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Positional Magnetic Resonance Imaging for People With Ehlers-Danlos Syndrome or Suspected Craniovertebral or Cervical Spine Abnormalities: An Evidence-Based Analysis

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ABSTRACT

Background

Ehlers-Danlos syndrome (EDS) is an inherited disorder affecting the connective tissue. EDS can manifest with symptoms attributable to the spine or craniovertebral junction (CVJ). In addition to EDS, numerous congenital, developmental, or acquired disorders can increase ligamentous laxity in the CVJ and cervical spine. Resulting abnormalities can lead to morbidity and serious neurologic complications. Appropriate imaging and diagnosis is needed to determine patient management and need for complex surgery.

Some spinal abnormalities cause symptoms or are more pronounced while patients sit, stand, or perform specific movements. Positional magnetic resonance imaging (pMRI) allows imaging of the spine or CVJ with patients in upright, weight-bearing positions and can be combined with dynamic maneuvers, such as flexion, extension, or rotation. Imaging in these positions could allow diagnosticians to better detect spinal or CVJ abnormalities than recumbent MRI or even a combination of other available imaging modalities might allow.

Objectives

To determine the diagnostic impact and clinical utility of pMRI for the assessment of (a) craniovertebral or spinal abnormalities among people with EDS and (b) major craniovertebral or cervical spine abnormalities among symptomatic people.

Data Sources

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies published from January 1, 1998, to September 28, 2014.

Review Methods

Studies comparing pMRI to recumbent MRI or other available imaging modalities for diagnosis and management of spinal or CVJ abnormalities were reviewed. All studies of spinal or CVJ imaging in people with EDS were included as well as studies among people with suspected major CVJ or cervical spine abnormalities (cervical or craniovertebral spine instability, basilar invagination, cranial settling, cervical stenosis, spinal cord compression, Chiari malformation).

Results

No studies were identified that met the inclusion criteria.

Conclusions

We did not identify any evidence that assessed the diagnostic impact or clinical utility of pMRI for (a) craniovertebral or spinal abnormalities among people with EDS or (b) major craniovertebral or cervical spine abnormalities among symptomatic people relative to currently available diagnostic modalities.

PLAIN LANGUAGE SUMMARY

Ehlers-Danlos syndrome (EDS) is a group of disorders affecting tissues that help hold the body together and support other tissues. This condition can lead to loose and unstable joints (hypermobility), which sometimes cause problems in the spine. Sometimes these problems affect the nerves in the neck or area where the brain and spine meet (craniovertebral junction [CVJ]). Several other conditions can also increase the risk of similar neck and CVJ problems. Identifying these problems is important to choose the best treatment for patients.

Magnetic resonance imaging (MRI) is often used to look at the spine and CVJ. Standard MRI requires patients to lie down, with very little movement. A new type of MRI, called positional MRI (pMRI), allows patients to sit, stand, or take various positions during scanning. This type of imaging might better capture abnormalities visible only when the patient is upright or during specific movements. Because EDS patients have such unstable joints when standing or moving, it has been thought that these patients might be helped by scanning while they are upright. Other patients with problems in their neck or CVJ might also be helped by pMRI.

This study reviewed the research on people with EDS or symptoms of neck or CVJ problems for cases when pMRI changed the diagnosis or treatment compared with standard imaging techniques.

This study did not find any published studies that compared pMRI with standard imaging techniques among people with EDS. This study also found no research comparing pMRI with standard imaging techniques for diagnosis or management of specific abnormalities in the neck or CVJ.

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LIST OF ABBREVIATIONS

CVJ	Craniovertebral junction
CT	Computed tomography
EDS	Ehlers-Danlos syndrome
MRI	Magnetic resonance imaging
pMRI	Positional magnetic resonance imaging
RCT	Randomized controlled trial

BACKGROUND

Objective of Analysis

The objective of this evidence review was to determine the diagnostic impact and clinical utility of positional magnetic resonance imaging (pMRI) relative to currently available screening modalities for the assessment of (a) craniovertebral or spinal abnormalities among people with Ehlers-Danlos syndrome (EDS), and (b) major craniovertebral or cervical spinal abnormalities among symptomatic people.

Technology/Technique

Imaging Technologies of the Craniovertebral Junction and Spine

Spinal abnormalities can be diagnosed and evaluated through a combination of currently available imaging modalities. Radiographs (x-rays), computed tomography (CT), CT-myelography, and magnetic resonance imaging (MRI) are among the most common. Each technology provides different levels of information and is selected on the basis of the patient's symptoms and the suspected abnormality.

Standard x-rays are often used to assess major bony abnormalities or ligamentous laxity; x-rays allow for weight-bearing flexion and extension views of the spine. Dynamic and upright x-ray images can reveal spinal instability, but provide only indirect signs of cord compression. Similarly, CT can reveal osseous anomalies of the spine that are difficult to interpret on x-ray, but can only indirectly assess the spinal cord and other soft tissues. Myelography involves injection of a contrast dye into the spinal column to allow imaging of the spinal cord, subarachnoid space, and other nearby structures. Myelography is often combined with CT to assess the spinal cord and nerve roots. Myelography with CT is an invasive procedure but can be a good alternative for people with contraindications for MRI. Magnetic resonance imaging is considered the most established spinal imaging modality and allows for noninvasive imaging of the soft tissues, spinal cord, vertebrae, nerves, and ligaments. (1-3)

Magnetic Resonance Imaging

Magnetic resonance imaging uses a combination of magnetic fields that surround the subject, radiofrequency waves, and a computer to produce detailed images of body tissues and organs. Magnetic resonance imaging can define the severity and extent of craniovertebral and spinal abnormalities causing spinal stenosis or compression and can assess the space available for the spinal cord. Just as it helps with diagnosis of major spinal abnormalities, MRI is instrumental in selecting appropriate patients and planning for major spinal surgery.

Conventional recumbent MRI scanners consist of a large, closed, cylindrical magnet, in which the patient lies flat, either supine or prone. The scanner allows for minimal movement, and the patient is required to remain motionless during imaging. Open, or semi-open MRI systems have also been developed where the patient is only partially surrounded by the magnet while recumbent. Open-bore MRI systems replace the cylindrical magnet to provide openings along the sides or consist of a shorter tunnel in which only the portion of the body being scanned is surrounded by the magnet. Imaging in open-bore MRI systems can alleviate potential patient anxiety or claustrophobia.

The strength of the magnetic field used by MRI machines is measured in Tesla (T) units. While no formal classification system exists, MRI units with magnetic field strengths of greater than 1.0

T are generally classified as high field strength, those between 0.5 and 1.0 T as medium field strength, and those less than 0.5 T as low field strength. (3) Stronger magnetic fields generally require shorter examination times and are reputed to elicit higher quality images, although various factors affect the time to obtain an image. (3) Standard closed-bore recumbent MRI machines generally have field strengths of 1.5 to 3.0 T; most open-bore scanners are medium field strength. (4) Evidence on the clinical effect of these parameters, however, is limited. (4, 5)

Positional Magnetic Resonance Imaging

For the purposes of this review, pMRI is used to describe MRI systems that allow images to be taken under loading stress. These scanners are open at the front and top with magnets placed on either side of patients. Patients are seated or stand within the gap and can either remain in a static position or perform movements, such as flexion, extension, or rotation, during imaging. These machines can also allow partially upright or recumbent positions. Other synonymous terms include weight-bearing, stress-loading, upright, or stand-up MRIs. Magnetic resonance imaging using non–weight-bearing protocols or devices (e.g., voluntary or device-supported movements during supine imaging, modifications to standard open- or closed-bore scanners, or simulated weight bearing with axial loading devices) was beyond the scope of this review.

Currently available pMRI scanners use medium-strength magnets of 0.5 to 0.6 T, thus requiring longer image acquisition times with potentially lower-resolution images. Longer imaging times are difficult for patients who are unstable in the upright position, who cannot remain still while upright, or who experience pain in upright or dynamic positions, thus increasing the potential for motion artifacts.

Contraindications for pMRI are the same as those with standard recumbent MRI and include cardiac pacemakers, metallic foreign bodies, aneurysm clips, or electronically, magnetically, or mechanically activated implants.

Regulatory Status

Health Canada has one active licence since 2002 for an upright MRI device—the Indomitable (FONAR Corporation).

Canadian and Ontario Context

In Canada, more than 95% of hospital MRI scanners are closed-bore scanners. A January 2013 jurisdictional scan by Health Quality Onatrio identified no pMRI scanners in Ontario. Across Canada there are two pMRI scanners, both in British Columbia. One is located in a private clinic and one is located in the Vancouver General Hospital (acquired through a grant and used only for research by the Centre for Hip Health and Mobility).

Requests for Ontario Health Insurance Plan (OHIP) out-of-country funding for pMRI through physician referrals have been minimal; however, the number of referrals has increased over time. Since 2010, there have been a total of 36 requests for pMRI, of which the most common indication (30% of requests) was for brain and cervical spine imaging among people with EDS. (Ontario Ministry of Health data from Health Services Branch, written communication, July 2014). The remainder of requests were for varied indications.

Clinical Need and Target Population

Description of Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is an inherited disorder that affects the connective tissue. (6) Genetic alterations with EDS affect the synthesis of collagen and are characterized by varying degrees of joint hypermobility, tissue hyperextensibility, skin fragility, and vascular fragility. (6) Consequently, the joints, skin, blood vessels, and internal organs can all be variably affected. Several neurologic manifestations, including chronic pain, fatigue, and headache, have also been observed. (7) There are six defined major types of EDS: classical, hypermobile, vascular, kyphoscoliotic, arthrochalasic, and dermatosparactic. Among these, the classical and hypermobile types are the most common. (6, 8) Diagnosis of EDS is typically confirmed through various clinical tests including assessment of joint hypermobility using the Beighton score, assessment of tissue fragility, and clinical features. Some types of EDS can be further confirmed by genetic testing; however, the genes that cause EDS hypermobility type are mostly unknown. Many cases are difficult to diagnose because phenotypes frequently overlap with joint hypermobility syndrome and similar disorders of the connective tissue. (8, 9)

Abnormalities of the Spine and Craniovertebral Junction

Ligamentous laxity in EDS has been linked to various skeletal and spinal manifestations. As a result of joint hypermobility, subluxation and dislocation of the shoulders, digits, elbows, and knees are common. (8, 9) Spinal abnormalities such as kyphosis, scoliosis and degenerative findings (such as early-onset spondylosis and disc hernias) have also been noted. (7-9)

Vertebral dislocation and instability in EDS may be poorly recognized, with minimal published evidence of the association or incidence of these abnormalities among people with EDS. However, increased ligamentous laxity associated with pediatric connective tissue disorders is known to sometimes result in craniocervical instability. (10, 11) Case reports and indirect studies have documented radiographic evidence of atlanto-axial instability and basilar invagination among people with various forms of EDS. (12, 13) One surgeon has reported preliminary, unpublished data from people with hereditary hypermobility connective tissue disorders and brainstem or spinal cord symptoms, suggesting an overall improvement in some self-reported symptoms after occipitocervical fusion. (14)

In a study of people with Chiari (Type I) malformations—a heterogeneous group of hindbrain disorders characterized by herniation of the cerebellar tonsils through the foramen magnum—12.7% had a hereditary disorder of the connective tissue; the majority had EDS. (12) This study was limited by patient selection criteria and was not designed as an epidemiologic study; therefore, the incidence of Chiari malformations among people with EDS has not been determined and the clinical relevance of this association remains uncertain.

Craniovertebral Spinal Abnormalities

The cervical spine represents the most mobile spinal segment and is made up of the upper (C1, atlas, and C2, axis) and lower cervical spine (C3–C7). The craniovertebral (or craniocervical) junction (CVJ) is a complex region incorporating the occiput (posterior skull base) and the upper cervical spine, and is a transition between the cranium and the cervical spine. (2)

In addition to EDS, various congenital, developmental, or acquired disorders can predispose patients to similar nontraumatic abnormalities of the CVJ or cervical spine. In particular, craniocervical spine instability is associated with various pediatric and adult disorders, such as

Down syndrome, Marfan syndrome, mucopolysaccharrdoses, Larsen's syndrome, rheumatoid arthritis, and ankylosing spondylitis. (11, 15, 16)

Cervical spine instabilities are generally defined by excessive movement between one cervical vertebra and another. This instability is most commonly observed as atlanto-axial instability (or subluxation) or subaxial subluxation. Vertical subluxation (basilar invagination or cranial settling) can also occur when the top of the odontoid process migrates upward and is frequently preceded by atlanto-axial instability. (2) Upper cervical spine instability is sometimes accompanied by other spinal pathology, including spinal stenosis (narrowing of the spinal canal), basilar impression, or Chiari malformations. (11, 15) These pathologies can cause or contribute to spinal cord or brainstem compression or impingement during movement of the cervical spine, which can cause significant morbidity and potentially irreversible neurologic complications. Appropriately diagnosing these CVJ abnormalities and potential spinal cord or brainstem compression is therefore vital in determining appropriate patient management and the need for high-risk surgical interventions.

Symptoms of these conditions can range from a complete absence of symptoms to system-wide symptoms: severe neck and joint pain, severe headaches, visual problems, facial numbness, swallowing difficulties, balance difficulties, gait abnormalities, vertigo and dizziness, apnea, or syncope. Compression of the cervical spinal cord can result in neck pain and cervical myelopathy; symptoms of which include weakness of the limbs, pain, tingling sensations, and bowel and bladder dysfunction.

Prevalence and Incidence

The prevalence of EDS has been estimated at 1 in 5,000 to 1 in 20,000; (10) however, some studies suggest a higher prevalence given the clinical variability in symptoms and physicians' increasing awareness of the disease. The proportion of EDS cases with abnormalities of the spine or CVJ is unknown, with little evidence published to date.

The prevalence of nontraumatic upper cervical spine instability and associated abnormalities in the general population is unknown, and varies among populations of people predisposed to these abnormalities.

Rationale for Using pMRI

Treatment of serious CVJ or spinal abnormalities can be needed to avoid permanent neurologic compromise; however, surgical interventions are often complex, high-risk procedures involving decompression or fusion of the spine. Diagnosis and treatment decisions about appropriateness of surgical interventions for these abnormalities often hinge on imaging investigations, particularly MRI.

Some symptoms associated with spinal abnormalities worsen or appear only when patients sit, stand, or perform specific movements. Often symptoms are relieved when patients lie down. Whereas flexion and extension radiography is performed while patients are upright to allow for physiologic loading, conventional MRI is performed while patients are static and recumbent. The advantage of spinal imaging with pMRI is the ability to assess patients in weight-bearing positions, potentially detecting changes in spinal cord compression, angulation, or alignment that occur only under loading or with combined physiologic movements. This information could, in theory, be useful in diagnosis and treatment of spinal disorders.

Several studies have shown physiologic and kinematic changes in the cervical spine in both symptomatic and asymptomatic cases when comparing the supine neutral position to the extremes of flexion and extension. (17-19) These studies, however, used various methods and techniques to assess dynamic movements and do not account for the impact of loading on the spine. Similar results have been shown in studies using pMRI to compare upright neutral views to upright flexion and extension views. (20-22) These findings suggest feasibility and potential value in imaging patients in the upright position with dynamic movement but do not demonstrate that observed changes in the spine changed diagnosis, therapeutic management, or patient outcomes relative to recumbent MRI or other currently available imaging options.

Experts have suggested that pMRI could be particularly beneficial in people with hereditary disorders of the connective tissue and suspected CVJ instability. One study among a subgroup of Chiari patients with EDS observed an increase in ligamentous laxity and cervical spine instability (on x-ray examination) in upright positions when compared with supine positions. This increase was also observed when EDS cases were compared with cases of only Chiari malformation. (12) Comparative studies between pMRI and other available imaging techniques (such as recumbent MRI) are needed to ascertain the diagnostic and clinical value of this technology.

EVIDENCE-BASED ANALYSIS

Research Questions

Question 1

What is the diagnostic impact and clinical utility of positional magnetic resonance imaging (pMRI) in the assessment of **craniovertebral or spinal abnormalities** among people **with Ehlers-Danlos syndrome (EDS)** relative to currently available diagnostic modalities?

Question 2

What is the diagnostic impact and clinical utility of pMRI in the assessment of **major craniovertebral or cervical spinal abnormalities**[1] among **symptomatic people** relative to currently available diagnostic modalities?

Research Methods

Literature Search Strategy

A literature search was performed on September 28, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and EBM Reviews, for studies published from January 1, 1998, to September 28, 2014. (Appendix 1 provides details of the search strategies.) The year 1998 was chosen as the start date of the literature search because prior health technology assessments did not identify any studies on pMRI. (3, 23) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 1998, and September 28, 2014

Question 1:

- Studies among people with EDS
- Spinal or craniovertebral junction imaging using pMRI
- Studies comparing pMRI with currently available diagnostic modalities (e.g., recumbent MRI, recumbent MRI plus x-ray, computed tomography [CT] or CT myelography, operative findings)
- Randomized controlled trials (RCTs), systematic reviews, meta-analyses, observational studies, diagnostic accuracy studies
- Studies assessing one or more outcomes of interest for any spinal or craniovertebral junction (CVJ) diagnosis

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[1]Specific major cervical or craniovertebral spinal abnormalities or consequences were defined on the basis of expert consultation: they included craniovertebral or cervical spine instability (atlanto-axial instability; vertical subluxation, basilar invagination, or cranial settling; and subaxial instability); cervical spine stenosis; Chiari malformation; and cervical spine compression or brainstem compression.

Question 2:

- Studies among symptomatic cases with suspected or established major cervical or craniovertebral spinal abnormalities
- Craniovertebral junction or lower cervical spine imaging using pMRI
- Studies comparing pMRI with currently available diagnostic modalities (e.g., recumbent MRI, recumbent MRI plus x-ray, CT or CT myelography, operative findings)
- Observational studies, RCTs, systematic reviews, meta-analyses, diagnostic accuracy studies
- Studies assessing one or more outcomes of interest for diagnosis or management of one of the major cervical or CVJ conditions or consequences listed in the research question

Exclusion Criteria

- Studies of pMRI for traumatic spinal injury, spinal fractures, spinal tumours, or cancer
- Studies of pMRI for low back pain or thoracic or lumbar spine imaging (Question 2 only)
- Studies evaluating only spinal kinematics or anatomic/morphologic changes in the spine
- Studies of axial-loading MRI, dynamic MRI that is not stress loading or weight bearing, functional MRI, cine MRI, or cerebrospinal fluid flow MRI
- Case reports or series, narrative reviews, editorials, commentaries, conference abstracts

Outcomes of Interest

Outcomes of interest pertained to diagnostic impact, clinical utility, and patient experience. All reported craniovertebral and spinal diagnoses were considered for Question 1, and only the major conditions listed for Question 2 were evaluated.

Diagnostic accuracy—Given the broad evaluation of CVJ and spinal diagnoses, and the absence of a criterion standard for diagnosis, concordance in diagnosis between pMRI and other imaging modalities was assessed.

Impact on diagnosis—Examples are percent change in clinicians' assessment or diagnosis after the test and frequency of cases where the test was determined to be useful in making the diagnosis or differential diagnosis.

Impact on therapeutic decisions—Examples are percentage of times therapy planned before the diagnostic test changed after the test and percentage of times the test was determined to be useful in patient management or treatment planning.

Patient outcomes—Examples are percentage of patients who improved with diagnosis after pMRI; morbidity or additional procedures avoided after diagnostic imaging; and pain, discomfort, or side effects during or after assessment.

Results of Evidence-Based Analysis

The database search yielded 3,390 citations published between January 1, 1998, and September 28, 2014 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. Full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

No studies met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand-searched to identify other relevant studies; no additional citations were included.

One 2007 health technology assessment by the Washington State Health Care Authority (3) and one 2011 technical brief by the Agency for Healthcare Research and Quality (AHRQ) (23, 24) that evaluated the effectiveness or utility of pMRI for a range of spinal or musculoskeletal conditions were identified through hand searching. Neither review identified any studies that met our inclusion criteria.

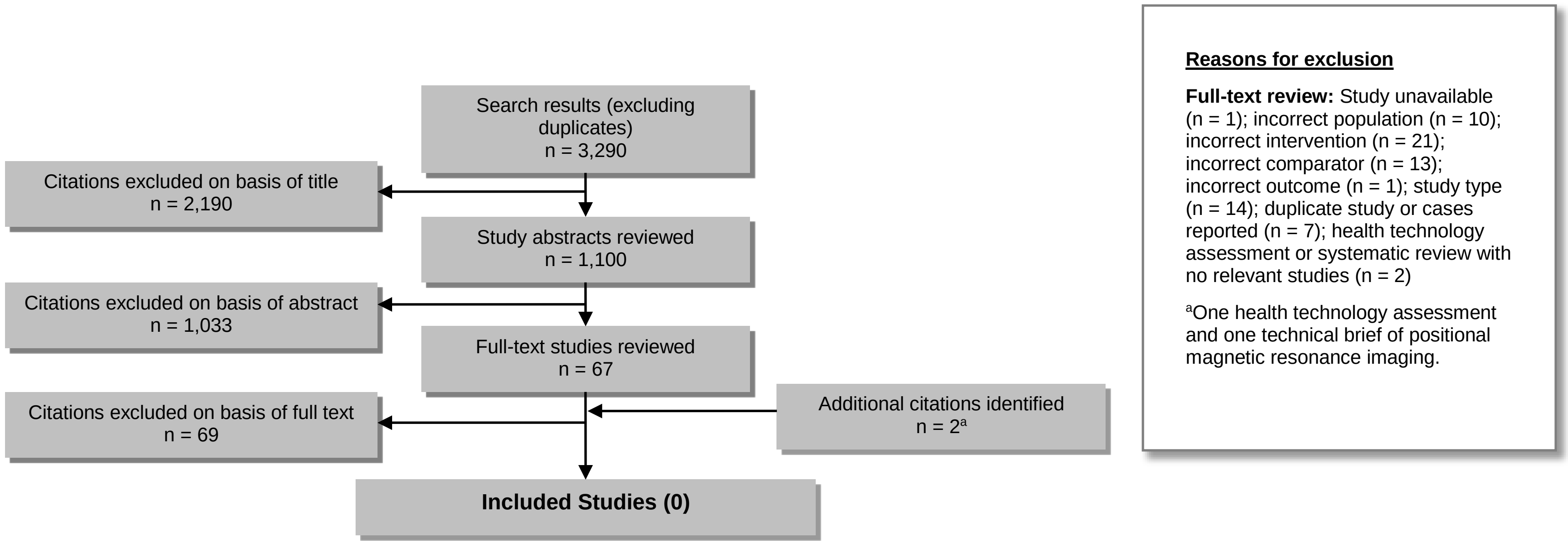

Figure 1: Citation Flow Chart

CONCLUSIONS

- We did not identify any evidence that assessed the diagnostic impact or clinical utility of positional magnetic resonance imaging (pMRI) in the assessment of craniovertebral or spinal abnormalities among people with Ehlers-Danlos syndrome relative to currently available diagnostic modalities.
- We did not identify any evidence that assessed the diagnostic impact or clinical utility of pMRI in the assessment of major craniovertebral or cervical spine abnormalities[2] among symptomatic people relative to currently available diagnostic modalities.

[2]Specific major craniovertebral or cervical spinal abnormalities or consequences were defined on the basis of expert consultation: they included craniovertebral or cervical spine instability (atlantoaxial instability; vertical subluxation, basilar invagination, or cranial settling; and subaxial instability); cervical spine stenosis; Chiari malformation; and cervical spine compression or brainstem compression.

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APPENDICES

Appendix 1: Literature Search Strategies

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2014>, EBM Reviews - ACP Journal Club <1991 to September 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <August 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2014>, Embase <1980 to 2014 Week 38>, Ovid MEDLINE(R) <1946 to September Week 2 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 19, 2014>
Search Strategy:

#	Searches	Results
1	exp Cervical Vertebrae/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	31471
2	cervical spine/ use emez	26906
3	Intervertebral Disc/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	11216
4	exp intervertebral disk/ use emez	10470
5	exp Neck/	61325
6	exp Spinal Diseases/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	97370
7	exp spine disease/ use emez	141604
8	Spinal Cord Compression/	21624
9	Joint Instability/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	15767
10	exp Spine/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	114500
11	and/9-10	1611
12	spine instability/ use emez	2257
13	Arnold-Chiari Malformation/	6378
14	Atlanto-Axial Joint/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Atlanto-Occipital Joint/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	3454
15	atlantoaxial joint/ use emez or atlantooccipital joint/ use emez	3089
16	Ehlers Danlos syndrome/	6146
17	((cervical adj (vertebrae or spine)) or ((intervertebral or slipped or herniated or displace* or prolapse*) adj (disk* or disc*)) or craniovertebra* or craniocervical or ((cervical or craniocervical) adj (instabilit* or subluxation or hypermobilit* or laxit*)) or cervical dis* disease* or (spinal cord adj2 (compression* or imping*)) or cord imping* or basilar invagination or (subaxial adj2 (subluxation or instabil*)) or conus medullaris syndrome* or (chiari adj2 (malformation or deformity or syndrome)) or spondylosis or (nerve root adj (inflammation* or disorder* or compression* or avulsion*)) or (stenos#s adj spinal) or spondylitis or spondylitides or joint hypermobilit* syndrome* or ((atlanto axial or atlatoaxial or atlanto occipital or atloido occipital) adj2 (joint* or instabilit* or subluxation)) or cranial settl* or ehlers danlos or EDS or cutis elastica).ti,ab.	148890
18	or/1-8,11-17	418857
19	exp Magnetic Resonance Imaging/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	327291
20	exp nuclear magnetic resonance imaging/ use emez	550446
21	(magnetic resonance or MR imag* or MRI).ti,ab.	741416
22	(FONAR or GE Medical Systems).mp.	2848
23	or/19-22	1085537

24	Patient Positioning/	15713
25	Weight-Bearing/	36163
26	exp body position/ use emez	96564
27	(dynamic or vertical or kinetic or upright or stand or stand up or standing or seated or seat or sitting or position* or (load* adj stress) or (bearing adj (weight or load*))).ti,ab.	1905558
28	or/24-27	1987530
29	23 and 28	81352
30	18 and 29	5571
31	limit 30 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	4959
32	limit 31 to yr="1998 -Current" [Limit not valid in DARE; records were retained]	4471
33	remove duplicates from 32	3329

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