a "condition" or merely normal adaptive phenomena that might even play a positive role in strengthening the spinal structures. In order to investigate the possible link between specific types of CDSC and symptoms, it would be necessary to perform population-based large scale studies including substantial subgroups of different ages. In such studies, modern visualization techniques (MRI-scan) should be utilized, and pain and disability should be appraised over longer periods as spinal pain is a recurrent disorder, not a yes/no condition. If an association between degenerative changes and symptoms is found, epidemiologic studies will be needed to demonstrate the relation between various work exposures and degenerative changes. Such studies should be more advanced than hitherto. Thus, it would be relevant to study the strength of associations and dose-response. It would also be necessary to take into account the genetic effect, which probably is substantial. This could be done through family studies, by the use of twins and by including genetic markers as possible modifiers of the results.

However, initially, we recommend a systematic critical literature review to be conducted in which, specifically, the link between symptoms, their frequency and severity should be studied in relation to the various types of "degeneration" (including Modic changes) in the entire cervical musculoskeletal system.

DANSK RESUMÉ

HVAD ER ÅRSAGERNE TIL DEGENERATIVE FORANDRINGER I HALSHVIRVELSØJLEN?

En systematisk kritisk litteraturoversigt

Svend Lings, Jonas Winkel Holm og Charlotte Leboeuf-Yde

Anbefalinger

Arten og antallet af undersøgelser dækker ikke det arbejdsmedicinske og administrative behov. Det ville derfor være ønskeligt at ressourcer blev tilført relevante områder med henblik på metodologisk tilfredsstillende forskning.

På nuværende tidspunkt er betydningen af degenerative forandringer (”slidgigt”) for smerter og andre symptomer uklar. Hovedspørgsmålet er hvorvidt sådanne forandringer skal betragtes som ”lidelser” eller bare som normale tilpasningsfænomener der endda kan tænkes at spille en positiv rolle ved at styrke de spinale strukturer. Undersøgelse af den mulige sammenhæng mellem specifikke former for degenerative forandringer og symptomer vil kræve store populationsstudier omfattende passende undergrupper af forskellig alder. Moderne billeddiagnostiske teknikker (MR-skanning) skulle benyttes, og symptomer og funktionshæmning skulle observeres over lange tidsrum da nakkesmerter er en tilbagevendende lidelse, ikke en enten/eller tilstand. Hvis en sammenhæng mellem degenerative forandringer og symptomer påvises, vil det være nødvendigt at gennemføre epidemiologiske undersøgelser af forholdet mellem forskellige arbejdsmæssige eksponeringer og forandringerne. Sådanne undersøgelser må være mere avancerede end de hidtidige. Det ville således være relevant at studere styrken af sammenhænge og dosis-respons. Det ville også være nødvendigt at se nærmere på genetiske forhold da deres betydning formentlig er væsentlig. Det kunne ske gennem tvillingeundersøgelser

Primært anbefales det dog at der gennemføres en systematisk kritisk litteraturgennemgang specifikt med henblik på undersøgelse af forholdet mellem symptomer, deres hyppighed og sværhedsgrad, og de forskellige former for ”degenerative” forandringer (herunder Modic-forandringer) i hele halsens muskuloskeletale system.

Introduktion

Nakkesmerter er næsten lige så almindelige i befolkningen som lændesmerter. Der er imidlertid stor uklarhed om sammenhængen mellem såkaldte degenerative forandringer i hvirvelsøjlen og smerter.

Et andet spørgsmål er hvorvidt disse degenerative forandringer kan forårsages, accelereres eller forværres af bestemte fysiske aktiviteter, kropsstillinger eller andre faktorer. Hovedformålet med denne litteraturgennemgang var at undersøge sidstnævnte aspekter, men vi forsøger også i en vis udstrækning at kaste lys over årsager i bredere betydning.

Vi fandt utilstrækkeligt grundlag for at afgøre hvorvidt ydre faktorer øger degenerative forandringer i halshvirvelsøjlen. De eneste faktorer der viste sig at have afgørende betydning, var alder og arveanlæg.

Baggrund

Degenerative forandringer i halshvirvelsøjlen ("slidgigt") omfatter afsmalning af båndskiven (diskus) mellem hvirvellegemer, knoglenydannelser udgående fra hvirvellegemerne (osteofytter, spondylose), forkalkning af hvirvlernes endeplader (sklerosering), defekter i båndskiven (rifter), frembuling af båndskiven (protrusion), eventuelt udposning af materiale (diskusprolaps), forskydning af hvirvellegemerne i forhold til hinanden, "Modic-forandringer" (et fænomen som kun ses ved MR-skanninger) samt slidgigt i hvirvlernes små facetled (facetledsartrose, uncovertebral artrose, spondylartrose). Disse fænomener er hverken særegne for mennesker eller af nyere dato. De findes også hos andre arter og er meget almindelige i præhistorisk menneskeligt materiale.

Man har længe vidst at degenerative forandringer i hvirvelsøjlen er produkter af livslange vævsprocesser. De begynder i diskus allerede i barndommen og tiltager med alderen, men både graden og arten varierer individuelt. På trods af betegnelsen "degenerative" synes disse forandringer at være tæt knyttede til processer som tilpasning og opheling. Udviklingen af forandringerne er dog ufuldstændigt udforsket.

Metode

En række computerbaserede litteratursøgninger blev gennemført med assistance fra forsknings-bibliotekar for at identificere relevant litteratur. Det krævedes at artiklerne repræsenterede originalt arbejde, var tilgængelige i fuld længde og var publiceret efter en videnskabelig, fagkritisk bedømmelse (peer-review). Endvidere skulle de degenerative forandringer være objektivt verificeret enten ved hjælp af billeddiagnostisk, anatomiske undersøgelser eller operationsjournaler. I artiklernes analyser skulle der være taget hensyn til alder. Alle de inkluderede arbejder blev systematisk gennemgået og kvalitetsvurderet ud fra en checkliste udarbejdet til formålet.

Resultater

Ved litteratursøgningerne identificeredes godt 12.000 muligvis relevante publikationer. Efter nærmere vurdering blev dog kun i alt 62 artikler fundet egnet til at indgå i den kritiske litteraturgennemgang.

Studiernes kvalitet var generelt lav. Kun fire opnåede maksimumpoint (10/10), andre 14 fik 8 eller 9. Atten fik 5 eller mindre. Kun i 30 tilfælde havde man sørget for ”blinding” så den der vurderede billederne ikke vidste hvad den undersøgte havde været udsat for. Dosis-respons var kun oplyst i fire tilfælde.

Tretten handlede om almene befolkningsgrupper eller patientgrupper, 19 om forskellige erhvervsgrupper (heraf syv alene om piloter), seks om personer der bar tunge byrder på hovedet, syv om forskellige sportsgrene, tre om patienter der havde ekstreme eller abnorme hovedbevægelser pga. sygdom, seks om dyreeksperimenter, to om arvelighedsforhold og endelig to om rygningens indflydelse på degenerative forandringer.

I fire tilfælde havde man forsøgt at belyse forekomsten af degenerative forandringer i den almene befolkning. Én undersøgelse viste en hyppighed på 13 % hos mænd i alderen 20-29 år, 5 % hos kvinder i samme aldersgruppe. I 40-49 års alderen var hyppigheden steget til 66 % hos mænd og 46 % hos kvinder. Ved 60-69 år var tallene 98 % respektive 91 %. En anden undersøgelse viste en hyppighed på 3 % i 15-års alderen, 100 % ved de 65.

De fleste undersøgelser viste en klar sammenhæng mellem alder og degenerative forandringer, og somme tider var alderen den eneste faktor der spillede en rolle. En tvillingeundersøgelse af høj kvalitet viste stærk arvelighed som kunne forklare omkring 70 % af variationen.

Nitten artikler handlede om hvorvidt bestemte erhvervsgrupper havde højere forekomst end andre. Kvalitetsscoren varierede fra 1/10 til 10/10. Tolv af disse artikler viste en eller anden forskel mens syv ikke gjorde. De to bedste undersøgelser pegede i hver sin retning. Det samme gjorde tre af acceptabel kvalitet idet en ikke viste nogen forskelle mens en anden viste sammenhæng med militær faldskærmstjeneste og en med arbejde hvor hovedet holdes bagudbøjet. Ikke mindre end syv handlede om professionelle piloter, men tegnede ikke noget klart billede. Seks som helhed dårlige artikler beskæftigede sig med personer der bar tunge byrder på hovedet. Den bedste viste at 89 % af disse havde degenerative forandringer i halshvirvelsøjlen i modsætning til 23 % af en kontrolgruppe, og der var dosis-responssammenhæng.

Syv handlede om betydningen af sport, nemlig to om rugby (amerikansk fodbold), to om fodbold, en om amatørdykning og to om forskellige sportsgrene. En mulig sammenhæng blev antydet mellem degenerative forandringer og amerikansk fodbold, boksning, fodbold og dykning, men kvaliteten var generelt lav.

Blandt de tre artikler om ekstreme og/eller abnorme hovedbevægelser ved forskellige sygdomme viste den bedste (spasmodisk torticollis) at der primært var slidgigtforandringer i den side af halshvirvelsøjlen som hovedet bevægedes imod.

To undersøgelser handlede om rygning. Den bedste viste ingen sammenhæng.

Seks dyreeksperimenter udført på mus, rotter og kaniner var generelt af høj kvalitet. De viste fremskreden diskusdegeneration hos mus med bindevævsdefekt, øget forekomst hos mus med arvelig kyfose (”pukkel”), samt hyppigere og mere udtalte forandringer hos forsøgsdyr som gennem måneder i lange perioder havde udført hyppigt gentagne halsbevægelser pga. elektrisk stimulation af halsmuskulaturen. Endelig fandtes degenerative forandringer i halshvirvelsøjlen hos forsøgsdyr nogle måneder efter at deres nakkemuskler og –sener var blevet bortopereret.

Overordnet kan man sige at det største problem i den fundne litteratur er at forskellige fysiske eksponeringer er tæt sammenvævede i de undersøgte sammenhænge. I langt de fleste tilfælde blev disse eksponeringer ikke nærmere beskrevet, ud over angivelse af stillingsbetegnelsen. Desuden blev dosis-responsspørgsmål ikke studeret. Der indgår kun få kvinder, og det er umuligt at sige om sammenhængen mellem fysiske faktorer og degenerative forandringer i halshvirvelsøjlen var kønsafhængig.

Konklusioner

Mængden og især den generelle kvalitet af den identificerede litteratur var forholdsvis beskeden, og der tegnes ikke et klart billede af relationen mellem erhvervsmæssige fysiske faktorer og degenerative forandringer i halshvirvelsøjlen. På den baggrund må vi konkludere:

- Der er utilstrækkelig evidens for en årsagsmæssig sammenhæng mellem degenerative forandringer i halshvirvelsøjlen og ekstreme hovedstillinger, gentagne bevægelser, vibrationseksponering, dykning, sport og alle undersøgte erhverv (bortset fra bæring af tunge byrder på hovedet).
- Der er utilstrækkelig evidens for dosis-responssammenhænge.
- Der er begrænset evidens for en årsagsmæssig sammenhæng mellem degenerative forandringer i halshvirvelsøjlen og kraftpåvirkning af halshvirvelsøjlen udefra, herunder bæring af tunge byrder på hovedet.

ABSTRACT

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Introduction

Neck pain is almost as common in the general population as low back pain. Today, however, there is great uncertainty regarding the relation between spinal degenerative changes and symptoms. Another question is whether the degenerative processes may be caused, accelerated or worsened by certain physical activities, postures or other factors. According to this literature review, there is insufficient evidence to determine whether any external exposures increase cervical spinal degeneration. The only factors we found to be of obvious significance were age and genetic disposition.

Background

Visualized cervical degenerative spinal changes (abbreviated CDSC) include reduced disc height, osteophytes, sclerosis of the vertebral endplates, anular tear, disc intensity alterations, disc bulging, disc herniation (prolapsed disc), spondylolisthesis, Modic changes, bony changes of the vertebral bodies and facet joint arthrosis. These phenomena are neither specific to humans nor of newer date. They are found in other species as well, and are very common in prehistoric human materials

For a long time it has been known that degenerative changes in the spine are products of lifelong tissue processes. Degenerative changes in the disc start already in late childhood and increase with age. However, the severity and specifics of the degenerative changes differ between individuals. In spite of the term "degenerative" the changes seem closely interlinked with processes of adaptive remodelling and healing.

The aetiologies are poorly explored. The main purpose of this review is to thoroughly evaluate the available epidemiological literature concerning potential physical risk factors of cumulative character, but we also try to shed light on the causes in a broader sense being, however, far from exhaustive.

Design

Systematic critical literature review.

Method

A series of librarian-assisted searches were performed in order to identify relevant literature. In addition, hand searches were made. Studies should represent an original work available in full-text and published in a journal with a peer-reviewed process. Degenerative changes could be objectively verified by imaging techniques, by pathoanatomical assessment or by collection of valid medical information regarding prior operation for CDSC. The analyses that had been performed in the articles should employ a certain minimum of controlling for age. All abstracts were screened independently by two persons. Abstracts that both considered relevant were secured as complete article texts. All article texts were screened for suitability. Each accepted article was then subjected to a systematic critical appraisal based on a checklist by two blinded authors. We selected some methodological items that we considered important when judging the credibility of research results: 1) sampling bias, 2) outcome variables, 3) potential predictor variables, 4) information bias, and 5) data analysis. Each aspect was then graded from 0 to 2. The maximum number of points that articles could achieve with our checklist system was 10. The reviewed articles were sorted into groups and the items transferred to evidence tables.

Results

The librarian-assisted literature searches resulted in 6481 abstracts, and a further 5711 titles from supplementary searches. A few, obtained through other sources, were included. The abstracts were screened by two of the authors. The 5711 titles contained at lot of doubles and were only screened by one. In all, 413 full articles were procured. No systematic critical literature review from the past twenty years was found. The full text articles were screened by two authors. Excluded were 121 because they actually failed to fulfil the inclusion criteria or were irrelevant to the subject. Finally, 62 studies were included in the critical systematic literature review.

Quality of studies

The quality of studies was generally poor. Only four of the reviewed articles obtained maximum scores (10/10), and a further 14 obtained 8 or 9 scores. 18 of the studies obtained only 5 scores or less. Only 30 studies had taken the precaution of separating the knowledge of exposure from the determination of the outcome measure (blinding), and dose-response was only reported in four.

Subjects

Thirteen dealt with general or clinical populations, 19 treated various occupational groups, seven studies were devoted to pilots, six reported on people who carried heavy burdens on their head, seven on various sports, three dealt with abnormal movements because of illness, six reported on animal experiments, two on genetics, and two on smoking.

General prevalence

In four studies it was attempted to establish the prevalence of degenerative changes in the general population. In a random sample drawn from a general practitioner's register, a prevalence of 13 % was found among males in the age group 20-29 years and 5 % among females in the same age group. By 40-49 years, the prevalence had risen to 66 % among males and 46 % among females. In 60-69 year olds the figures were 98 % and 91 % respectively. In another study an overall prevalence of 42 % was found in men and 37 % in women. In 15 year olds the prevalence was 3 %, by 65 years 100 %. Most studies showed a clear association between age and degenerative changes. In general, age was found to be positively associated with CDSC; indeed, sometimes it turned out to be the only variable having an influence in an almost linear fashion. A twin study of very high quality showed a strong heritability for degeneration with estimates around 70 %.

Occupation

There were 19 studies on various occupational groups. The quality scores ranged from 1/10 to 10/10. They all dealt with the question of whether specific occupations resulted in more degeneration than others with, presumably, less physical exposure. Twelve studies showed a difference of some kind while seven did not. The two occupational studies of highest methodological quality pointed in opposite directions. Of the three studies of acceptable quality one found no clear association with occupation while one showed association to parachuting and another to work with the neck extended. A professional group that has attracted interest is pilots, on the assumption that they are exposed to strong gravitational forces. Seven studies were identified. They failed to produce a coherent picture. Six studies dealt with groups of people who carried heavy loads on their heads. Their quality scores were generally low. The study of best quality concluded that 89 % of carriers had degenerative changes vs. 23 % of the controls and a dose-response was apparent.

Sports

Seven studies on sports were identified: two on rugby players, two on soccer players, two on various sports and one on amateur diving. The methodological quality was mainly poor. A possible association with rugby, boxing, soccer and diving was indicated.

Abnormal movements

Excessive and awkward movements were investigated in three studies, one on patients with spasmodic torticollis, one on patients with athetoid movements, and one on habitual wheel-chair users. The one dealing with patients who suffered from spasmodic torticollis concluded that osteoarthritis developed predominantly on the side of the direction into which the head turned.

Smoking

Two studies dealt with smoking. In the study of highest quality, no association with smoking was found.

Experimental animal studies

Six studies reported experiments on mice, rabbits or rats. The quality score was generally high. They showed advanced disc degeneration in transgenic mice with a collagen defect, more degenerative changes at the levels C5-Th3 in mice with heritable kyphosis, and degenerative changes were shown to be more frequent and more pronounced in animals stimulated in trapezius cyclically through a long time. In experiments on mice, rats and rabbits, posterior cervical paravertebral muscles were detached, ligaments resected and the animals killed at intervals. Histological changes were seen two months postoperatively and radiological degenerative changes in all operated animals several months after operation.

General problems in the literature

The major problem in the existing literature is that different physical exposures are closely interwoven in the investigated settings. In only a minority of the studies efforts were made to describe the physical exposures more specifically than solely by job title. On top of this, the reported data did not make it possible to calculate risk estimates with confidence intervals as our intention was from the beginning. In general, the literature also failed to address the issue of dose-response, and it was impossible to conclude whether the relation between physical exposures and CDSC was influenced by gender.

Associations between degenerative changes and symptoms?

Whether associations exist between the varieties of degeneration and symptoms is not clear. The results of eight studies found on this subject went in different directions.

Conclusions

There is insufficient evidence of a causal association between CDSC and prolonged tangential or rotational strain (i.e., "extreme" head postures), repetitive movements of the cervical spine without external impulse loading, vibration exposure, diving, sports, and all occupations dealt with in the existing literature, head carrying being the only exception.

There is limited evidence for an association between CDSC and repetitive movements of the cervical spine with external impulse loading, and for an association between CDSC and prolonged heavy axial cervical strain.

INTRODUCTION

This document was prepared on the initiative and with support of The Danish Working Environment Research Fund. It is a systematic critical scientific review with the aim to provide an evidence-based reference resource primarily summarizing the existing knowledge of possible causal associations between occupational physical factors and degenerative changes in the cervical spine.

Neck pain is almost as common in the general population as low back pain [1], and it is a frequently encountered symptom in clinical practice. Many patients consulting for localized neck pain with or without radiating pain into the arms are likely to be submitted to some form of imaging examination. A very small minority of such examinations will reveal serious pathologies, but in most cases, still, the clinician is left with a picture of some spinal structures that do not look quite right. Degenerative changes, whether of the posterior spinal elements, the vertebral bodies or of the intervertebral discs, would commonly be found. It is tempting to attach special importance to these changes in an attempt to explain the patient's symptoms.

Today, however, there is great uncertainty regarding the relation between degenerative changes and symptoms. Some therapists think that particularly degenerated discs, narrow spinal canals and osteophytes in the vicinity of nerve roots are possible causes of neck pain and radiating pain. But accumulating evidence seems to indicate that this is not the case. Obviously, it would be relevant to appraise the literature in order to establish if there is or is not a link between degenerative changes of the cervical spinal and neck problems.

Another question that arises is whether the degenerative processes may be caused, accelerated or worsened by certain physical activities, postures or other factors. The main purpose of this report is to study these latter aspects, but we also try to shed light on the causes in a broader sense being, however, far from exhaustive.

Literature references are inserted in angular brackets continuously (not alphabetically).

BACKGROUND

Visualized cervical degenerative spinal changes (abbreviated CDSC) include reduced disc height, osteophytes, sclerosis of the vertebral endplates, anular tear, disc intensity alterations, disc bulging, disc herniation (prolapsed disc), spondylolisthesis, Modic changes, bony changes of the vertebral bodies and facet joint osteoarthrosis.

These phenomena are neither specific to humans nor of newer date. They are found in other species as well, are very common in prehistoric human materials [2-4], and excavations from the Middle Ages have shown that CDSC were approximately as prevalent as today [5].

The aetiologies are poorly explored. The main purpose of this review is to thoroughly evaluate the available epidemiological literature concerning potential physical risk factors of cumulative character of CDSC, but as mentioned before, we also try to shed light on the causes in a broader sense, not being exhaustive. Thus literature concerning animal experiments, pathoanatomical and in vitro studies is included.

The cervical spine does not carry the same burden as the lumbar spine, but is designed for higher mobility in exchange of less stability [6;7]. It is a complex system with seven vertebrae, discs between them, 37 synovial joints, ligaments and muscles. The two top vertebrae, atlas and axis, are highly specialised for large mobility. The second most mobile areas are between the fifth and sixth vertebra (C5/C6) followed by C4/C5 and C6/C7.

The disc is an avascular tissue with cells (chondrocytes) in a structurally intricate matrix. It consists of three distinct components, the circumferential anulus fibrosus, the central gelatinous nucleus pulposus, and the two cartilaginous endplates adhering to the nearby vertebral bodies.

For a long time it has been known that degenerative changes in the spine are products of lifelong tissue processes [8]. In spite of the term “degenerative” (according to Webster’s dictionary “falling below a normal or desirable level”), disintegrating or degrading processes seem closely interlinked with processes of adaptive remodelling and healing involving cell proliferation [9;10].

Even though the picture in some instances seems complicated, the degenerative changes can to some degree be conceived as three subsequent phases in a common “degenerative cascade” involving 1) a “dysfunction phase” characterised by incipient degenerative changes, still without biomechanical impact, 2) an instability (or hypermobility) phase of segmental instability due to progressing degeneration and 3) a restabilisation phase characterised by adaptive remodelling to counteract[11] the hypermobility [12;13].

Degenerative changes in the disc start already in late childhood with progressive desiccation and decompression of the gelatinous nucleus, primarily due to declining content of the water-binding proteoglycans [8;14-16]. Later in the degenerative process, the nucleus becomes increasingly fibrotic and disintegrated, often divided in several lumps by intranuclear clefts and separated from the cartilaginous endplate by softer material [17;18]. Also in the cartilaginous endplate, degenerative changes commence early in life, including erosions and cracking and later calcification [19;20].

In the anulus fibrosus degenerative changes have also been shown from late childhood. This includes, apart from some desiccation, disorganisation of the annular microarchitecture which leave the anulus increasingly stiffer and weaker [21;22] with progression to development of fissures or tears of different types [23;24].

It is a relative new knowledge that degeneration of lumbar discs with disrupted cartilaginous endplates often is accompanied by oedema in the surrounding bone marrow of the adjoining vertebral bodies, with formation of fibrovascular tissue between the thickened bone trabeculae. These changes, radiologically exclusively detectable with MRI, are called “Modic changes” [25;26]. They have also been described in the cervical spine, especially at the C5/C6 level [27]. Histologically, they constitute an inflammatory “discovertebritis” which probably represent a mechanical and/or chemical tissue reaction to the degenerated endplate and disc. Usually, two types of Modic changes are encountered, “Type 1” and “Type 2”, the latter probably being regenerative. Another common proliferative change is the subchondral osteosclerosis of the vertebral endplates [28].

“Osteophytes” gradually proliferate from the vertebral margins. They can eventually fuse with osteophytes from neighbouring segments to form bony bridges. This makes the spine more rigid.

The disc degeneration is regularly accompanied by osteoarthrosis in the adjacent synovial joints, “spondylarthrosis” [29]. Advanced bony proliferative changes, posteriorly located osteophytes and gross facet joint deterioration can lead to secondary stenosis of the intervertebral foramina, the nerve root canals or the spinal canal. The subsequent mechanical or chemical irritation of spinal nerve roots can give rise to brachial radiculopathy, or, when the medulla is affected, to myelopathy [30-33]. Also disc herniation (“disc prolapse”) can produce these clinical syndromes.

Terminology

As mentioned above, no commonly accepted definitions of the different degenerative changes exist.

The bony changes in the vertebral bodies are often mentioned under the collective names *spondylosis*, *spondylosis deformans* or sometimes *osteochondrosis* [34]. Conceptual vagueness is regularly met in the literature. The term spondylosis is used synonymously for both disc degeneration and the formation of osteophytes only.

Osteoarthrosis in the facet joints is normally distinguished from the concepts of disc and vertebral body degeneration with the terms *spondylarthrosis*, *facet joint arthrosis*, *uncovertebral arthrosis*, *spondylarthritis* or *facet joint arthritis*.

Diagnostic imaging

The common imaging techniques in detecting degenerative spinal changes are conventional radiography (X-ray imaging), computed tomography (CT) and magnetic resonance imaging (MRI).

X-ray visualises soft tissues poorly and cannot display the disc tissue as such, but secondary phenomena of the disc degradation can be seen, primarily disc space narrowing, and sometimes also disc calcification and gas accumulation (vacuum phenomenon) in the disc.

With MRI, and in minor degree also with CT, soft tissue changes are substantially better visualised, and MRI is at present the method of choice in visualising discs, ligaments and the other spinal soft-tissues. More detailed information can also be visualised with MRI including disc bulging, disc protrusion, disc herniation, fissures and clefts in the nucleus and “high intensity zones” in the anulus representing tears. Also finer disc tissue details can be displayed, such as scarring and calcification and defects in the endplates. However, histological features, i.e. tears, rim lesions and prolapse of nucleus material, may be poorly recognised [35]. The Modic changes of the vertebral bodies are described earlier.

Bony changes of the vertebrae, including *s*pondylosis and facet joint arthrosis are visible with all three main imaging modalities. However, CT-scan is (followed by MRI) superior in demonstrating osseous structures. In the facet joints a typical osteoarthrosis is revealed for example as subchondral sclerosis and cysts, osteophytosis, joint space narrowing, and sometimes also as intra-articular vacuum, increased joint fluid or ligamentous thickening [36].

Natural course of cervical degenerative spinal changes

CDSC increases with age. However, the severity and specifics of the degenerative changes differ between individuals [37;38].

Degenerative spinal changes are normally expected to assume a slowly progressing, chronic course. However, at least as far as disc degeneration is concerned, the picture appears more complicated, since recent observations indicate that annular fissures and even disc height narrowing can “recover” spontaneously [39], just as it is known for disc protrusions.

Relation of cervical degenerative spinal changes to clinical syndromes

Neck pain is very common in the general population [40;41], and, if once emerged, it will recur or continue in at least half of the cases [42]. In a large population-based questionnaire study, 4.6 % of the adult population described severe neck pain significantly restricting their activities of daily living [43]. But all in all, the efforts of correlating CDSC with local neck pain are still controversial. In a recent review, which critically appraised results of the literature on assessment strategies of neck pain, one of the conclusions was that “there is non-conclusive evidence that common changes on cervical MRI-scan are strongly correlated with neck symptoms” [44]. However, this statement was based on an absence of evidence rather than evidence of no association, as such.

Analytical epidemiology, hypotheses of pathology

The aetiologies of CDSC are poorly explored, but disc degeneration in the lumbar spine is somewhat better investigated. Evidence exists that a number of external and internal risk factors may contribute to lumbar disc degeneration. Among these, different aspects of mechanical strain have traditionally been regarded as important and have been supposed to act by a slowly detrimental “wear-and-tear” effect of repetitive microtrauma [45]. In the occupational field, many epidemiologic studies have suggested that heavy material handling [46;47] and perhaps also vehicular whole body vibration [48] are occupational risk factors for lumbar disc degeneration and disc herniation, but the overall picture is still not quite consistent [49-51].

A number of risk factors for lumbar disc degeneration related to life style and constitution have been suspected to contribute including age, smoking habits, gender, body height, weight and body mass index [52-54]. However, recent twin studies have provided crucial results displaying that genetic factors play a dominant role, probably accounting for as much as ¾ of the variance of disc degeneration among adults [55]. Thus, in a recent twin study, occupational lifting history only explained 1 % of the variance of disc narrowing [56].This leaves a more modest role for environmental factors, including occupational or athletic physical factors. Whether a similar etiological spectrum applies to the cervical spine is not clear at the present time.

METHOD

The literature search

A series of librarian-assisted searches were performed in order to identify relevant literature (JWH, for detailed information, see Appendix 1). In addition, a hand search was made using the reference lists of relevant articles and the participants' own databases.

Inclusion and exclusion criteria

In order to assess the retrieved papers for suitability, the following criteria were applied:

1. Studies should represent an original work available in full-text and published in a journal with a peer-reviewed process. There were no time limitations to original articles.
2. Also PhD and doctoral theses were acceptable.
3. Letters to the editor, conference proceedings, and editorials were thus excluded but could serve as background literature.
4. Information in the article should concentrate on the relation between physical factors of prolonged nature and should objectively describe cervical degenerative changes. Studies only treating the effect of single traumas to the neck were excluded.
5. Cervical degenerative changes could be objectively verified by imaging techniques (X-ray, MRI, CT) or by pathoanatomical assessment or by collection of valid medical information regarding prior operation for CDSC (in practice, cervical disc herniation).
6. The analyses that had been performed in the articles should employ a certain minimum of controlling for age (by matching, age restriction, or statistical control), or at least be reported for different age-groups.
7. The design of the study had to be cross-sectional, case-control, longitudinal, experimental observational study with a well-defined base population, pathoanatomical or histological. Randomised controlled studies or interventional studies were also accepted. Case studies and case-series were excluded.
8. The following languages were accepted: English, German, French, Danish, Swedish and Norwegian.
9. Systematic critical literature reviews published within the last twenty years would be included.

Screening of abstracts

All abstracts were screened independently by two persons (CLY and SL). Abstracts that both considered relevant were secured as complete article texts. When only one of the readers suggested an abstract, a discussion with the second author was undertaken and a joint decision made, usually in the positive direction.

Screening of articles

All article texts were screened for suitability (CLY and SL), and some of them were left out. Each accepted article was then subjected to a systematic critical appraisal based on a checklist (see below) by two blinded authors (mainly CLY and SL). The results of their reviews were noted on the checklists to be compared. In case of disagreement, the article was read once more followed by a consensus discussion. A random check was then undertaken by the first author (JWH).

Literature review

Checklists

Although checklists exist to assess methodological quality of research articles (such as the one recommended by The Cochrane Collaboration for clinical trials), there is none suitable specifically to assess the quality of epidemiologic articles on causality. For this reason, we designed such a checklist (Appendix 2). It consisted of three main components which were used 1) to describe the study, 2) to assess its quality, and 3) to provide the main results. This checklist could be somewhat modified to suit particular study types.

1. Describing the studies

All reviewed studies were briefly described to make it possible to identify the article (author, year, country), and to appreciate the main concept of the study (design, type of study population, and exposure in relation to degenerative changes and dose-response e.g. in terms of load and years of exposure). In addition, all imaging/histological definitions were categorized and noted in the checklist.

2. Assessing the quality

Different methods can be used to judge the quality of research articles. Reports can be given points according to a predefined set of criteria. These points can be added up to a final score with each score carrying equal weight, or the scores can be weighted, with the more important aspects of the study resulting in higher marks. The final score can be reported for the reader to take into consideration. A cut-off point can be defined, and studies below this point disregarded in the interpretation phase of the study, or certain minimal criteria can be selected and decided to be necessary before admitting an article for further assessment. In research circles, there is, however, no consensus on which method to use [57].

For the quality aspect, we selected some methodological items that we considered important when judging the credibility of research results. The five main aspects were 1) sampling bias, 2) outcome variables, 3) potential predictor variables, 4) information bias, and 5) data analysis. Each of these aspects was provided with a number of items that might be relevant to judge the quality of that particular aspect. Aided by these items, each aspect was then graded from 0 to 2. For details, please refer to the evidence tables**.** Some minor adaptations were made to the checklists used for genetic studies, general populations, and animal studies, to suit the differences in study designs.

The maximum number of points that articles could achieve with our checklist system was 10. We did not select a cut-off point for quality, but we took special notice of whether the assessment of the outcome variable was done without bias. Usually this meant whether the persons who determined the type and level of degeneration was blinded as to the factors examined that might have an influence on the degenerative findings. In the case of genetic studies, the method of ascertainment of twins and the determination of zygosity status were considered especially important. An overview of the quality scores for each article is found in Table 1.

Another important variable on the checklist was of course the definition of cervical spine degeneration. This item was specifically noted for each article.

3. Evidence tables

The reviewed articles were sorted into groups according to the subject. Some of the items on the checklists, including the final quality score, were transferred to evidence tables. These tables are included at the end of the report. Blinded assessment of degenerative changes (or of zygosity status in the case of twin studies) was noted specifically in the table. If information was available on an association between degeneration and age or sex, these findings were entered into the tables. Data interpretation was then undertaken on the basis of these combined informations.

4. Deduction of information

The results of the best studies were first taken into consideration on basis of the evidence tables. Thereafter it was investigated whether the other articles obtained similar findings or not. In the case of contradictory results, explanations were sought in the study material, study design and/or general quality of the articles.

RESULTS

The literature search

The librarian-assisted literature searches resulted in 6481 abstracts, and a further 5711 titles from supplementary searches in the three common library resources *Svemed+*, *bibliotek.dk* and *Libris.* A few articles obtained through other sources (authors' own registers and references in other articles) were included.

The screening of abstracts

The 6481 abstracts, some of which were doubles, were screened by two of the authors. The 5711 titles contained at lot of doubles and were only screened by one. In all, 413 full articles were procured. No systematic critical literature review from the past twenty years was found.

Screening of articles

The full text articles were screened by two authors. Of these, 121 were excluded because they actually failed to fulfil the inclusion criteria or were irrelevant to the subject. A number of interesting articles were left to be used as background reading, and some of them were used in the discussion section. Finally, 62 studies were included in the systematic critical literature review.

Quality of studies

The quality of studies was generally poor. Only four of the reviewed articles obtained maximum scores (10/10), and a further 14 obtained 8 or 9 scores. Eighteen of the studies obtained only 5 scores or less. Even more worrying, only 30 studies had taken the precaution of separating the knowledge of exposure from the determination of the outcome measure (blinding).

The most commonly missed quality item, according to our quality table, was sampling bias followed by information bias (typically lack of blinding when reading films) and dataanalysis, see Table 1.

In general the study samples were small and the matching either not described or insufficient to assure comparability between groups.

The method section often included information on a number of degenerative changes on which data were collected, but not reported upon.

Dose-response was only reported in four of the studies [58-61].

Table 1. *Quality score*

Good = 2, acceptable = 1, not acceptable = 0. Maximal obtainable score = 10 (in two articles of a special kind only 8)

Author Year Country	**Sampling bias**	**Outcome variables**	**Potential predictor variables**	**Informa-tion bias**	**Data analy-sis**	**Total quality score**
An 1994 USA	2	2	1	0	1	6/10
Aydog 2004 Turkey	2	1	2	1	1	7/10
Baogan 2000 China	1	2	2	1	2	8/10
Bartsch 2001 Germany	0	2	2	2	0	6/10
Beck 1951 Germany	0	0	1	0	0	1/10
Berge 1999 France	0	1	2	0	1	4/10
Bremner 1968 Jamaica	2	2	2	2	2	10/10
Chawda 2000 UK	2	2	2	2	0	8/10
Ebara 1989 Japan	0	2	2	0	0	4/10
Echarri 2002 Congo	0	2	2	0	0	4/10
Echarri 2005 Congo	0	2	1	0	0	3/10
Ernst 2005 Belgium	0	2	NA	2	1	5/8
Gore 2006 USA	1	2	2	2	2	9/10
Hartwig 2003 Germany	0	2	2	0	1	5/10
Hämäläinen 1993 Finland	2	1	2	2	1	8/10
Hendriksen 1999 Holland	2	1	2	2	1	8/10
Hult 1954 Sweden	1	2	1	0	2	6/10
Hult 1954 Sweden	1	2	2	0	1	6/10
Humphreys 1998 USA	0	2	2	0	0	4/10

Irvine 1965 UK	2	2	2	2	2	10/10
Jäger 1997 Sierra Leone	1	2	1	2	2	8/10
Jensen 1996 Denmark	1	2	2	NA	1	6/8
Joosab 1994 Zimbabwe	0	1	0	0	0	1/10
Jung 1975 Germany	0	2	1	0	0	3/10
Kartal 2004 Turkey	0	2	2	2	0	6/10
Katevuo 1985 Finland	1	2	2	2	0	7/10
Kellgren 1952 UK	1	2	1	2	0	6/10
Kellgren 1958 UK	2	1	1	1	0	5/10
Kimura 1996 Japan	2	2	2	0	1	7/10
Kojima 1997 Japan	0	0	2	0	1	3/10
Kopacz 1999 USA	2	2	NA	2	0	6/8
Landau 2006 Israel	0	2	2	2	0	6/10
Lawrence 1961 UK	1	2	2	2	1	8/10
Lawrence 1969 UK and Rhondda	0	2	1	2	2	7/10
Lee 2001 Hong Kong	2	2	2	2	2	10/10
Lehto 1994 Finland	0	2	2	1	2	7/10
Mahbub 2006 Bangladesh	2	2	2	0	0	6/10
Mason 1984 UK	2	1	2	0	1	6/10
Mason 1996 USA	2	1	2	2	1	8/10
Matsumoto 1998 Japan	1	2	2	2	2	9/10
Mehring 1998 Sierra Leone	0	2	2	2	0	6/10
Miyamoto 1991 Japan	2	2	2	0	2	8/10
Mundt 1993 USA	1	2	2	2	0	7/10
Mustajoki 1978 Finland	0	1	2	2	2	7/10
Obisesan 1999 Nigeria	1	1	2	0	1	5/10
Palmer 1984 USA	0	0	0	0	0	0/10
Petrén-Mallmin 1999 Sweden	0	2	2	2	0	6/10
Petrén-Mallmin 2001 Sweden	2	2	2	2	1	9/10
Rellan 1969 India	0	2	2	0	0	4/10
Reul 1995 Germany	0	2	2	2	1	7/10

Sambrook 1999 UK and Australia	1	2	2	2	2	9/10
Scher 1990 South Africa	0	2	2	0	0	4/10
Schröter 1959 Germany	0	1	2	0	0	3/10
Siivola 2002 Finland	2	2	2	2	0	8/10
Sortland 1982 Norway	0	1	2	0	2	5/10
Takamiya 2006 Japan	0	2	1	2	2	7/10
Tsirikos 2001 Greece	0	1	2	0	0	3/10
Wada 1992 Japan	2	2	2	0	1	7/10
Wang 2006 China	2	2	2	2	2	10/10
Zapletal 1997 Holland	2	2	2	0	2	8/10
Zejda 2003 Poland	1	1	2	0	2	6/10
Ålund 1994 Sweden	0	2	2	2	0	6/10

The literature review

Of the 62 articles included into the systematic critical review, thirteen (Evidence Table 1) dealt with general or clinical populations. Nineteen (Table 2) treated various occupational groups, seven (Table 3) studies were devoted to pilots, six (Table 4) reported on people who carried heavy burdens on their head, seven (Table 5) to various sports, three (Table 6) with abnormal movements because of illness, six (Table 7) reported on animal experiments, two (Table 8) with genetics, two (Table 9) dealt with smoking. Three articles [62-64] dealt with two of these subjects. In addition, we reviewed some archaeological studies [65-67], but not critically.

The prevalence of degenerative changes of the neck in the general population

In four studies it was attempted to establish the prevalence of degenerative changes in the general population:

In a random sample of 20-90+ year olds (N = 490) drawn from a general practitioner's register, Irvine et al. 1965 [68] found a prevalence of 13 % among males in the age group 20-29 years and 5 % among females in the same age group. By 40-49 years, the prevalence had risen to 66 % among males and 46 % among females. In 60-69 year olds the figures were 98 % and 91 % respectively.

Lawrence 1969 [69] investigated three general population samples from UK and one from Rhondda, all more than 14 years old. They found a clear association between age and degenerative changes. The overall prevalence was 42 % in men and 37 % in women. In 15 year olds the prevalence was 3 %, by 65 years 100 %.

Asymptomatic Japanese volunteers were examined by Matsumoto et al. 1998 [70]. They found that degenerative changes increased linearly with age and were seen in 12-17 % of discs in the twenties and 86-89 % after 60 years.

From these and other studies it clearly appears that the level C 5/6 primarily is involved followed by the levels below and above. Zapletal et al. 1997 [71] studied the atlantoaxial joint on radiographs of the nasal sinuses. They saw no abnormalities before the sixth decade, but linear progression with age thereafter: 5.4 % in the sixties, 18 % in the nineties.

Of the articles listed in Evidence Table 1 "General or clinical populations", additionally eight were dealing with the significance of age. A positive age association was demonstrated in six. In the remaining two, Kopacz et al. 1999 [72] found no association specifically between age and cervical spondylolisthesis, and Humphreys et al. 1998 [73] found no association with the ratio cord/canal, although he did note age associations with other variables.

On the basis of this it must be concluded that degenerative changes in the cervical spine are normal phenomena that inevitably develop during life and advance with age. But what are the causes? And which factors influence course and extent?

Causes of degenerative changes in the cervical spine

Intrinsic factors

All studies included in our review had taken age into consideration, in one way or another, because not relating the material to age simply resulted in exclusion. In general, age was found to be positively associated with CDSC; indeed, sometimes it turned out to be the only variable having an influence.

There was not sufficient detailed information on the various types of degeneration in relation to age to provide exact estimates of the speed of degeneration. Also many studies had but smallish study samples which would provide unstable estimates. However, it became clear that, regardless of how frequent the finding was, it would increase with age. This was the case in an almost linear fashion. For instance, this applies to disc degeneration, posterior disc protrusion, disc space narrowing and foraminal stenosis according to a study with 497 study subjects [74]. In another study with 697 study subjects, a linear progression was noted for reduction of intervertebral disc height and osteophyte formation [75]. Also when a particular degenerative change appeared late in life, the frequency increased with age, as

Zapletal 1997 [76] demonstrated for lateral atlantoaxial osteoarthrosis, a condition that was found to start in the sixth decade.

We identified two studies on the heritability of degenerative changes of the cervical spine, one of which was of inferior quality [77]. The second, a twin study of very high quality, showed a strong heritability for degeneration with estimates around 70 % [78].

In nine of the reviewed articles, differences between genders were specifically reported. In five of these there were no differences, in three the prevalence estimates were higher among men, and in one the number of discs affected was largest among women. In two large studies from the UK, men had a higher prevalence of disc degeneration than women [79;80] and also more severe degeneration [81].

External forces, loading, posture

1. Various occupations

There were 19 studies on various occupational groups, nine employing the exposed/non-exposed study design, nine others using internal control groups, and one register study. The oldest study was from 1951, the newest from 2006. One was Japanese, the rest European. The study samples ranged from 45 to almost 90,000 (the register study). The quality scores ranged from 1/10 to 10/10. They all dealt with the question of whether specific occupations resulted in more degeneration than others with, presumably, less physical exposure. Twelve studies showed a difference of some kind while seven did not.

Hult 1954 [82] compared 114 forest workers to 163 industrial workers and found that degenerative changes were more frequent and started earlier in the forest workers. In another study by the same author [83] it was found that changes developed earlier in heavy work than in light work, but the differences disappeared when the changes were more pronounced.

Irvine et al. 1965 [84] showed more prevalent changes in miners with heavy work than in other occupations with light work.

Jensen et al. 1996 [85] in a large register study found an association between frequency of hospitalization for disc herniation and professional driving, but age differences between groups seem to undermine the result.

Lawrence 1961 [86] studied cotton mill workers and non-manual workers and found that the cotton mill workers had *less* changes than the controls. In another study by the same author [87], the prevalence of degeneration was not clearly associated with occupation, but the most pronounced forms were seen in manual workers.

Mustajoki 1978 [88] found a prevalence of 40 % in parachutists and only 20 % in unexposed volunteers, and a positive dose-response relation.

Schröter 1954 [89] concluded that dentists had the same frequency as office workers, miners and carriers of heavy burdens, but more severe changes. Katevuo 1985 [90] found degenerative changes in 52 % of dentists but only in 19 % of farmers.

Takamiya [91] demonstrated a higher frequency of degenerative changes in work with neck extension, i.e. grape growing, compared to eggplant growing.

Tsirikos [92] claimed a higher incidence in jockeys, but the figures are unclear.

Ålund 1994 [93] compared former steel work grinders with neck symptoms to white collar workers who had been X-rayed because of minor trauma or neck complaints. They found more foraminal narrowing in the grinders because of osteophytes, but the disc heights were the same.

In the seven negative studies, various occupations were compared: professional military divers to non-divers [94], miners using compressed air tools to unexposed heavy workers and "brain workers" [95], office workers, drivers, machine workers and heavy workers to each other [96], underground miners, other manual workers and office workers to each other [97], cotton mill workers to a random sample of the general population [98], various occupations to each other [99], and coalminers with hand-arm vibration disease to blue collar surface workers with non-specific neck complaints [100].

Six studies dealt with groups of people who carried heavy loads on their heads. In five of them, African carriers were compared to non-carriers. The sample sizes ranged from 20 to 98 with publication dates from 1994 to 2006. Their quality scores were generally low, and in only two studies were the images read blindly. The study of best quality concluded that 89 % of carriers had degenerative changes vs. 23 % of the controls and a dose-response was apparent. All but the methodologically most inferior study also showed positive associations with carrying burdens on the head.

In conclusion, the two occupational studies of highest methodological quality were performed by Irvine [101] and Lawrence [102], pointing in opposite directions. Of the three studies of acceptable quality [103-106] one found no clear association with occupation while one showed association to parachuting and another to work with the neck extended.

2. Pilots

Another professional group that has attracted interest is pilots, on the assumption that they are exposed to strong gravitational forces.

Seven studies from 1993-2006 were identified, all using an exposed/non-exposed design, four with very small study samples (N = 24-30) and two with large samples (N=316 and 934, respectively). One study used register data with aviator years as the denominator. The quality scores were generally medium, but high particularly in relation to blind assessment of the outcome variables. According to the study with the best study design there were no consistent associations, and also the two studies with the largest study samples and of acceptable methodology failed to produce a coherent picture.

3. Sports

Seven studies on sports were identified: two on rugby players, two on soccer players, two on various sports and one on amateur diving. They were from 1975-2004 and used sample sizes of 58-510. The methodological quality was mainly poor. A possible association with rugby, boxing, soccer and diving was indicated.

4. Awkward movements

Excessive and awkward movements were investigated in three studies, one on patients with spasmodic torticollis [107], one on patients with athetoid movements [108], and one on habitual wheel-chair users [109]. The sample sizes were 34, 57 and 287, respectively. The one dealing with patients who suffered from spasmodic torticollis, being of high quality, concluded that osteoarthritis developed predominantly on the side of the direction into which the head turned, and that it occurred at higher levels than usually, namely at C2/3 and C3/4.

Smoking

We found two studies from 1994-2006 in which an association between smoking and degenerative changes was investigated.

In the study of highest quality (score 9/10), 100 asymptomatic smokers were compared to 100 asymptomatic non-smokers [110]. No association with smoking was found.

In the second study, of low quality, a case-control design was used to compare 42 patients operated for a cervical discal prolapse with radiating arm symptoms to an unknown number of patients without such symptoms [111]. A relatively strong association with smoking was noted, but it failed to include blind assessment of the outcome variables, and the cases were all patients who had symptomatic neck problems, making it unclear if the association was confused by selection bias based on symptoms that might cloud the picture.

Alcohol and diet

We found no information on these subjects, although the authors of one archaeological article hypothesized that differences between study samples might partially be explained by dietary circumstances.

Animal experiments

Six studies from 1984-2006, all Asian but one, reported experiments on mice [112-114], rabbits [115;116] or rats [117]. The quality score was generally high (6/10 – 10/10).

Kimura [112] found more advanced disc degeneration in transgenic mice with a collagen defect. Mason [113] showed more degenerative changes at the levels C5-Th3 in mice with heritable kyphosis. Wada [118] implanted electrodes unilaterally in the trapezius muscle of rabbits and stimulated cyclically resulting in muscle contractions during three periods up to three months. In the most exposed group (200.000 cycles during two months) degenerative changes were shown to be more frequent and more pronounced histologically, but not radiologically.

In the three remaining experiments on mice, rats and rabbits respectively, posterior cervical paravertebral muscles were detached, ligaments resected and the animals (experimental and controls) killed at intervals. Miyamoto [119] saw histological changes two months postoperatively and radiological degenerative changes in all operated animals 12 months after operation, but not before and not in controls. Baogan [115] observed that osteophytes arised from proliferation of articular cartilage through endochondral ossification. After three months the operated animals showed more degenerative changes similar to those in the controls after eight months. By histological and biochemical analyses Wang [120] showed progressive degenerative changes with inflammation from three months on in the experimental group.

Post-hoc analysis

Association between degeneration of the neck and symptoms

Whether associations exist between the varieties of degeneration and symptoms is not clear. The results of eight studies found on this subject went in different directions.

A Jamaican population was compared to a British population and found to have more severe and widespread degeneration yet complained less of symptoms [121]. Echarri [122] also found no correlation between symptoms and degeneration, and noted that the women who had the highest pain scores had the least degenerative changes. In a study of dentists, it was noted that the majority (88%) had degenerative changes but that the minority (39%) had symptoms [123]. In a study of military parachutists, CDSC were associated with stiffness, but not with headaches or neck pain [124].

On the other hand, Humphreys [125] noted no association with symptoms and lordosis or disc height, but an association was found with foraminal width. Siivola [126], in a small study of young people, claimed a significant association between disc herniation and pain, but in fact the p-value was only 0.1. Two studies reported a significant association: Mahbub [127], in a randomly selected sample of coolies from Bangladesh, reported that neck symptoms were more common in those with degeneration. Lawrence, in a 1969 report from the UK [128], found that people with disc degeneration had longer duration of pain and loss of work from cervico-brachial pain, and that this was more common in men with major degeneration than in those with minor degeneration.

DISCUSSION

In summary, we conclude that so called “degenerative changes” in the cervical spine should be considered a biological phenomenon that begins in teenagers and progresses with a clear age-association. In old age, everybody will have them. Further, the speed with which it develops is probably strongly genetically determined. The amount and quality of the existing literature does not yield a clear picture of possible associations between occupation and degenerative changes in the cervical spine, specific exposures, dose-response relations and gender differences not to mention. It has been relatively convincingly shown that prolonged awkward positions, as well as extremely repetitive movements of the neck and carrying heavy loads on the head, will induce early changes, but the differences disappear as the changes progress over time. It is possible that head trauma contributes as well, and probably rheumatoid arthritis and various kinds of spondylitis, but these inflammatory diseases will leave specific characteristic alterations besides the CDSC.

Strengths and weaknesses of this review

A thorough librarian-assisted literature search was undertaken, which should have captured most relevant literature in this area. The review was systematic and performed independently by two authors, with few points of disagreement. Issues of quality were taken into account in a non-rigid manner, painstaking aiming at objectivity.

However, the search may have failed to capture some relevant literature, and the same might have happened during the screening process. The check-list items, used to describe the articles and judge their quality, had to be designed specifically for this study, and another approach may have rendered somewhat different results. Although the quality assessment was performed systematically, aided by key words for each quality item, it had of course a subjective element to it. Also, because the quality of studies in general was low, it is likely that a certain tolerance crept into the assessment, resulting in higher marks than deserved.

Strengths and weaknesses of the literature

Only few studies have been devoted to this topic. Those that exist are generally simplistic in style, and only a minority fulfilled all or most of our quality criteria. The vast majority were therefore of doubtful value.

It was obvious that this is not a prioritized research area. Most investigations appear to have been designed in an ad hoc fashion, as single studies, and not as part of a long-term research program. Pilots have attracted a fair bit of interest whereas larger occupational groups have been studied only rarely. Also head carriers have attracted some attention, but unfortunately the quality of these studies was mainly low. No other occupational group has been studied several times. It was therefore not possible to classify occupations according to cervical load and movement and study the amount of degeneration in a “descending” order.

Another weakness of the literature is that there was no serious information on dosage, neither in terms of work load nor in relation to duration of exposure, and modifying factors have not been studied in a convincing manner.

It was also not possible to evaluate specific diagnostic entities. Only some researchers had taken the precaution of using previously described standardized definitions of the degenerative changes. Many preferred to use their own definitions, whereas some even failed to define what they meant by “degeneration”. This resulted in a fair bit of heterogeneity of outcome measures, making comparisons between studies difficult or impossible.

In addition, the method sections of articles often included a list of degenerative changes whereas not all were reported upon in the result section in an unequivocal manner. This clouds the interpretation. Why were some degenerative phenomena studied but not reported? A natural explanation would be that nothing was found. This approach results in publication bias, and is a nuisance factor that results in an over-emphasis on positive findings.

Interestingly, some of the better studies were the very first ones to appear [129;130]. They included clear definitions of degeneration, used blinded radiologic assessment, and dealt with clinically relevant occupational groups.

Apart from some narrative reviews of questionable quality, only one systematic review of older date concerning the relation between physical occupational factors and CDSC (among other shoulder-neck diagnoses) was found [131]. In this review, published at a time when the literature of course was even sparser than now, a possible elevated risk of CDSC was suggested for miners, dentists, and people with heavy work. This is not contradicted by the present review, but then again, the field has not become much more clarified during the elapsed 21 years.

Evidence synthesis regarding physical exposures: Causation

All occupations involve a complex mixture of various exposures to the cervical spine. In a thorough gathering of evidence one must consider if common exposure characteristics between the described occupations and other settings within reason can be identified and related to cervical CDSC. In this respect, some main groups of physical exposures are treated in the reviewed literature: *1. vibration exposure, 2. prolonged axial cervical strain, 3. prolonged tangential or rotational static strain* (i.e., “extreme” head postures)*, 4. repetitive movements of the cervical spine without external impulse loading, 5. repetitive movements of the cervical spine with external impulse loading,* and *6.diving*.

The major problem in the existing literature is that different physical exposures are closely interwoven in the investigated settings. In only a minority of the studies efforts were made to describe the physical exposures more specifically than solely by job title. An illustrative example of the problem is *vibration exposure* which was primarily represented in the studies of professional drivers and jet pilots (whole body vibration) and of miners (hand-arm vibration). In these studies, no attempts to describe the actual levels of vibration exposure were made, and vibration was mixed with other relevant exposures (e.g. for jet pilots G-forces, acceleration/deceleration, and neck traumas during in-flight situations).

Prolonged axial cervical strain in this context is an exception to some degree since this exposure must be considered the dominant one in the studies of head carrying, in which some convergence of findings were found, indicating that this exposure increases the risk of CDSC.

Prolonged tangential or rotational static strain (“extreme” head postures) is probably primarily met in the studies of dentists [132] and grape growers [133]. Indeed, both studies suggested augmented risks of CDSC, but the specific pattern of neck positions was only superficially described. It was not clear to which degree the neck postures were also dynamic, i.e. the repetition of neck movements was not stated. Miners can be presumed to have extra tangential-rotational cervical strain due to the weight of the helmet, but given the vagueness of findings on this occupation they do not further clarify the subject.

Repetitive movements of the cervical spine without external impulse loading are, in the reviewed human literature, only present in the two special settings of patients with spasmodic torticollis (with sudden, repetitive neck movements) and wheelchair users (with frequent repetitive neck flexion/extensions). Both studies displayed an association between patient status and CDSC suggesting that repetitive movements in some circumstances might be a causative factor. This is supported by the animal experiment of Wada [134] where 200.000 neck extension/flexion movements (within physiological motion range) during two months lead to CDSC.

Repetitive movements of the cervical spine with external impulse loading is a somewhat heterogeneous exposure group characterised by differences in the externally applied forces, the direction of the movements, and the degree of repetition. Different types of neck movements combined with external force are undoubtedly present among parachutists, rugby players, boxers and soccer players. Of the six studies treating these special forceful activities, five indicated an elevated risk of CDSC. This indicates that forceful impulse loadings to the cervical spine during a certain period of time are entailed by elevated risk of CDSC. Still, however, the studies did not allow any reasonable clear assessment of exposure-response relations.

Hereto, one must consider that in such forceful activities, also major traumas to the neck are common which can be partly responsible for the elevated risk of CDSC. Major neck trauma as predictor of CDSC, a topic not covered in this review, seems to be only sporadically touched in the literature. In the well-designed population-based study of Irvine [135], however, significant but only slightly higher prevalence of CDSC was recorded in men recollecting head or neck injuries.

Two animal cadaver studies displayed that a combination of prolonged cervical axial strain and repetitive flexion-extensions often produces cervical disc herniation [136;137], but these findings do not have any human epidemiological counterpart at present.

Dose-response

In general, the literature failed to address the issue of dose-response, both in terms of actual exposure and in terms of duration. However, it is possible indirectly to deduce that CDSC does arise in some dose-response manner. For example, carrying loads on the head or on the upper back with a band across the forehead entails a strong strain on the cervical spine. This way of transporting burdens probably was common in ancient times [138] but is now practised only in some developing countries. According to the literature, this is likely to induce degenerative changes in the spine. Although this has no relevance to modern western civilizations, it illustrates that excessive mechanical loads on the spine are capable of giving rise to degenerative changes. The same can be said about work with the head in extreme postures such as prolonged extension, e.g. when a grapegrower is looking upwards much of the time. And it applies to repetitive abnormal, extreme head movements, as has been shown in patients with spasmodic torticollis [139]. Findings in experimental animals point in the same direction.

Gender

It was impossible to conclude whether the relation between physical exposures and CDSC was influenced by gender. Among the very few studies including both genders and not only men, the difference in occupational spectrum was too large to permit any interpretation.

Prognostic factors

The vast majority of studies were of cross-sectional nature. Such a design does not allow disentangling of risk factors precipitating or influencing the course (prognosis) of a condition.

Relation between CDSC and symptoms

Whether associations exist between the varieties of degeneration and symptoms is not clear. The results of eight studies found on this subject went in different directions.

A Jamaican population was compared to a British population and found to have more severe and widespread degeneration yet complained less of symptoms [140]. Echarri [122] also found no correlation between symptoms and degeneration, and noted that the women who had the highest pain scores had the least degenerative changes. In a study of dentists, it was noted that the majority (88%) had degenerative changes but that a minority (39%) had symptoms [141]. In a study of military parachutists, CDSC were associated with stiffness, but not with headaches or neck pain [142].

On the other hand, Humphreys [143] noted no association with symptoms and lordosis or disc height, but an association was found with foraminal width. Siivola [144], in a small study of young people, claimed an association between disc herniation and pain. Two studies reported a significant association: Mahbub [145], in a randomly selected sample of coolies from Bangladesh, reported that neck symptoms were more common in those with degeneration, while Lawrence [146] found that people with disc degeneration had longer duration of pain and loss of work from cervico-brachial pain, and that this was more common in men with major degeneration than in those with minor degeneration.

As a whole, we found no clear association between CDSC and symptoms. In comparison, the question of what is the source of pain has been investigated in the lumbar spine. In a recent report based on a population-generated sample of 40 years old Danish men, who had an MRI-scan of the lumbar spine and responded to a questionnaire on back symptoms and consequences, it was found that disc degeneration, per se, was not clearly associated with pain reporting, but that the presence of Modic changes were [147]. Modic changes are visible on MRI only. They are supposed to consist of cracked vertebral endplates surrounded by oedema in the vertebral body. Almost all persons with Modic changes in that study reported having had low back pain in the past year vs. about 50 % of those with severe disc degeneration without Modic changes. In fact, the prevalence of low back pain among those with severe disc degeneration without Modic changes resembled that among those individuals in the study who did not have severe disc degeneration.

No such investigations have been done on the cervical spine. To our knowledge, only one study is published on the presence of Modic changes in this region [27], which in a retrospective analysis noted a prevalence of 16 % among 118 patients, most common at the C5-6 level.

Grading of evidence

Different systems for grading of evidence are usable, for instance GRADE However, as this is a publication initiated by Danish institutions, we have chosen the system specified by the Scientific Committee of the Danish Society of Occupational and Environmental Medicine, see Appendix 3.

CONCLUSIONS

The amount and quality of the existing literature does not yield a clear picture of possible associations between occupation and degenerative changes in the cervical spine, specific exposures, dose-response relations and gender differences not to mention. On basis of this, the only conclusions that can be drawn are:

There is insufficient evidence of a causal association between CDSC and prolonged tangential or rotational strain (i.e., "extreme" head postures), repetitive movements of the cervical spine without external impulse loading, vibration exposure, diving, sports, heavy work and all occupations dealt with in the existing literature, head carrying being the only exception.

There is limited evidence for an association between CDSC and repetitive movements of the cervical spine with external impulse loading, and for an association between CDSC and prolonged heavy axial cervical strain.

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Appendix 1

Literature search

Data sources

Data sources

The main data source was a systematic literature search employing the *PubMed* and *Ovid Embase* databases from their beginning, i.e. for PubMed 1966 (a minor body of literature however already from 1865), for Embase 1980 and unto the date of the final search. The final literature search was done the 26 June 2008.

In order to make a more comprehensive search for primarily Scandinavian doctoral and PhD theses, additional searches were run in three common Scandinavian librarian databases, i.e. the Danish bibliotek.dk which records all literature of Danish public and research libraries, and two Swedish internet resources Libris (which registers literature of Swedish research libraries and specialised libraries published from 1976 and onwards) and Svemed+, which covers Swedish and much other Scandinavian medical literature from 1977 and onwards.

Search strategy

Concerning the outcomes, a broad approach was applied, which by and large covered any pathology in the cervical spine, at the same time avoiding diffuse searching in the total spine literature. Different free text words and medical subject headings were combined (using Boolean logical operators), including terms such as *neck, neck pain, neck injury, cervical, spine, disc, cervical spine, radiculopathy, cervical spondylosis, cervicobrachial neuralgia, cervical myelopathy, spine, spinal diseases, prolapse, intervertebral disk hernia, intervertebral disk degeneration* and *osteophyte*.

The other search group addressing the exposures and study types of interest covered a broad spectrum of physical-mechanical factors (not single traumas) including both studies of epidemiological and experimental design (see below). In the same manner as with the outcome searches, different free text words and Mesh words were combined with Boolean logical operators. For the partial searches addressing the epidemiological studies, terms as the following were used: *occupational, occupational diseases, occupational exposure, work*, materials handling, physical activity, carry*, transportation, aerospace medicine, vibration, gravitation, G-force*, biomechanics, mechanics, accelerat**, and *sports medicine*.

For the partial searches aiming at human and animal experimental studies, central terms were *cadaver*, anatomic models, in vitro, autopsy, experiment*, human experimentation, animal*, "models, animal"* etc.

As an aid in the searching for background literature regarding non-physical potential risk factors of CDSC, the constructed outcome search syntax was combined (using the Boolean operator "AND") with search terms such as *risk, causality, epidemiology, aetiology, physiopathology* and *pathology* etc.

Searches

The searches below were performed in PubMed. Due to minor differences in indexing terms between databases, smaller changes were made when the searches were run in the Ovid Embase.

In the common librarian databases Svemed+, Libris, and bibliotek.dk the number of hits were much smaller. It was therefore not necessary to combine the outcome searches with exposure study design searches. Moreover, additional but equivalent searches were done in the Scandinavian languages.

Group 1: Outcome search

The final outcome search terms consisted of an anatomical component combined with a pathological-diagnostic component. The anatomical component contained a cervical and a spinal subcomponent.

A. Anatomical component	Search term / search syntax	Number of hits
A1. Cervical items		
A1-1	neck[title/abstract]	97987
A1-2	neck[mesh]	18390
A1-3	neck pain[mesh]	2328
A1-4	neck injuries[mesh]	5051
A1-5	cervical*[title/abstract]	117970
A1-6	cervikal*[title/abstract]	1
A1-comb	A1.1 OR A1.2 OR A1.3 OR A1.4 OR A1.5 OR A1.6	213455
A2. Spinal items		
A2-1	Spine[mesh]	79680
A2-2	Spine[title/abstract]	51408
A2-3	disc[title/abstract]	31776
A2-4	disci[title/abstract]	17
A2-5	discal[title/abstract]	421
A2-6	vertebra*[title/abstract]	88801
A2-7	disk[title/abstract]	17928
A2-8	diski[title/abstract]	0
A2-9	diskal[title/abstract]	69
A2-10	intervertebra*[title/abstract]	9331

A2-11	columna*[title/abstract]	7303
A2-comb	A2-1 to A2-11 combined with OR	215988
A. Combined cervical and spinal items (final anatomical component)		
A1	A1-comb AND A2-comb	31192
A2	cervical vertebrae[mesh]	22742
A3	“Zygapophyseal Joint”[mesh]	439
A4	“Atlanto-Axial Joint”[mesh]	1563
A5	"Atlanto-Occipital Joint"[Mesh]	1107
A-comb	A1 to A5 combined with OR	38699

B. Pathological-diagnostic component	Search term / search syntax	Number of hits
B1	"spinal diseases"[MeSH Terms]	72642
B2	"radiculopathy"[MeSH Terms]	2321
B3	"prolapse"[MeSH Terms] AND "spine"[Mesh]	21
B4	"prolapse"[MeSH Terms] AND "spinal diseases"[Mesh]	15
B5	"Spine/abnormalities"[Mesh]	5185
B6	"Spine/pathology"[Mesh]	11814
B7	"Spine/physiopathology"[Mesh]	4589
B8	"osteophyte"[Mesh]	48
B9	“Zygapophyseal Joint/anatomy and histology”[mesh]	221
B10	"Zygapophyseal Joint/pathology"[Mesh]	140
B11	"Zygapophyseal Joint/physiology"[Mesh]	165
B12	"Zygapophyseal Joint/physiopathology"[Mesh]	100
B13	“Atlanto-Axial Joint/anatomy and histology”[mesh]	393
B14	"Atlanto-Axial Joint/pathology"[Mesh]	234
B15	"Atlanto-Axial Joint/physiology"[Mesh]	203
B16	"Atlanto-Axial Joint/physiopathology"[Mesh]	154
B17	“Atlanto-Occipital Joint/anatomy and histology”[mesh]	421
B18	"Atlanto-Occipital Joint/pathology"[Mesh]	125
B19	"Atlanto-Occipital Joint/physiology"[Mesh]	133
B20	"Atlanto-Occipital Joint/physiopathology"[Mesh]	79
B21	spondylos*[title/abstract]	1879
B22	spondylar*	2002
B-comb	B1 to B22 combined with OR	86621
Final outcome search	A-comb AND B-comb	15297

Group 2. Exposure and study type search

The total exposure and study type syntax consisted of a search group concerning occupational and physical exposures, a search group concerning sporting activities and a search group concerning experimental human or animal studies. The search group concerning experimental studies generated especially large amounts of literature on non-relevant topics. Therefore some search limitations were applied as specified below. A corresponding strategy was employed in Ovid Embase.

Occupational and physical-mechanical exposures	Search term / search syntax	Number of hits
C1	Workplace[mesh]	7586
C2	Workload[mesh]	10022
C3	Work[mesh]	10233
C4	Occupational Exposure[mesh]	36890
C5	Occupational Medicine[mesh]	20919
C6	Occupational Diseases[mesh]	91933
C7	Occupational Health[mesh]	18330
C8	Occupational Groups[mesh]	322618
C9	Industry[mesh]	160204
C10	Employment[mesh]	39260
C11	Occupations[mesh]	22180
C12	work[title/abstract]	352059
C13	working[title/abstract]	102077
C14	worke*[title/abstract]	105158
C15	workload*[title/abstract]	10882
C16	workplace*[title/abstract]	15104
C17	work-relat*[title/abstract]	6275
C18	occupati*[title/abstract]	83287
C19	miner[title/abstract]	477
C20	miners*[title/abstract]	3654
C21	mining[title/abstract]	7143
C22	minework*[title/abstract]	75
C23	rural[All Fields]	80922
C24	dentist*[title/abstract]	42548
C25	lumberjack*[title/abstract]	68
C26	porter*[title/abstract]	1003
C27	coolie*[title/abstract]	7
C28	stevedore*[title/abstract]	19
C29	woodbear*[title/abstract]	1
C30	slaughterhouse work*[title/abstract]	69
C31	docker*[title/abstract]	214
C32	"meat carrier"[title/abstract]	0
C33	"meat carriers"[title/abstract]	0
C34	heavy worker*[title/abstract]	20
C35	bearer*[title/abstract]	1009
C36	"transportation"[mesh]	39326
C37	"aerospace medicine"[mesh]	12105
C38	driving[title/abstract]	25798

Occupational and physical-mechanical exposures (continued)	Search term / search syntax	Number of hits
C39	driver*[title/abstract]	11456
C40	automobile*[title/abstract]	4095
C41	car[title/abstract]	8943
C42	"motor vehicle"[title/abstract]	6319

C43	"motor vehicles"[title/abstract]	1059
C44	aviat*[title/abstract]	3443
C45	flight*[title/abstract]	24984
C46	aeroplane*[title/abstract]	109
C47	airplane*[title/abstract]	729
C48	aircraft*[title/abstract]	3913
C49	pilot*[title/abstract]	55234
C50	fighter*[title/abstract]	850
C51	helicopter*[title/abstract]	1767
C52	"Automobile Driving"[mesh]	10004
C53	vibration[mesh]	13984
C54	vibrat*	34496
C55	gravitation	11233
C56	Gz	1591
C57	gravity	23759
C58	G-force*	306
C59	biomechanics	523014
C60	mechanics	507208
C61	lifted	1693
C62	lifting	8418
C63	load*	162112
C64	carry*	99155
C65	carried	270732
C66	bearing	89620
C67	burden	47412
C68	"material handling"	140
C69	"Cumulative Trauma Disorders"	2639
C70	repetit*	69729
C71	overuse	3288
C72	cumulat*	58085
C73	strenuous	3287
C74	strain*	643430
C75	unphysiological*	699
C76	nonphysiological*	700
C77	non-physiological*	805
C78	stress	353363
C79	accelerat*	112076
C80	decelerat*	7544
C81	"Human Engineering"[Mesh]	32029
C82	ergonomic*[title/abstract]	4286
C83	climate	34146
C84	draft*	5934
C85	draught*	240
C86	weather	321711
C87	temperature	444935
C88	cold*	86234
C89	heat*	206722
C-comb	C1 to C89 combined with OR	2826660

Sporting activities	Search term / search syntax	Number of hits
D1	sports[mesh]	74764
D2	“sports medicine”[mesh]	8039
D3	“athletic injuries”[mesh]	15817
D4	barotrauma[mesh]	5438
D5	sport*[title/abstract]	25807
D6	jumper*[title/abstract]	451
D7	gymnast*[title/abstract]	1767
D8	athlet*[title/abstract]	22392
D9	parachute*[title/abstract]	466
D10	soccer*[title/abstract]	2087
D11	football*[title/abstract]	2830
D12	rugby*[title/abstract]	885
D13	swimm*[title/abstract]	12816
D14	diver[title/abstract]	619
D15	diving[title/abstract]	3576
D16	jockey*[title/abstract]	178
D17	riding[title/abstract]	2025
D-komb	D1 to D17 combined with OR	118084
Experimental studies		
E1	“anatomic models"[Text Word]	9261
E2	"models, anatomic"[MeSH Terms]	10671
E3	models, anatomic[Text Word]	9231
E4	cadaver*[title/abstract]	30605
E5	cadaver[mesh]	28431
E6	autopsy	67348
E7	"in vitro"[Publication Type]	349023
E8	"in vitro"[title/abstract]	650909
E9	"in vivo"[title/abstract]	448755
E10	"dissection"[MeSH Terms]	5702
E11	dissec*[title/abstract]	79347
E12	specimen*[title/abstract]	194807
E13	experiment*[title/abstract]	1013984
E14	Human Experimentation[MeSH Terms]	10079
E15	Humans[Mesh]	10280879
E16	"animals"[MeSH Terms:noexp]	4233908
E17	“Models, animal”[Mesh]	294861
E18	animal*[title/abstract]	599932
E19	porcine[title/abstract]	46231
E20	swine*[title/abstract]	23216
E21	pig[title/abstract]	96951
E22	pigs[title/abstract]	74389
E23	rat[title/abstract]	650237
E24	rats[title/abstract]	558363
E25	goat*[title/abstract]	19228
E26	monkey*[title/abstract]	67050
E27	sheep[title/abstract]	62560
E28	rabbit*[title/abstract]	203046
E29	canin*[title/abstract]	56192

Experimental studies (continued)	Search term / search syntax	Number of hits
E30	mouse[title/abstract]	324173
E31	mice[title/abstract]	431273
E32	caprine[title/abstract]	1803
E33	dog[title/abstract]	65016
E34	dogs[title/abstract]	109623
E35	cow[title/abstract]	12651
E36	cows[title/abstract]	23200
E-comb	E1 to E36 combined with OR	13999909
Limitations **(applied on experimental studies)**		
Limitations as regards disease, specialty etc.		
F1	NOT Dislocations[MeSH Terms]	-
F2	NOT "Surgical Fixation Devices"[MeSH Terms]	-
F3	NOT "Prostheses and Implants"[MeSH Terms]	-
F4	NOT Spondylarthropathies[MeSH Terms]	-
F5	NOT "Fractures, Bone"[MeSH Terms]	-
F6	NOT "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[MeSH Terms]	-
F7	NOT "Hyperostosis, Diffuse Idiopathic Skeletal"[MeSH Terms]	-
F8	NOT Vertebral Artery Dissection[MeSH Terms]	-
F9	NOT therapeutics[mesh]	-
F10	NOT "surgical procedures, operative"[MeSH Terms]	-
F11	NOT "specialties, surgical"[MeSH Terms]	-
F12	NOT "whiplash injuries"[MeSH Terms]	-
F13	NOT "Bone Diseases, Metabolic"[MeSH Terms]	-
F14	NOT "Spinal Cord Injuries" [MeSH Terms]	-
F15	NOT Paleontology[MeSH Terms]	-
F16	NOT "Toxic Actions"[MeSH Terms]	-
F17	NOT "Neurodegenerative Diseases"[MeSH Terms]	-
F-Comb	F1 to F17 combined with AND	-
Limitations as regards language		
G1	English[lang]	-
G2	German[lang]	-
G3	Danish[lang]	-
G4	Norwegian[lang]	-
G5	Swedish[lang]	-
G-comb	G1 to G5 combined with OR	

Limitations (continued)	Search term / search syntax	Number of hits
Limitations as regards study design and publication type		
H1	Clinical Trial[ptyp]	-
H2	Meta-Analysis[ptyp]	-
H3	Randomized Controlled Trial[ptyp]	-
H4	Review[ptyp]	-
H5	Classical Article[ptyp]	-
H6	Clinical Trial, Phase I[ptyp]	-
H7	Clinical Trial, Phase II[ptyp]	-
H8	Clinical Trial, Phase III[ptyp]	-
H9	Clinical Trial, Phase IV[ptyp]	-
H10	Comment[ptyp]	-
H11	Comparative Study[ptyp]	-
H12	Controlled Clinical Trial[ptyp]	-
H13	Corrected and Republished Article[ptyp]	-
H14	Duplicate Publication[ptyp]	-
H15	Evaluation Studies[ptyp]	-
H16	Historical Article[ptyp]	-
H17	Journal Article[ptyp]	-
H18	Published Erratum[ptyp]	-
H19	Scientific Integrity Review[ptyp]	-
H20	Twin Study[ptyp]	-
H21	Validation Studies[ptyp]	-
H-comb	H1 to H21 combined with OR	-
Final search as regards experimental studies		
I-comb	E-comb AND F-comb AND G-comb AND H-comb	3710426

Final combined searches (Group 1 and Group 2 in combination)

J1	C-comb AND Final outcome search	2040
J2	D-comb AND Final outcome search	244
J3	I-comb AND Final outcome search	478
Final search	J1 OR J2 OR J3	2471

In addition to the literature searches addressing physical risk factors of CDSC described above, a number of supplementary searches, addressing the literature on non-physical potential risk factors were performed. In these searches, the aforementioned final outcome search was combined (using the Boolean operator “AND”) with search terms including *risk, causality, epidemiology, aetiology, physiopathology* and *pathology*, *tobacco, tobacco use disorder, smoking, cigar**, *Body Weight, obes*, Nutrition Disorders, life-style, Biometry, Disease susceptibility, recurrence, prognosis, disease progression* and *rheumatoid arthritis/complications.*

Appendix 2

CHECKLIST FOR NECK-STUDIES

1. First author	
2. Year of publication	
Basic criteria fulfilled?	a) Age issues (narrow band, report by subgroups or statistical control) Yes□ No□ b) Imaging employed: X-ray □ CT □ MRI □
3. Design	cross-sectional □ prospective □ RCT □ retrospective □ case-control □ register □
4. Country of study/ethnicity of study population	
5. Type of study population	
6. Age description	
7. Size ***study group N*** Response rate % Response rates follow up %	
8. Size ***control group N*** Response rate % Response rates follow up %	
9. Definitions of degeneration (including severity)	
10. Definition of potential risk factors (including dose in amount or duration)	
11. Summary of results in relation to degeneration	

(summary of results continued)	
12. Comments	

Quality score	Yes clearly = 2 Yes reasonably = 1 Not really or no = 0 Not applicable (NA)
Sampling bias	Score:
E.g. data source (target population) well described; sampling method suitable; matching satisfactory; size of study sample substantial; response rates sufficiently high; comparison of responders and non-responders reveals no major differences; description of study sample indicates no anomalies	
Outcome variables	Score:
E.g. clear definition of variables; method of measurement has previously been validated; method of measurement has previously been validated and found acceptable; method of measurement is validated in present study; method of measurement is investigated for inter-examiner reliability; method of measurement is investigated for intra-examiner reliability; method of measurement is investigated for repeatability	
Potential predictor variables	Score:
E.g. clear definition of each relevant predictor variable; method of measurement has previously been validated; method of measurement has previously been validated and found acceptable; method of measurement is validated in present study; method of measurement is investigated for inter-examiner reliability; method of measurement is investigated for intra-examiner reliability; method of measurement is investigated for repeatability	
Information bias	Score:
E.g. image interpretation done blindly when needed?	
Data analysis	Score:
E.g. was the study sample sufficiently large for all analyses? (N=50 for one variable, **+ 10?** for each additional variable); were the variables utilized sufficiently (e.g. dose response)? Was the choice of confounders/modifiers explained or tested for? Were all the results reported (not only the positive ones)? Was statistical significance tested or confidence intervals reported, where relevant?	

Appendix 3

Criteria for grading evidence of causality

Criteria for assessing the degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome, as specified by the Scientific Committee of the Danish Society of Occupational and Environmental Medicine.

Strong evidence of a causal association [+++]

A causal relationship is *very likely*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association [++]

A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association [+]

A casual relationship is *possible*. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association [0]

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association [–]

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments

The classification does not include a category for which a causal relation is considered as established beyond any doubt. The key criterion is the epidemiological evidence. The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of ”high quality” studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of causal association.

Evidence tables

Evidence Table 1

General or clinical populations

Author Year Country	Population	Study design	Sample sizes Resp. rate %	Type of degeneration	Results	Quality score Blind assessment Yes/No
Bremner 1968 Jamaica	General population 35-64 years old	Cross-sectional	536 89 %	X-ray Uncovertebral arthrosis "Disc degeneration" Standard Atlas of Radiographs	More common and more severe disc degeneration in Jamaicans (65 %) than in Europeans (39 %).	10/10 Yes
Ernst 2005 Belgium	Volunteers	Cross-sectional	30 ? %	MRI-scan Anular tear Bulging and protrusion according to Jensen 1994 Reduced disc height Disc intensity	Degenerative changes frequently found in an asymptomatic population. Positive age association.	5/10 No
Hartwig 2003 Germany	Patients seeking a private clinic for workers compensation	Retrospective	153 with work stress on lumbar	X-ray Reduced disc height Osteophytes Grading according to Kellgren	No correlation between cervical degenerative changes and lumbar load. Positive age association.	5/10 No

			spine and 333 without ? %			
Humphreys 1998 USA	Symptomatic and asymptomatic volunteers	Cross-sectional	43 ? %	MRI-scan Curvature deviance Reduced disc height Spinal canal diameter	Age positively associated with facet hypertrophy and foraminal narrowing, but not with ratio cord/canal. Symptomatic persons have narrower foramen.	4/10 No
Irvine 1965 UK	General population. Sample drawn randomly from GP's register	Cross-sectional	490 94.5 %	X-ray Reduced disc height Osteophytes	Association with age and gender. 20-29 years: 13 % in ♂, 5 % in ♀. 60-69 years: 98 % in ♂, 91 % in ♀. More prevalent in miners with heavy work, and in men with a history of head trauma	10/10 Yes
Kopacz 1999 USA	Patients X-rayed for other reasons than neck pain	Descriptive	454 67 % 174 selected for study	X-ray Spondylolisthesis	5.2 % had 2-4 mm anterior spondylolisthesis at one level. No association with age.	6/8 No

Lawrence 1969 UK and Rhondda	3 general populations in UK and 1 in Rhondda above 14 years of age	Cross-sectional	3947 86 %	X-ray Reduced disc height Standard Atlas of Radiographs	Association with age, but not clearly with occupation. Overall prevalence 42 % in ♂ and 37 % in ♀. Prevalence 3 % at 15 years, 100 % at 65. More severe changes and more discs involved in men.	7/10 Yes
Lee 2001 Hong Kong	Patients with cervical X-rays	Retro-spective study	150 ? %	X-ray C5 only Sclerosis of the vertebral endplates	Endplate sclerosis increases with age. No correlation with neck pain.	10/10 Yes
Lehto 1994 Finland	Four asymptomatic age groups. Origin not stated (1. schoolchildren, 2. medical students, 3. doctors and sedentary workers, 4. not described)	Cross-sectional	89 ? %	MRI-scan Disc intensity Graded according to Tertti	Degenerative changes are common in asymptomatics after 30 years and increases with age. No gender difference.	7/10 No, but 2/3 radiologists must agree
Matsumoto 1998 Japan	Asymptomatic volunteers with a variety of occupations	Cross-sectional	497 ? %	MRI-scan Reduced disc height Disc bulging Foraminal narrowing Disc intensity Other rating scale	Degeneration increases linearly with age, is seen in 12-17 % of discs in the twenties and 86-89 % above 60 years. No gender differences except that	9/10 Yes

					posterior disc protrusion is more common in females.	
Obisesan 1999 Nigeria	Women requesting cervical X-rays but not for trauma	Cross-sectional	400 ? %	X-ray Modified Grading according to Kellgren	Degeneration commences in the fourth decade and progresses with age.	5/10 No
Siivola 2002 Finland	Randomly selected high school students	Cross-sectional study as part of a prospec-tive study	15 cases with neck and shoulder pain and 16 without ? %	MRI-scan Curvature deviance Disc intensity Anular tear Disc bulging Disc herniation Uncovertebral arthrosis Other rating scale	MRI-scan findings common. No clear correlation with pain.	8/10 Yes
Zapletal 1997 Holland	Patients referred for radiographs of nasal sinuses	Retrospective	355 NA	X-ray Uncovertebral arthrosis Narrowing of atlantoaxial joint space, articular osteophytes and subchondral sclerosis	No abnormalities before sixth decade, linear progression with age thereafter: 5.4 % in the sixth decade, 18.2 % in the ninth.	8/10 No

Evidence Table 2

Various occupations

Author Year Country	Population	Controls	Study design	Sample sizes Response rates %	Exposure measure	Type of degeneration	Results	Quality score Blind assessment (Yes/No)
Bartsch 2001 Germany	Professional military divers	Non-divers	Cross-sectional	24 divers ? % 24 controls ? %	Diving years	MRI-scan Disc bulging Bulging and protrusion according to Jensen 1994	No increased prevalence of disc protrusion in divers.	6/10 Yes
Beck 1951 Germany	Miners using compressed air tools	People not using air-tools: heavy workers, "brain workers" and women (!)	Cross-sectional	500 miners ? % 500 controls ? %	Use of air-tools yes/no	X-ray No definitions	No differences	1/10 No
Hult 1954 Sweden	Forest workers and industrial workers	Internal	Cross-sectional	114 forest workers ? % 163 industrial	Job title	X-ray Reduced disc height Osteophytes	Findings more frequent and earlier in forest workers. Positive	6/10 No

				workers ? %		Other rating scale	age association.	
Hult 1954 Sweden	Only men: shop assistants, light sedentary workers, light industry workers, stevedores, and workers in heavy food industry, construction, and heavy metal industry	Internal	Cross-sectional	666 with heavy jobs % ? 471 with light jobs ? %	Heavy work or light work	X-ray Reduced disc height Osteophytes Other rating scale	Changes develop earlier in heavy work than in light work, but no difference for pronounced degeneration. Positive age association (prevalence 5 % by 25-29, 90 % by 59).	6/10 No
Irvine 1965 UK	General population. Sample drawn randomly from GP's register	Internal	Cross-sectional	490 94.5 %	Job with more than 10 years experience. Heaviness of work. Previous head trauma	X-ray Reduced disc height Osteophytes	More prevalent in miners with heavy work, and in men with a history of head trauma. Association with age and gender.	10/10 Yes
Jensen 1996	Nationwide in-hospital register: All	Internal: Type of driving.	Register	89,146 male drivers	Professional driving	Disc herniation	Association between frequency	6/8

Denmark	professional drivers treated for prolapsed cervical disc	Comparison to all economically active people in Denmark			yes/no Types of work	Hospital diagnosis	of hospitalization for herniation and professional driving. Drivers with heavy lifting had lower ratio (137) than those without (184).	NA
Jung 1975 Germany	Patients referred to an X-ray department for other reasons than neck pain: office workers, drivers, machine workers, heavy workers	Internal	Cross-sectional	510 males ? %	Job title Type of sport	X-ray Reduced disc height Osteophytes Uncovertebral arthrosis Sclerosis of the vertebral endplates Curvature deviance	No association with work. Boxing increases frequency. Positive age association.	3/10 No
Katevuo 1985 Finland	Dentists	Farmers	Cross-sectional	119 dentists 82 % 192 farmers ? %	Job title	X-ray Reduced disc height Sclerosis of the vertebral endplates Osteophytes Uncovertebral	Changes in 52 % of dentists and 19 % of farmers. Positive age association.	7/10 Yes

						arthrosis		
Kellgren 1952 UK	Underground miners, other manual workers, office workers	Internal	Cross-sectional	84 miners 89 % 45 other manual workers 95 % 42 office workers 89 %	Job titles	X-ray Reduced disc height Osteophytes Sclerosis of the vertebral endplates Vertebral body shape Mobility Other rating scale	No significant differences between occupational groups.	6/10 Yes
Kellgren 1958 UK	Random sample of 55-64 years old	Internal	Cross-sectional	481? 79 %?	Job titles	X-ray Reduced disc height Osteophytes Collins rating scale	Prevalence in men 83 %, in women 72 %. CDSC more pronounced in men. Cotton workers a little more CDSC than miners and “others”.	5/10 No
Lawrence 1961 UK	Employees at cotton mills ≥45 years of age Previously studied random sample added	Non-manual workers	Cross-sectional	Unclear 197? 87 %? 345 (?) added from a previous	Various tasks at a mill	X-ray Grading according to Kellgren	Less changes in cotton mill workers than in controls. Positive age association. Females had more discs affected.	8/10 Yes

				study ? %				
Lawrence 1969 UK and Rhondda	Three general populations in UK and one in Rhondda above 14 years of age	Internal	Cross-sectional	3947 86 %	Job titles	X-ray Reduced disc height Standard Atlas of Radiographs	No clear association with occupation although most severe forms were seen in manual workers. Association with age.	7/10 Yes
Mustajoki 1978 Finland	Parachutists	Volunteers	Cross-sectional	50 parachutists ? % 50 volunteers ? %	Number of jumps	X-ray Reduced disc height Osteophytes Uncovertebral arthrosis	Association with parachuting (40 % versus controls 20 %). Dose-response relation. Positive age association.	7/10 Yes
Rellan 1969 India	Sedentary workers, housewives, moderately heavy manual workers, heavy manual workers, scooter rickshaw drivers	Internal	Cross-sectional	250, fifty in each group ? %	Heaviness of work; rickshaw driving	X-ray Reduced disc height Osteophytes	More CDSC in heavy manual workers and rickshaw drivers than in sedentary workers and housewives.	4/10 No
Schröter 1959	Patients in an occupational medical	Internal	Retro-spective	100, 113, 84 and 90	Job title	X-ray “Spondylosis” or	Dentists same frequency as	3/9

Germany	clinic: carriers, office workers, miners and dentists			respectively. NA		"osteochondrosis"	others, but more severe changes.	No
Takamiya 2006 Japan	Grape growers	Eggplant growers	Cross-sectional	177 grape growers ? % 191 eggplant growers ? %	Working years	X-ray Osteophytes Reduced disc height Jäger's scoring system	Work with neck extension (grape growing) asso-ciated with dege-nerative changes. Positive age association.	7/10 Yes
Tsirikos 2001 Greece	Jockeys	?	Prospec-tive	32 jockeys ? % 35 controls ? %	Professional horse riding yes/no	X-ray Other rating scale	Claims higher incidence in jockeys.	3/10 No
Zejda 2003 Poland	Coalminers with hand-arm vibration disease	Blue collar surface workers with non-specific neck complaints	Cross-sectional	685 miners ? % 68 controls ? %	Duration of employment	X-ray Reduced disc height Osteophytes	Age the only explanatory variable.	6/10 No

Ålund 1994 Sweden	Former steel work grinders with neck symptoms	White collar workers Patients with light work X-rayed because of minor neck or head trauma or neck complaints	Cross-sectional	15 grinders ? % 15 office workers ? % 15 patients ? %	Heaviness of work	X-ray Reduced disc height Spondylolisthesis Curvature deviance Foraminal narrowing Uncovertebral arthrosis Other rating scale	More foraminal narrowing in the grinders because of osteophytes, but disc height the same.	6/10 Yes

Evidence Table 3

Pilots

Author Year Country	Population	Controls	Study design	Sample sizes Response Rates %	Exposure measure	Type of degene-ration	Results	Quality score Blind assessment (Yes/No)
Aydog 2004 Turkey	Jet pilots Transport pilots Helicopter pilots	Office workers Traffic control workers	Cross-sectional	Exposed: 732 ? % Controls: 202 ? %	Type of aircraft. Total flying hours	X-ray Sclerosis of the vertebral endplates Curvature deviance Reduced disc height Vertebral body shape Spondylolisthesis Osteophytes Disc herniation	Helicopter pilots and tall jet pilots had more degenerative changes, but the helicopter pilots were 2-3 yrs older and had more flying hours than the rest. Positive age association.	7/10 No, but 2 radiologists and a 3rd if disagreement
Hämäläinen 1993 Finland	Pilots	Ground personnel in the air force	Cross-sectional	12 exposed ? % 12 controls	Pilot yes/no	MRI-scan Disc bulging Other rating	C3/C4 more degenerated in pilots, not the other discs	6/10 Yes

				(one later excluded because of anatomical variation) ? %		scale		
Hendriksen 1999 Holland	Pilots	Student pilots	Cross-sectional	188 exposed ? % 128 controls ? %	Flying hours	X-ray Osteophytes Curvature deviance Reduced disc height?	No consistent associations	8/10 Yes
Landau 2006 Israel	Jet pilots Transport pilots Helicopter pilots	Internal	Cross-sectional	10 in each group	Type of aircraft, total flight hours and current weekly hours.	MRI-scan Disc herniation Foraminal narrowing Osteophytes Disc bulging Other rating scale	Degenerative findings not associated to air craft type, but to age. Dose-response not reported.	6/10 Yes
Mason 1996 USA	All army aviators		Register 1987-92	Not reported	Registrated as an aviator	Disc herniation	Rate increasing over time for unknown reasons	6/8 NA
Petrén-Mallmin 1999	Asymptomatic experienced pilots and	Volunteering non-pilots	Cross-sectional	Exposed: 16 ? %	Flying experience	MRI-scan Disc bulging Osteophytes	More degenerative changes in experienced pilots than in controls	6/10 Yes

Sweden	young pilots			Controls: 13 ? %		Foraminal narrowing Uncovertebral arthrosis Reduced disc height Disc intensity Other rating scale		
Petrén-Mallmin 2001 Sweden	Pilots	Volunteering non-pilots	Follow-up	Exposed: 14 87 % Controls: 14 93 %	Pilot yes/no	MRI-scan Disc bulging Osteophytes Foraminal narrowing Reduced disc height Disc intensity Other rating scale	Fighter pilots at increased risk in young age, but the difference diminishes with age	7/10 Yes

Evidence Table 4

Head carriers

Author Year Country	Population	Controls	Study design	Sample sizes Response rates %	Exposure measure	Type of degeneration	Results	Quality score Blind assessment (Yes/No)
Echarri 2002 Congo	Women carrying wood on the head during ≥12 years	Women not with the same occupation	Cross-sectional	72 exposed ? % 44 controls ? %	Duration of work	X-ray Reduced disc height Vertebral body height Spinal canal diameter Spondylolisthesis Osteophytes Curvature deviance Grading according to Kellgren	More degenerative changes in younger woodbearers. No gender difference.	4/10 No
Echarri	Two groups of	Controls:	Cross-	Exposed	Duration of	X-ray	Load bearing on the	3/10

2005 Congo	head carriers: 1. carrying heavy loads 2. carrying bundles	Building and industry workers	sectional	group 1: 28 72 % Exposed group 2: 33 72 % Controls: 36 86 %	work	Osteophytes Spondylolisthesis Vertebral body shape Curvature deviance Grading according to Kellgren	head associated to more degenerative signs, particularly heavy loads. Positive age association.	No
Jäger 1997 Sierra Leone (same material as Mehring 1998?)	Head porters attending clinic for diseases unrelated to neck. No past history of neck injury or arthritis, no pain or stiffness at time of study.	Non-head porters. No past history of neck injury or arthritis, no pain or stiffness at time of study.	Cross-sectional	35 ? % 35 ? %	Duration of work and average weight of load. Heavy and light loads	X-ray Reduced disc height Osteophytes Other rating scale	Carriers more frequently degenerative changes (88.6 %) than controls (22.9 %). Positive dose-response relation. Positive age association. No gender differences.	8/10 Yes
Joosab 1994 Zimbabwe	Victims of assault and road accidents who during work carried loads on the head	Victims of assault and road accidents not carrying loads on the head	Cross-sectional	20 exposed ? % 25 controls ? %	Load carrying yes/no	X-ray Curvature deviance Spinal canal diameter Reduced disc height	No association with head-carrying, but positively with age.	1/10 No

Mahbub 2006 Bangladesh	Random sample of coolies who had worked for >1 year and had no history of neck injury	NA	Cross-sectional	98 98 %	Duration of occupation. Weight of loads.	X-ray Osteophytes Reduced disc height	Positive association with duration of occupation, weight of loads carried on the head and with age.	4/10 No
Mehring 1998 Sierra Leone	Professional head carriers treated for other reasons than neck trouble	Matched non-carriers	Retro-spective	35 exposed ? % 35 controls ? %	Weight-time-dose	X-ray Reduced disc height Osteophytes Other rating scale	Head carriers more degenerative changes than non-carriers. Positive age association.	6/10 Yes (probably same material as Jäger 1997)

Evidence Table 5

Sports

Author Year Country	**Population**	**Controls**	**Study design**	**Sample sizes** **Response rates %**	**Exposure measure**	**Type of degene-ration**	**Results**	**Quality score** **Blind assess-ment (Yes/No)**
Berge 1999 France	Rugby players	Non-playing healthy volunteers without history of neck problems	Cross-sectional	47 exposed ? % 40 controls ? %	Rugby yes/no	MRI-scan Modic changes Curvature deviance Spinal canal diameter Vertebral body height Vertebral body shape Sclerosis of the vertebral endplates Osteophytes	Rugby players more changes than controls. Positive age association.	4/10 No

Jung 1975 Germany	Patients referred to an X-ray department for other reasons than neck pain: office workers, drivers, machine workers, heavy workers	Internal	Cross-sectional	510 males ? %	Job title Type of sport	X-ray Reduced disc height Osteophytes Uncovertebral arthrosis Sclerosis of the vertebral endplates Curvature deviance	No association with work. Boxers more changes. Positive age association.	3/10 No
Kartal 2004 Turkey	1: Active soccer players < 30 years of age 2: Veterans >30 years of age who had played ≥10 years	Age matched university students and staff	Cross-sectional	Exposed: 1: 15 ? % 2: 15 ? % Controls: 1: 13 ? % 2: 15 ? %	Active soccer playing at least 10 years	X-ray MRI-scan Spondylolisthesis Curvature deviance Uncovertebral arthrosis Spinal canal diameter Ankylosis	A tendency towards early changes in soccer players. Positive age association.	6/10 Yes
Mundt 1993 USA	Patients with neck pain <1 yr with radio-logical evidence of	Patients without neck pain in the same age range	Case-control	68 cases ? % 63 controls	Type of sport	Disc herniation X-ray	No association between sports and herniation. No asso-	5/8 No

	discal hernia			? %		CT-scan MRI-scan	ciation with age.	
Reul 1995 Germany	Amateur SCUBA-divers	Non-diving sportspeople	Cross-sectional	52 exposed ? % 50 controls ? %	Diving more than 4 years	MRI-scan Disc bulging Disc herniation	More disc bulging/herniated discs in divers (46) than in controls (13)	7/10 Yes
Scher 1990 South Africa	Volunteer asympto-matic rugby players selected to fit into one of three age groups	Persons referred for X-ray (of what?) but without neck or arm pain	Cross-sectional	150 exposed ? % 150 controls ? %	Rugby yes/no	X-ray Reduced disc height Sclerosis of the vertebral endplates Osteophytes Uncoverteb ral arthrosis	Higher frequency of changes in rugby players. Positive age association.	4/10 No
Sortland 1982 Norway	Former soccer players at the national Norwegian team	Working people without history of neck trauma	Cross-sectional	43 exposed ? % 43 controls ? %	Soccer yes/no ???	X-ray Osteophytes Reduced disc height? Other rating scale	Earlier onset and higher frequency in soccer players.	5/10 No

Evidence Table 6

Abnormal movements

Author Year Country	Population	Controls	Study design	Sample sizes Response rates %	Exposure measure	Type of degeneration	Results	Quality score Blind assessment (Yes/No)
Chawda 2000 UK	Patients with spasmodic torticollis referred for surgery	Internal	Descriptive	34 conse-cutive ? %	Duration and severity of torticollis	CT-scan Uncovertebral arthrosis	Arthrosis predominantly found on the side of the main direction of the head turns, and mainly at level C2/C3 and C3/C4.	8/10 No
Ebara 1989 Japan	Patients with athetoid cerebral palsy	None	Descriptive	57 ? %	Athetoid movements	X-ray Spondylolisthesis Rotation Curvature deviance	Segmental instability "proved to be common" . "Whether instability leads to premature spondylosis still remains unsolved."	4/10 No
Kojima 1997 Japan	Wheelchair users because of spinal cord damage	Whiplash injured	Case-control	87 cases ? % 200 controls ? %	Duration of use of wheelchair	X-ray "Spondylosis"	Spondylosis more frequent in paraplegics. Positive age association.	3/10 No

Evidence Table 7

Animal experiments

Author Year Country	**Experimental animals**	**Controls**	**Experiment**	**Sham experi-ment Yes/No**	**Type of degenera tion**	**Results**	**Quality score**
Baogan 2000 China	10 rabbits	10 rabbits	Posterior paravertebral muscles detached and posterior ligaments resected. Rabbits killed 3 and 8 months postoperatively.	Yes	Histologi c examinati on	Osteophytes arise from proliferation of articular cartilage through endochondral ossification. Operated animals showed more degenerative changes, and after 3 months the findings in operated animals were similar to those in controls after 8 months.	8/10
Kimura 1996 Japan	25 transgenic mice with collagen defect	20 non-transgenic mice	Killed at intervals up to the age of 26 months.	NA	X-ray Reduced disc height Osteophyt es Spondylol isthesis Histologi	Disc degeneration more advanced in transgenic mice.	7/10

					c examinati on Other rating scale		
Mason 1984 UK	28 mice from a strain with heritable kyphosis	28 mice without heritable kyphosis	Both groups killed at ages of 50 and 252 days, respectively.	NA	Histologi c examinati on Various changes	In kyphotic mice degenerative changes were found between C5 and T3 with individual variation.	6/10
Miyamoto 1991 Japan	30 ICR-strain mice	28 normals	Posterior paravertebral muscles detached, spinous processes with ligaments resected, 1/3 killed after 2, 6 and 12 months, respectively.	No	X-ray Reduced disc height Osteophyt es Spondylol isthesis Histologi c examinati on Other rating	Radiologically degenerative changes were seen in all operated animals 12 months after operation, but not before and not in controls. Histological changes appeared already 2 months postoperatively.	8/10

					scale		
Wada 1992 Japan	10 female rabbits	10 rabbits	Electrodes implanted unilaterally in trapezius muscle. Cyclic stimulation resulting in muscle contrac-tions during three periods up to three months.	Various doses	X-ray Histologic examination Vernon-Roberts grading system	In the most exposed group (200.000 cycles during 2 months) degenerative changes were shown to be more frequent and more pronounced histologically, but no changes visible radiologically.	7/10
Wang 2006 China	30 rats	30 rats	Posterior paravertebral muscles detached, ligaments excised. Killed at intervals.	Yes	Histologic examination Bioche-mical analyses	Progressive degenerative changes with inflammation from 3 months on in the experimental group.	10/10

Evidence Table 8

Twin studies

Author Year Country	Population	Type of twin study	Sample sizes MZ DZ	Types of degeneration	Results	Quality score Blind assessment (Yes/No)
Palmer 1984 USA	Twins without cervical spine complaints	Convenience MZ-DZ study	23 pairs/200 who had a co-twin living near by	X-ray Reduced disc height Osteophytes Spondylolisthesis Vertebral body shape	"Twins look alike". Results reported in a narrative fashion.	0/10 No
Sambrook 1999 UK and Australia	Responders to advertisements with blinded purpose	Twin control study	86 MZ pairs 77 DZ pairs	MRI-scan Reduced disc height Disc intensity Osteophytes Standard Atlas of Radiographs	About 2/3 of the variability of cervical degeneration is genetically determined.	9/10 Yes

				Other rating scale		

Evidence Table 9

Smoking

Author Year Country	Population	Controls	Study design	Sample sizes Response rates %	Exposure measure	Type of degenera-tion	Results	Quality score Blind assessment (Yes/No)
An 1994 USA	Consecutive patients with pro-lapsed disc (con-firmed through symptoms/signs, imaging and surgery)	Other medi-cal or surgi-cal patients from same hospital (not neck surge-ry)	Case-control	42 cases ? % Controls: 205? (exact number not stated)	Non-smokers, ex-smokers or current smokers	Operation X-ray CT-scan MR-scan Disc herniation	More smokers among operated than among controls. No gender modification.	6/10 No
Gore 2006 USA	Asymptomatic smokers	Asymptoma-tic non-smokers	Cross-sectional	100 smokers ? % 100 controls ? %	Number of cigarettes per day Duration of smoking	X-ray Curvature deviance Reduced disc height Sclerosis of the vertebral endplates Osteophytes	Smoking is not associated with degenerative changes. Positive age association. No gender diffe-rences.	9/10 Yes

						Other rating scale		