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REVIEW ARTICLE

Do MRI findings identify patients with low back pain or sciatica who respond better to particular interventions? A systematic review

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Abstract
Purpose Magnetic resonance imaging (MRI) can reveal a range of degenerative findings and anatomical abnormalities; however, the clinical importance of these remains uncertain and controversial. We aimed to investigate if the presence of MRI findings identifies patients with low back pain (LBP) or sciatica who respond better to particular interventions.
Methods MEDLINE, EMBASE and CENTRAL databases were searched. We included RCTs investigating MRI findings as treatment effect modifiers for patients with LBP or sciatica. We excluded studies with specific diseases as the cause of LBP. Risk of bias was assessed using the criteria of the Cochrane Back Review Group. Each MRI finding was examined for its individual capacity for effect modification.
Results Eight published trials met the inclusion criteria. The methodological quality of trials was inconsistent. Substantial variability in MRI findings, treatments and outcomes across the eight trials prevented pooling of data. Patients with Modic type 1 when compared with patients with Modic type 2 had greater improvements in function when treated by Diprospan (steroid) injection, compared with saline. Patients with central disc herniation when compared with patients without central disc herniation had greater improvements in pain when treated by surgery, compared with rehabilitation.
Conclusions Although individual trials suggested that some MRI findings might be effect modifiers for specific interventions, none of these interactions were investigated in more than a single trial. High quality, adequately powered trials investigating MRI findings as effect modifiers are essential to determine the clinical importance of MRI findings in LBP and sciatica (PROSPERO: CRD42013006571).

Keywords Magnetic resonance imaging · Low back pain · Sciatica · Subgroup analysis · Randomised controlled trial · Systematic review

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Background

Low back pain (LBP) is an extremely common health problem [1], with an enormous global burden [2]. While some progress has been made in the management of LBP; the best options provide only small or moderate treatment effects [3, 4]. One explanation for the failure to identify treatments with large treatment effects is the current inability to identify a specific cause for LBP in most people [3]. As a result, a single intervention is usually provided to heterogeneous groups of patients with potentially different causes of their pain. Identifying more homogenous subgroups of LBP patients has been identified as a key

research priority in the field [5]. Most previous research in this area has focussed on identifying clinical and psychosocial variables associated with patients who respond better to different interventions [6, 7]. However, very little attention has focussed on identifying subgroups based on biological mechanisms or anatomical structures. Some early work has investigated subgroups based on different pain mechanisms [8–10] due to increasing evidence for the role of central mechanisms in the development of chronic LBP [11]. Subgrouping based on possible spinal pathoanatomical causes of LBP has received little attention and its value is unknown.

The importance of magnetic resonance imaging (MRI) findings such as disc herniation, facet joint arthropathy and modic changes (bone marrow and endplate lesions visible on MRI) in identifying the source of an individual patient's LBP remains unclear and controversial. Many MRI findings are common in people without LBP, yet these findings are typically more common in people with LBP than those without [12–14]. Research into the importance or otherwise of MRI findings has been frustrated by the lack of a widely accepted gold standard [14]. An alternate approach in such cases is to investigate if the presence of MRI findings predicts different response to interventions [15]. If this was the case, it would provide evidence for the importance of such findings and a logical rationale for selecting specific interventions for individual patients.

To our knowledge, there has been no review of a range of MRI findings as effect modifiers for LBP interventions. Therefore, the aim of this systematic review was to investigate if the presence of MRI findings at baseline identifies patients with LBP or sciatica who respond better to particular interventions.

Methods

The review protocol was specified in advance and registered on PROSPERO: international prospective register of systematic reviews (refer to this link for full access of the protocol, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006571). The PRISMA statement was used to guide the conduct and reporting of the study [16].

Search strategy

A sensitive search was performed of MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials to identify potential studies from the earliest records up to 20th of June, 2015. We used a search strategy based on the recommendations of the Cochrane Back Review Group [17] for randomised controlled trials (RCTs) and LBP, combined with Medical Subject Headings and keywords related to 'MRI' and 'effect modification/subgroups'. After piloting the search strategy, we decided to use two different searches and then combine the results.

Search 1 included terms from each of the following domains: (1) RCTs, (2) LBP/sciatica and (3) MRI. Search 2 included terms from each of the following domains: (1) RCTs, (2) LBP/sciatica and (3) effect modification/subgroup. Searches 1 and 2 were merged to generate the final search strategy (Refer to Appendix Tables 4 and 5 for the full search strategy). Reference and citation tracking of relevant articles were performed. A final list of the included studies was sent to two experts in the field who reviewed the list for possible omissions.

Study selection

To be included, studies were required to meet all the following criteria:

(1) Participants: recruited samples of populations with current LBP or sciatica, who were not diagnosed with serious disease (e.g. cancer, spinal infection, spinal fracture, inflammatory arthritis or cauda equina syndrome) as the source of LBP.
(2) Interventions: investigated any type of intervention for LBP, including conservative, surgical, or placebo. Included studies needed to have compared any intervention for LBP or sciatica, with any type of intervention, placebo or no treatment control.
(3) Outcome: reported for either pain (e.g. measured by the visual analogue scale, numerical rating scale) or disability (e.g. measured by the Roland Morris Disability Scale, Oswestry Disability Index). In studies that included participants with a primary complaint of LBP, self-reported LBP was considered the primary outcome while in trials of sciatica self-reported leg pain was considered the primary outcome [3].

Study design: included studies needed to be an RCT which had used methods capable of identifying whether patients with a specific MRI finding had a different treatment effect than those without the MRI finding or with a different MRI finding. Studies were required to have included and reported a patient's results separately for either (1) sample with and without a particular MRI finding (i.e. disc herniation) or (2) people with a different type or severity of MRI finding (i.e. mild vs. severe disc degeneration).

One reviewer screened titles and abstracts of each citation and excluded clearly irrelevant studies. For each potentially eligible study, the full text was retrieved and two reviewers independently assessed whether the study

fulfilled the inclusion criteria. In cases of disagreement, a third reviewer was consulted and a decision made by consensus. The search had no language restrictions.

Data extraction

Relevant data were independently extracted by two reviewers using a standardised form. In cases of disagreement, a joint review of the original article was performed until consensus was reached. The extraction form included the following criteria: clinical settings, sample, age, treatment groups, MRI findings and point estimates and measures of variability for outcomes. Outcome data were extracted for short-term outcomes (0 to ≤6 months) and long-term outcomes (>6 months). When multiple time points fell within the same category, we used the one closest to 3 months for short-term and closest to 12 months for long-term.

Risk of bias

There is no established method to assess the risk of bias for studies of effect modification. We, therefore, chose to use the risk of bias tool recommended by the Cochrane Back Review Group [17] to assess the conduct of the RCTs included in our review. The risk of bias findings was, therefore, not emphasised in the interpretation of results, as would be common in a review of an intervention. Two reviewers independently assessed the criteria of all included studies. In cases of disagreement, a third reviewer was consulted and a decision made by consensus (refer to Appendix Table 6 for further details on the criteria list for the methodological quality assessment). Data pooling was appropriate only if the studies were considered homogeneous with regard to population sample, MRI measure, clinical outcomes and treatment.

Analysis

Due to the small number of included trials and the heterogeneity between them in terms of MRI findings, treatment and clinical outcomes, we were unable to undertake the pre-specified meta-analysis. Therefore, each MRI finding of the lumbar spine was examined for its individual capacity for effect modification and interaction. The results are presented descriptively for LBP and sciatica populations.

We extracted (1) mean difference and 95 % confidence intervals (95 % CI) from studies that reported continuous outcomes, (2) hazard ratios (HR) and 95 % CI from studies that reported time-to-event categorical outcomes, and (3) contingency table data to calculate Odds Ratios (OR) for categorical outcomes. If not reported or provided, the effect modification and subgroup interaction were calculated using the method suggested by Kent et al. [7] for continuous outcomes and the method suggested by Hancock et al. [18] for categorical outcomes. In brief, for continuous outcomes this involved using the following formulae:

((in subgroup and received intervention treatment) − (in subgroup and received comparison treatment)) − ((not in subgroup and received intervention treatment) − (not in subgroup and received comparison treatment)).

For dichotomous outcomes, the approach involves recreating a replication of the data set and running logistic regression.

Four studies had key information not available from published manuscripts and additional information was requested [19–22]. Two studies reported combined RCT and observational cohort data [19, 20]. The separated RCT data for the intention-to-treat analysis were requested. The effect modification and/or the subgroup interaction were calculated by the current review authors, for six studies [19, 20, 23–26].

In this review, the term subgroup interaction refers to how much more effective (compared with the control intervention) the intervention is in the subgroup (MRI positive) than for those not in the subgroup (MRI negative).

Results

Study selection

The search identified 7163 papers. After review of titles and abstracts, we excluded 7096 (Fig. 1). Based on full-text review of 67 papers, we excluded a further 59 and included eight trials in the review [19–26]. The primary reasons for the exclusion of trials retrieved in full-text are noted in Appendix Table 7. No additional studies were identified after contacting two experts in the field of MRI and LBP or sciatica.

Risk of bias

The risk of bias assessments for the included studies is shown in Table 1. Randomisation, drop-out rate, co-interventions and outcome timing were the only criteria scored ‘yes’ in all trials. Participant blinding, outcome assessor blinding and the absence of selective outcome reporting were the criteria most commonly scored ‘no’.

Study characteristics

The characteristics of the included studies are shown in Table 2. Three trials studied patients with LBP [24–26] and

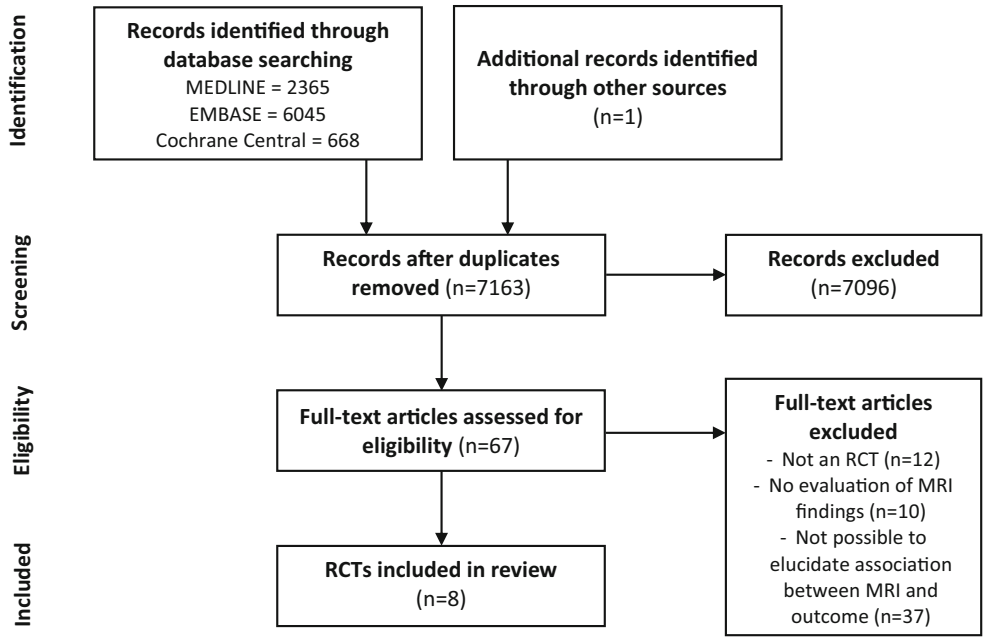

Fig. 1 Flow diagram of review process

five studied patients with sciatica [19–23]. The samples were recruited from secondary health care [19–21, 23, 24], and tertiary health care [22, 25, 26] settings. The number of participants varied from 120 to 472 and most studies sampled predominantly adults in their middle age. The treatments evaluated in the trials included surgery, injections and rehabilitation. No study had the primary aim of investigating MRI effect modifiers. LBP duration was categorised as acute (<6 weeks), sub-acute (6–12 weeks) and chronic (greater than 12 weeks) [17].

Results of the review

Due to the heterogeneity of samples, MRI findings, clinical outcomes and treatment, it was not possible to perform meta-analysis of the results for any of the included studies. For ease of interpretation, the studies were grouped into LBP population [24–26] or sciatica population [19–23] as the importance of MRI findings might be quite different in these two populations. Detailed findings of all included studies are presented in Table 3.

Low back pain population samples

One study reported a population with sub-acute LBP (symptoms ≥6 weeks) [25] and two reported populations with chronic LBP (symptoms ≥1 year) [24, 26]. All three studies investigated Modic changes (Modic changes type 1 corresponding to vertebral body oedema and hyper-vascularity; Modic changes type 2 reflecting fatty replacements of the red bone marrow; and Modic changes type 3 consisting of subchondral bone sclerosis [27, 28]) as effect modifiers [24–26], while one study investigated disc herniation and facet joint arthritis [26].

Cao et al. [25] investigated various intradiscal injection regimens for patients with Modic changes ($n = 120$). Patients with Modic changes type 1, when compared with patients with Modic changes type 2, have a little more improvement in disability in the short-term (3 months) when treated by Diprospan (steroid) injection, compared with saline (mean difference 8.30; 95 % CI 1.01–15.59, on a 0–100 disability scale). Other subgroup interactions for pain and disability with Modic changes were not significant.

Hellum et al. [26] investigated whether features of degenerative disc were effect modifiers for disc prosthesis compared with multidisciplinary rehabilitation at two-year follow-up ($n = 154$). The presence of Modic changes type 1 and/or 2 was not a significant effect modifier for improvements in disability (percentage of patients improved ≥15 points on a 0–100 scale, categorised by yes/no), with OR ranging from 0.63 (95 % CI 0.15–2.65) to 2.96 (95 % CI 0.65–13.52). Similarly, disc herniation, facet joint arthropathy and high intensity zone were not significant effect modifiers for improvement in disability when treated with surgery, compared with rehabilitation [26].

Buttermann [24] investigated whether Modic changes type 1 was an effect modifier for spinal injection and steroid, compared with discography alone at 1–3 and 12–24 months ($n = 171$). The presence of Modic changes

Table 1 Risk of bias of the included studies

References	Method criteria[a]											
	Randomisation	Concealed allocation	Participant blinding	Clinicians blinding	Outcome assessor blinding	Acceptable drop-out rate	Analysed according to treatment allocation	Free of selective outcomes	Baseline similarity	Co-interventions	Compliance	Outcome timing
Arts et al. [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Buttermann [24]	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	NA	Yes
Cao et al. [25]	Yes	?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes
Hellum et al. [26]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Pearson et al. [19]	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Pearson et al. [20]	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Peul et al. [22]	Yes	Yes	No	No	No	Yes	?	Yes	Yes	Yes	Yes	Yes
Tafazal et al. [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes

Each criterion was scored as yes, unclear (?), not applicable (NA) or no, where yes indicates that the criterion has been met

[a] Quality of included studies based on the Cochrane Back Review Group method [17]

Table 2 Individual study characteristics

References	Clinical setting	Sample	Age, mean (SD)	Outcomes (threshold)	Treatment groups	Follow-up, duration (%)[a]
Arts et al. [21]	Secondary care (neurosurgical outpatient clinic)	325 patients with sub-acute sciatica (>6–8 weeks)	41.45 (10.75)	Recovery ('complete recovery' and 'almost complete recovery were coded as recovered)	1. Surgery: conventional micro-discectomy; 2. Surgery: Tubular discectomy	12 months (100 %)
Buttermann et al. [24]	Secondary care (spine institute)	171 patients with chronic LBP (>1 year)	42.83 (8.66)	Success (was coded 'yes' or 'no' based on overall opinion as to whether patients thought their injection was successful in the treatment of their symptoms)	1. Injection: discography and steroid; 2. Injection: discography only	1–3 (100 %) and 12–24 months (100 %)
Cao et al. [25]	Tertiary care (hospital)	120 patients with sub-acute LBP (≥6 weeks)	42.30 (8.72)	Pain (VAS, ranges from 0 to 10, with 0 corresponding to no pain); Disability (ODI ranges from 0 % to 100 %, with 0 % corresponding to no disability)	1. Injection: 3 mL Diprospan; 2. Injection: 1 mL Diprospan and 2 mL Songmeile; 3. Injection: 3 mL normal saline	3 months (100 %)
Hellum et al. [26]	Tertiary care (five Norwegian university hospitals)	154 patients with chronic LBP (≥1 year)	41.20 (7.00)	Disability (ODI, ranges from 0 % to 100 %, with 0 % corresponding to no disability. Percentage of patients improved ≥15 ODI points categorised by yes/no)	1. Surgery: replacement of the degenerative lumbar disc with an artificial lumbar disc; 2. Rehabilitation: multidisciplinary treatment consisted of a cognitive approach and supervised physical activity	24 months (100 %)
Pearson et al. [19]	Secondary care (11 multidisciplinary spine practices)	278 patients with chronic sciatica (≥12 weeks)	? (?)	Disability (ODI, ranges from 0 % to 100 %, with 0 % corresponding to no disability)	1. Surgery: standard open decompressive laminectomy; 2. Rehabilitation: usual care– at least physical therapy, education and counselling with home exercises, and non-steroidal anti-inflammatory drugs	3 (88.49 %) and 12 months (87.41 %)
Pearson et al. [20]	Secondary care (11 multidisciplinary spine practices)	472 patients with chronic sciatica (≥12 weeks)	? (?)	Pain (Pain bothersomeness, ranges from 0 to 6, with 0 corresponding to not bothersome)	1. Surgery: standard open discectomy with examination and decompression of nerve root; 2. Rehabilitation: usual care—at least physical therapy, education and counselling with home exercises, and non-steroidal anti-inflammatory drugs	3 (86.02 %) and 12 months (87.5 %)
Peul et al. [22]	Tertiary care (9 hospitals)	283 patients with sub-acute sciatica (>6–8 weeks)	42.55 (9.30)	Recovery ('very much improved' and 'much improved' were coded as recovered)	1. Surgery: discectomy; 2. Rehabilitation: Education, pain medication, physiotherapy if necessary	12 months (100 %)
Tafazal et al. [23]	Secondary care (specialist spine clinic)	150 patients with sub-acute sciatica (≥6 weeks)	51.90 (?)	Pain (VAS, ranges from 0 to 100, with 0 corresponding to no pain); Disability (ODI, ranges from 0 % to 100 %, with 0 % corresponding to no disability)	1. Injection: 2 mL of 0.25 % bupivacaine and 40 mg of methylprednisolone (Depomedrone); 2. Injection: 2 mL of 0.25 % bupivacaine alone	3 months (82.66 %)

? data not available, *VAS* visual analogue scale, *ODI* oswestry disability index

[a] Percentage based on the sample available for the subgroup interaction

Table 3 Subgroup treatment effect and interaction for low back pain and sciatica population

MRI feature	MRI threshold		References	Treatment		Treatment effect for MRI +	Treatment effect for MRI −	Clinical outcome (time), threshold	Subgroup Interaction, mean difference (95 % CI), unless otherwise indicated
	Positive (+)	Negative (−)		Treatment 1 (N)	Treatment 2 (N)				
Low back pain populations									
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan (20)	Saline (20)	5.20 (4.44 to 5.96)	5.20 (4.60 to 5.80)	Pain (ST), 0–10	0.00 (−0.98 to 0.98)
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan + songmeile (20)	Saline (20)	5.00 (4.29 to 5.71)	5.20 (4.60 to 5.80)	Pain (ST), 0–10	−0.20 (−0.74 to 1.14)
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan + songmeile (20)	Diprospan (20)	0.20 (−0.40 to 0.80)	0.00 (−0.54 to 0.54)	Pain (ST), 0–10	0.20 (−0.62 to 1.02)
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan (20)	Saline (20)	28.90 (22.52 to 35.28)	20.60 (15.69 to 25.51)	Disability (ST), 0–100	8.30 (1.01 to 15.59)[a]
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan + songmeile (20)	Saline (20)	28.40 (21.95 to 34.85)	20.20 (15.17 to 25.23)	Disability (ST), 0–100	8.20 (−0.11 to 16.51)
Modic type	Type 1	Type 2	Cao et al. 2011	Diprospan + songmeile (20)	Diprospan (20)	0.50 (−1.21 to 2.21)	0.40 (−1.35 to 2.15)	Disability (ST), 0–100	0.10 (−2.39 to 2.59)
Modic type 1	Present	Absent	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	6.07 (1.66 to 22.12)[b]	2.05 (0.92 to 4.55)[b]	Disability (LT), 0–100, ≥15points	2.96 (0.65 to 13.52)[b]
Modic type 1 and 2	Present	Absent	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	3.21 (0.66 to 15.59)[b]	2.94 (1.40 to 6.16)[b]	Disability (LT), ODI 0–100, ≥15points	1.10 (0.19 to 6.27)[b]
Modic type 2	Present	Absent	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	2.16 (0.67 to 6.93)[b]	3.43 (1.48 to 7.93)[b]	Disability (LT), 0–100, ≥15points	0.63 (0.15 to 2.65)[b]
Modic type 1	Present	Absent	Buttermann [24]	Discography + steroid (86)	Discography (85)	76.85 (9.47 to 623.52)[b]	9.68 (1.15 to 80.91)[b]	Success (ST), yes	7.94 (0.40 to 156.46)[b]
Modic type 1	Present	Absent	Buttermann [24]	Discography + steroid (86)	Discography (85)	12.33 (1.49 to 101.86)[b]	5.61 (0.63 to 50.02)[b]	Success (LT), yes	2.20 (0.11 to 45.98)[b]
Disc herniation	Height reduction	No height reduction	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	2.61 (1.17 to 5.82)[b]	3.64 (1.04 to 12.78)[b]	Disability (LT), 0–100, ≥15points	0.72 (0.16 to 3.18)[b]
Disc herniation	Signal intensity	No signal intensity	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	2.51 (1.23 to 5.13)[b]	12.00 (1.05 to 136.79)[b]	Disability (LT), 0–100, ≥15points	0.21 (0.02 to 2.64)[b]
Facet joint arthropathy	≥moderate	<moderate	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	0.78 (0.06 to 10.86)[b]	3.15 (1.55 to 6.38)[b]	Disability (LT), 0–100, ≥15points	0.25 (0.20 to 3.79)[b]
High intensity zone	Present	Absent	Hellum et al. [26]	Surgery (88)	Rehabilitation (66)	3.35 (1.16 to 9.72)[b]	2.83 (1.16 to 6.93)[b]	Disability (LT), 0–100, ≥15points	1.18 (0.29 to 4.75)[b]
Sciatica populations									
Disc herniation	Central	No Central	Pearson et al. [20]	Surgery (198)	Rehabilitation (208)	1.80 (0.30 to 3.30)	0.10 (−0.40 to 0.60)	Pain (ST), 0–6	1.70 (−0.07 to 3.47)
Disc herniation	Central	No Central	Pearson et al. [20]	Surgery (202)	Rehabilitation (211)	1.60 (0.10 to 3.10)	0.00 (−0.40 to 0.40)	Pain (LT), 0–6	1.60 (0.17 to 3.03)[a]
Disc herniation	Posterolateral	No posterolateral	Pearson et al. [20]	Surgery (198)	Rehabilitation (208)	0.20 (−0.30 to 0.70)	0.50 (−0.50 to 1.50)	Pain (ST), 0–6	−0.30 (−1.45 to 0.85)

Table 3 continued

MRI feature	MRI threshold		References	Treatment		Treatment effect for MRI +	Treatment effect for MRI −	Clinical outcome (time), threshold	Subgroup Interaction, mean difference (95 % CI), unless otherwise indicated
	Positive (+)	Negative (−)		Treatment 1 (N)	Treatment 2 (N)				
Disc herniation	Posterolateral	No posterolateral	Pearson et al. [20]	Surgery (202)	Rehabilitation (211)	0.00 (−0.50 to 0.50)	0.60 (−0.40 to 1.60)	Pain (LT), 0–6	−0.60 (−1.78 to 0.58)
Disc herniation	Protrusion	No protrusion	Pearson et al. [20]	Surgery (198)	Rehabilitation (208)	0.60 (−020 to 1.40)	0.10 (−0.40 to 0.60)	Pain (ST), 0–6	0.50 (−0.45 to 1.45)
Disc herniation	Protrusion	No protrusion	Pearson et al. [20]	Surgery (202)	Rehabilitation (211)	0.30 (−0.50 to 1.10)	0.10 (−0.40 to 0.60)	Pain (LT), 0–6	0.20 (−0.76 to 1.16)
Disc herniation	Sequestrated	Contained	Peul et al. [22]	Surgery (NS)	Rehabilitation (NS)	1.84 (1.23 to 2.75)[c]	1.96 (1.40 to 2.74)[c]	Recovery (LT), ≥much improved	0.94 (0.56 to 1.57)[c]
Disc herniation	Sequestrated	Contained	Arts et al. [21]	Tubular discectomy (166)	Conventional microdiscectomy (159)	1.10 (0.82 to 1.46)[c]	0.73 (0.49 to 1.09)[c]	Recovery (LT), ≥almost complete recovery	0.66 (0.41 to 1.09)[c]
Disc herniation	Enhancement	No enhancement	Peul et al. [22]	Surgery (NS)	Rehabilitation (NS)	2.32 (1.43 to 3.77)[c]	1.97 (1.38 to 2.83)[c]	Recovery (LT), ≥much improved	0.85 (0.47 to 1.54)[c]
Disc herniation	>1/3 of spinal canal	≤1/3 of spinal canal	Arts et al. [21]	Tubular discectomy (166)	Conventional microdiscectomy (159)	0.93 (0.70 to 1.24)[c]	1.00 (0.66 to 1.49)[c]	Recovery (LT), ≥almost complete recovery	0.94 (0.57 to 1.53)[c]
Disc herniation	Mediolateral and lateral	Median	Arts et al. [21]	Tubular discectomy (166)	Conventional microdiscectomy (159)	0.91 (0.67 to 1.24)[c]	0.98 (0.68 to 1.40)[c]	Recovery (LT), ≥almost complete recovery	1.07 (0.67 to 1.72)[c]
Spinal stenosis	Central	No central	Pearson et al. [19]	Surgery (115)	Rehabilitation (131)	0.60 (−5.40 to 6.60)	−11.00 (−25.70 to 3.70)	Disability (ST), 0–100	11.60 (−4.79 to 27.99)
Spinal stenosis	Central	No central	Pearson et al. [19]	Surgery (120)	Rehabilitation (123)	2.30 (−3.40 to 7.90)	−2.40 (−16.90 to 12.10)	Disability (LT), 0–100	4.70 (−10.55 to 19.95)
Spinal stenosis	Lateral recess	No lateral recess	Pearson et al. [19]	Surgery (115)	Rehabilitation (131)	−1.80 (−7.80 to 4.20)	2.80 (−11.50 to 17.10)	Disability (ST), 0–100	−4.60 (−20.33 to 11.13)
Spinal stenosis	Lateral recess	No lateral recess	Pearson et al. [19]	Surgery (120)	Rehabilitation (123)	2.50 (−3.20 to 8.20)	−3.80 (−17.60 to 9.90)	Disability (LT), 0–100	6.30 (−8.13 to 20.73)
Spinal stenosis	Neuroforaminal	No neuroforaminal	Pearson et al. [19]	Surgery (115)	Rehabilitation (131)	−3.20 (−12.80 to 6.30)	−0.40 (−6.90 to 6.10)	Disability (ST), 0–100	−2.80 (−14.33 to 8.73)
Spinal stenosis	Neuroforaminal	No neuroforaminal	Pearson et al. [19]	Surgery (120)	Rehabilitation (123)	0.50 (−8.80 to 9.90)	2.00 (−4.30 to 8.20)	Disability (LT), 0–100	−1.50 (−12.85 to 9.85)
Spinal stenosis	Severe	Mild/moderate	Pearson et al. [19]	Surgery (115)	Rehabilitation (131)	3.40 (−4.10 to 10.90)	−5.60 (−13.40 to 2.20)	Disability (ST), 0–100	9.00 (−1.87 to 19.87)

Table 3 continued

MRI feature	MRI threshold		References	Treatment		Treatment effect for MRI +	Treatment effect for MRI −	Clinical outcome (time), threshold	Subgroup Interaction, mean difference (95 % CI), unless otherwise indicated
	Positive (+)	Negative (−)		Treatment 1 (N)	Treatment 2 (N)				
Spinal stenosis	Severe	Mild/moderate	Pearson et al. [19]	Surgery (120)	Rehabilitation (123)	3.40 (−3.80 to 10.70)	−0.30 (−7.90 to 7.30)	Disability (LT), 0–100	3.70 (−6.85 to 14.25)
Spinal stenosis	Lateral recess	No lateral recess	Arts et al. [21]	Tubular discectomy (166)	Conventional microdiscectomy (159)	0.63 (0.34–1.15)[2]	1.03 (0.80 to 1.32)[2]	Recovery (LT), ≥almost complete recovery	1.64 (0.85 to 3.15)[c]
Disc height	≥7 mm	<7 mm	Arts et al. [21]	Tubular discectomy (166)	Conventional microdiscectomy (159)	0.92 (0.71–1.18)[2]	1.24 (0.70 to 2.20)[2]	Recovery (LT), ≥almost complete recovery	1.35 (0.73 to 2.52)[c]
Herniation/ stenosis	Disc prolapse	Spinal stenosis	Tafazal et al. [23]	Bupivacaine + steroid (65)	Bupivacaine (59)	3.10 (−11.23 to 17.43)	−1.30 (−15.21 to 17.81)	Pain (ST), 0–100	4.40 (−18.13 to 26.93)
Herniation/ stenosis	Disc prolapse	Spinal stenosis	Tafazal et al. [23]	Bupivacaine + steroid (65)	Bupivacaine (59)	−0.20 (−9.34 to 9.47)	−5.00 (−3.73 to 13.73)	Disability (ST), 0–100	4.80 (−9.06 to 18.66)

Mean difference and 95 % CI positive values favour treatment effect for MRI positive (+)

NS Not specified, *ST* short-term (0 to ≤6 months), *LT* long-term (>6 months)

[a] Statistically significant

[b] Values are represented as odds ratios and 95 % confidence intervals. An odds ratio greater than 1 favours treatment effect for MRI positive (+)

[c] Values are represented as hazard ratio and 95 % confidence intervals. A hazard ratio greater than 1 favours treatment effect for MRI positive (+)

type 1 was not a significant effect modifier for injection success (coded as 'yes' if the overall opinion about their injection was considered successful) at short- (OR 7.94; 95 % CI 0.40–156.46) or long-term follow-up (OR 2.20; 95 % CI 0.11–45.98).

Sciatica population samples

Three studies reported potential MRI effect modifiers in one population sample with sub-acute sciatica (symptoms ≥6 weeks) [21–23] and two with chronic sciatica (symptom ≥12 weeks) [19, 20]. Three studies investigated disc herniation [20–22], two investigated spinal stenosis [19, 21], one investigated disc height [21] and one investigated different types of MRI findings (disc prolapse vs. spinal stenosis) [23] as effect modifiers.

Pearson et al. [20] studied whether features of disc herniation were effect modifiers for discectomy, compared with conservative rehabilitation at three and 12 months follow-up ($n = 472$). Patients with central disc herniation, when compared with patients without central disc herniation, had a substantially better response to surgery at long-term follow-up (12 months), mean difference 1.60; 95 % CI 0.17–3.03 (0–6 point Likert scale). In patients with central herniation, one-year pain outcomes were substantially better (mean difference 1.60; 95 % CI 0.10–3.10; 0–6 point Likert scale) for those receiving surgery compared with rehabilitation. In those without central herniation, surgery was no better than rehabilitation (mean difference 0.00; 95 % CI −0.40 to 0.40; 0–6 point Likert scale). Other disc herniation characteristics (e.g. posterolateral and protrusion) were not associated with significant treatment interactions.

Peul et al. [22] investigated if disc herniation was an effect modifier for response to early surgery compared with prolonged conservative care ($n = 283$). Sequestrated disc herniation (Hazard ratio, 0.94; 95 % CI 0.56–1.57) and disc herniation enhancement (Hazard ratio, 0.85; 95 % CI 0.47–1.54) did not have any significant interaction with treatment, for 12 month outcomes (very much improved and much improved were coded as recovered).

Arts et al. [21] investigated if disc herniation, spinal stenosis and disc height were effect modifiers for response to tubular discectomy, compared with conventional microdiscectomy, at one-year follow-up ($n = 325$). None of the MRI findings produced significant interactions with treatment for long-term recovery outcomes.

Pearson et al. [19] investigated whether features of spinal stenosis were effect modifiers for response to surgery, compared with rehabilitation, in 278 patients at three and 24 months follow-up. Spinal stenosis did not produce any significant interactions with treatment for short- and long-term disability outcomes.

Tafazal et al. [23] investigated whether features of disc herniation (disc prolapse) or lumbar spinal stenosis were effect modifiers for the efficacy of corticosteroids injection in 150 patients. Neither MRI features produced significant interactions with bupivacaine (a local anaesthetic) and steroid or bupivacaine alone at short-term follow-up.

Discussion

Statement of principal findings

This review could only identify eight studies, which provided adequate data to assess if MRI findings were treatment effect modifiers. Three studies reported data from people with LBP and five studies reported data from people with sciatica. The included studies investigated 38 interactions for combinations of different MRI findings, interventions and outcomes. No effect modifiers were consistently identified across more than one study. A single study shows that patients with Modic changes type 1 have a little more improvement on disability when compared with patients with Modic changes type 2, in the short term when treated by Disprosan injection, compared with saline (mean difference 8.30; 95 % CI 1.01–15.59, on a 0–100 disability scale). A single study reported that patients with sciatica and central disc herniation (compared with those without central disc herniation) have substantially greater benefits from surgery than rehabilitation (mean difference 1.60; 95 % CI 0.17–3.03, on a 0–6 point Likert scale). However, these are single study results and caution should be taken when interpreting the findings. Some other subgroup interactions presented trends and confidence intervals that included potentially important interactions; however, these trials were underpowered due to their small sample sizes.

Strengths and weaknesses of the study

We believe that this is the first systematic review of RCTs to investigate if a range of MRI findings are effect modifiers for interventions in people with LBP and/or sciatica. The strength of this review is the use of a pre-specified protocol and the comprehensive approach to identifying all suitable RCTs. We also provide data for all included trials on the interaction effect as well as the subgroup effects for those with and without the MRI finding of interest. We used a sensitive search strategy and contacted experts in the field, reducing the risk of missing any important trial. A limitation of our review is that the inconsistency of MRI findings, interventions and outcomes investigated across the studies inhibited our ability to perform meta-analysis. Furthermore, most trials were not powered for subgroup interaction analysis, as it was not the primary aim of the

study. As a result, some non-significant findings may include a potentially important interaction (e.g. OR 7.94; 95 % CI 0.40–156.46) [24]. Another limitation of our review is the possibility of publication bias as we did not attempt to identify unpublished trials that might have been found in other clinical trials registries and in conference proceedings. Furthermore, this review could have missed important trials that for some reason were not captured by our search, not cited by a relevant study or unknown to our experts in the field.

In our review, we used the Cochrane Risk of Bias tool to assess quality of RCT conduct; however, this tool does not necessarily reflect the risk of bias associated with effect modification analyses. Currently, there is no validated measure to assess risk of bias in effect modification analyses. Factors including the use of an appropriate test of interaction, adequate power for interaction test and a priori hypothesis of direction of effect may be important to the risk of bias in effect modification studies but are not included in Cochrane risk of bias tool [29, 30].

The reliability of different MRI findings is important for the interpretation of this study. Carrino et al. [31] reported the reliability of lumbar MRI findings to be generally moderate to good. For example, they reported Kappa values of 0.66, 0.55, 0.59 and 0.54 for disc degeneration, spondylolisthesis, Modic changes and facet arthroplasty, respectively. The type of MRI machine used and the experience of the image readers may influence reliability. A recent study found that Modic changes Type 1 was detected more often using low field MRI (0.3 Tesla), whereas Modic changes Type 2 was detected more often when using high field MRI (1.5 Tesla) [32].

Comparison with other studies

Three previous reviews have investigated effect modifiers for LBP treatments. Two of these reviews investigated effect modifiers for specific interventions (manual therapy/exercise and psychosocial intervention) [6, 7]. These reviews did not include MRI findings as potential effect modifiers. The third review specifically investigated Modic changes as effect modifiers [33]. Interestingly, all reviews found a limited number of suitable studies, which had inconsistent findings, had small sample sizes, and provided limited evidence for strong effect modifiers. These results corroborate our findings. The review investigating Modic changes as an effect modifier for different LBP treatments had several method limitations [33]; for example, the inclusion of single subgroup designs (i.e. studies including all people with Modic changes and no people without Modic changes) as these types of studies cannot robustly test if effect modification occurred [34].

Meaning of the study

From 38 treatment effect modification interactions investigated, only two were positive: one for LBP and one for sciatica populations. These positive findings could represent spurious findings. However, the lack of statistically significant interactions may also be partly due to most studies being underpowered for this type of analysis. Consequently, it remains unclear whether MRI findings are important effect modifiers for interventions for LBP and sciatica populations. What is clear is that there are very few trials and most of these are underpowered, reinforcing the need for more and larger trials in this potentially important and evolving area.

Recommendations for future research

Studies on subgroup interaction are a research priority in LBP [5] and well-conducted trials provide the possibility to answer the important and controversial question about the importance or otherwise of MRI findings. The need for larger, high-quality trials is evident. Due to the nature of subgroup and interaction analyses, such trials need a larger sample size than if their only interest was the main effect of treatment. One way to gain statistical power would be to combine several sets of individual patient data, to acquire an adequate number of individuals with and/or without an MRI finding of interest. Furthermore, it is important that future studies use standardised definitions of LBP, sciatica, MRI findings and clinical outcomes. Without this, it is very difficult to perform meta-analyses or compare findings between studies.

A key finding from our review was that only trials including surgery or injections had investigated MRI findings as effect modifiers for LBP interventions. We could find no evidence for the importance or otherwise of MRI findings for conservative interventions. While we recommend the need for larger, high-quality trials, it is important to note that limited evidence exists for the use of surgery in most patients with LBP [35].

Conclusions

This review identified eight studies that investigated if MRI findings identify patients with LBP and/or sciatica who respond better to a variety of interventions. Included studies recruited participants from secondary and tertiary health care settings. While two statistically significant interactions were found between specific MRI findings and response to treatment, the limited number of suitable studies and the heterogeneity between them did not permit definitive conclusions about effect modification. Further well-designed, adequately powered studies are required.

Acknowledgments We thank Professor Michele Crites-Battie and Professor Jeffrey G. Jarvik for reviewing included studies and suggesting possible additional studies. We also thank authors from the included studies for providing additional information.

Compliance with ethical standards

Conflict of interest None.

Appendix

See Tables 4, 5, 6 and 7.

Table 4 Search strategy 1

MEDLINE via Ovid and Cochrane Central of Controlled trials via The Cochrane Library

1. (Randomised controlled trial or controlled clinical trial or comparative study or clinical trial or clinical trials or randomised or placebo$ or random allocation or random$ or double-blind method or single-blind method).mp

[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

2. Animal/not human/
3. 1 not 2
4. (Low back pain or back pain or back strain or simple back pain or non-specific back pain or low back syndrome or low back dysfunction or lumbar pain or backache or lumbago or sciatica or radiculopathy).mp

[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

5. 3 and 4
6. (Magnetic resonance imaging or mri or magnetic resonance or nmr or nuclear magnetic resonance or disc degeneration or desiccation or loss of disc height or bulge or protrusion or extrusion or nerve root compromise or annular tear or endplate changes or stenosis or facet degeneration or high intensity zone or modic changes or degenerative disc disease or spondylolisthesis).mp

[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

7. 5 and 6

EMBASE (www.embase.com)

1. 'Randomised controlled trial'/exp OR 'randomised controlled trial' OR 'controlled study'/exp OR 'controlled study' OR 'double-blind procedure'/exp OR 'double-blind procedure' OR 'placebo'/exp OR 'placebo' OR 'random allocation'/exp OR 'random allocation' OR 'clinical trial'/exp OR 'clinical trial' OR 'clinical trials'/exp OR 'clinical trials' OR 'double blind' OR 'single blind'
2. 'Animal'/exp OR 'animal' OR 'not human'
3. #1 NOT #2
4. 'Low back pain'/exp OR 'low back pain' OR 'back pain'/exp OR 'back pain' OR 'lumbar pain'/exp OR 'lumbar pain' OR 'backache'/exp OR 'backache' OR 'lumbago'/exp OR 'lumbago' OR 'radiculopathy'/exp OR 'radiculopathy' Or 'sciatic$'
5. #3 AND #4
6. 'Magnetic resonance imaging'/exp OR 'magnetic resonance imaging' OR 'mri'/exp OR 'mri' OR 'nuclear magnetic resonance'/exp OR 'nuclear magnetic resonance' OR 'nmr'/exp OR 'nmr' OR 'disc degeneration'/exp OR 'disc degeneration' OR 'desiccation'/exp OR 'desiccation' OR 'loss of disc height' OR 'bulge' OR 'protrusion' OR 'extrusion' OR 'nerve root compression'/exp OR 'nerve root compression' OR 'annular tear' OR 'endplate changes' OR 'stenosis'/exp OR 'stenosis' OR 'facet degeneration' OR 'high intensity zone' OR 'modic changes' OR 'degenerative disc disease' OR 'spondylolisthesis'/exp OR 'spondylolisthesis'
7. #5 AND #6

Table 5 Search strategy 2

MEDLINE via Ovid and Cochrane Central of Controlled trials via The Cochrane Library
1. (Randomised controlled trial or controlled clinical trial or comparative study or clinical trial or clinical trials or randomised or placebo$ or random allocation or random$ or double-blind method or single-blind method).mp
[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. Animal/not human/
3. 1 not 2
4. (Low back pain or back pain or back strain or simple back pain or non-specific back pain or low back syndrome or low back dysfunction or lumbar pain or backache or lumbago or sciatica or radiculopathy).mp
[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 3 and 4
6. (Target intervent$ or targeted treatment$ or subgroup$ or treatment effect or effect mod$ or effect med$ or subgroup anal$).mp
[mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. 5 and 6
EMBASE (www.embase.com)
1. 'Randomised controlled trial'/exp OR 'randomised controlled trial' OR 'controlled study'/exp OR 'controlled study' OR 'double-blind procedure'/exp OR 'double-blind procedure' OR 'placebo'/exp OR 'placebo' OR 'random allocation'/exp OR 'random allocation' OR 'clinical trial'/exp OR 'clinical trial' OR 'clinical trials'/exp OR 'clinical trials' OR 'double blind' OR 'single blind'
2. 'Animal'/exp OR 'animal' OR 'not human'
3. #1 NOT #2
4. 'Low back pain'/exp OR 'low back pain' OR 'back pain'/exp OR 'back pain' OR 'lumbar pain'/exp OR 'lumbar pain' OR 'backache'/exp OR 'backache' OR 'lumbago'/exp OR 'lumbago' OR 'radiculopathy'/exp OR 'radiculopathy' Or 'sciatic$'
5. #3 AND #4
6. 'Target intervent$' OR 'targeted treatment$' OR 'subgroup$' OR 'treatment effect' OR 'effect mod$' OR 'effect med$' OR 'subgroup anal$'
7. #5 AND #6

Table 6 Criteria list for the risk of bias assessment

1. Randomisation: a random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colours, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number
2. Concealed allocation: assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient
3. Participant blinding: this item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful
4. Clinicians blinding: this item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful
5. Outcome assessor blinding: adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or
for patient-reported outcomes in which the patient is the outcome assessor (e.g. pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"
for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g. clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination
for outcome criteria that do not suppose a contact with participants (e.g. radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome

Table 6 continued

for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g. co-interventions, hospitalisation length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes";

for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data

6. Acceptable drop-out rate: The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop outs does not exceed 20 % for short-term follow-up and 30 % for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature)

7. Analysed according to treatment allocation: all randomised patients are reported/analysed in the group they were allocated to by randomisation for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions

8. Free of selective outcomes: in order to receive a "yes", the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment

9. Baseline similarity: in order to receive a "yes", groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s)

10. Co-interventions: this item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups

11. Compliance: the reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single session interventions (e.g. surgery), this item is irrelevant

12. Outcome timing: timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments

Table 7 List of excluded full-text articles and the primary reason for exclusion

References	Title	First reason for excluding
Ackerman et al. 1997	Persistent low back pain in patients suspected of having herniated nucleus pulposus: Radiologic predictors of functional outcome—implications for treatment selection	Not an RCT
Ahn et al. 2002	Comparison of clinical outcomes and natural morphologic changes between sequestered and large central extruded disc herniations	Not an RCT
Albert et al. 2013	Antibiotic treatment in patients with chronic low back pain and vertebral bone oedema (Modic type 1 changes): a double-blind randomised clinical controlled trial of efficacy	Not possible to elucidate association between MRI and outcome
Archer et al. 2014	Improving surgical spine outcomes through a targeted postoperative rehabilitation approach	No evaluation of MRI findings
Arts et al. 2011	Tubular diskectomy vs conventional microdiskectomy for the treatment of lumbar disk herniation: 2-Year results of a double-blind randomised controlled trial	Not possible to elucidate association between MRI and outcome
Brouwer et al. 2009	Effectiveness of percutaneous laser disc decompression versus conventional open discectomy in the treatment of lumbar disc herniation; design of a prospective randomised controlled trial	Not an RCT
Browder et al. 2007	Effectiveness of an extension-oriented treatment approach in a subgroup of subjects with low back pain: a randomised clinical trial	No evaluation of MRI findings
Brown 2012	A double-blind, randomised, prospective study of epidural steroid injection vs. the mild procedure in patients with symptomatic lumbar spinal stenosis	Not possible to elucidate association between MRI and outcome
Brox et al. 2010	Four-year follow-up of surgical versus non-surgical therapy for chronic low back pain	Not possible to elucidate association between MRI and outcome
Brox et al. 2003	Randomised clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration	Not possible to elucidate association between MRI and outcome
Chen et al. 2013	Efficacy analysis of sacral canal injection in patients with lumbar disc herniation associated with non-sciatica	Not possible to elucidate association between MRI and outcome
Childs et al. 2004	A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study	No evaluation of MRI findings

Table 7 continued

References	Title	First reason for excluding
Dahdaleh et al. 2013	Outcome following unilateral versus bilateral instrumentation in patients undergoing minimally invasive transforaminal lumbar interbody fusion: a single-center randomised prospective study	Not possible to elucidate association between MRI and outcome
El Barzouhi et al. 2013	Magnetic resonance imaging in follow-up assessment of sciatica	Not possible to elucidate association between MRI and outcome
El Barzouhi et al. 2013	Predictive value of MRI in decision making for disc surgery for sciatica: clinical article	Not possible to elucidate association between MRI and outcome
El Barzouhi et al. 2014	Back pain's association with vertebral end-plate signal changes in sciatica	Not possible to elucidate association between MRI and outcome
Erginousakis et al. 2011	Comparative prospective randomised study comparing conservative treatment and percutaneous disk decompression for treatment of intervertebral disk herniation	Not possible to elucidate association between MRI and outcome
Filiz et al. 2005	The effectiveness of exercise programmes after lumbar disc surgery: a randomised controlled study	Not possible to elucidate association between MRI and outcome
Forsth et al. 2014	No benefit from fusion in decompressive surgery for lumbar spinal stenosis. 2-year results from the swedish spinal stenosis study, a multicenter RCT of 229 patients	Not possible to elucidate association between MRI and outcome
Freburger et al. 2006	Effectiveness of physical therapy for the management of chronic spine disorders: a propensity score approach	Not an RCT
Fritz et al. 2007	Is there a subgroup of patients with low back pain likely to benefit from mechanical traction? Results of a randomised clinical trial and subgrouping analysis	No evaluation of MRI findings
Fritzell et al. 2001	Lumbar fusion versus nonsurgical treatment for chronic low back pain. A multicenter randomised controlled trial from the Swedish Lumbar Spine Study Group	Not possible to elucidate association between MRI and outcome
Fritzell et al. 2002	Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomised study from the Swedish Lumbar Spine Study Group	Not possible to elucidate association between MRI and outcome
Froholdt et al. 2011	No difference in long-term trunk muscle strength, cross-sectional area, and density in patients with chronic low back pain 7–11 years after lumbar fusion versus cognitive intervention and exercises	Not possible to elucidate association between MRI and outcome
Goldberg et al. 2015	Oral steroids for acute radiculopathy due to a herniated lumbar disk: a randomised clinical trial	Not possible to elucidate association between MRI and outcome
Goren et al. 2010	Efficacy of exercise and ultrasound in patients with lumbar spinal stenosis: a prospective randomised controlled trial	Not possible to elucidate association between MRI and outcome
Gudavalli et al. 2006	A randomised clinical trial and subgroup analysis to compare flexion–distraction with active exercise for chronic low back pain	Not possible to elucidate association between MRI and outcome
Hellum et al. 2011	Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two-year follow-up of randomised study	Not possible to elucidate association between MRI and outcome
Hemmila et al. 2002	Long-term effectiveness of bone-setting, light exercise therapy, and physiotherapy for prolonged back pain: a randomised controlled trial	Not possible to elucidate association between MRI and outcome
Huda et al. 2010	The efficacy of epidural depo-methylprednisolone and triamcinolone acetate in relieving the symptoms of lumbar canal stenosis: A comparative study	Not possible to elucidate association between MRI and outcome
Hurri et al. 1998	Lumbar spinal stenosis: assessment of long-term outcome 12 years after operative and conservative treatment	Not an RCT
Jarvinen et al. 2015	Association between changes in lumbar Modic changes and low back symptoms over a two-year period Clinical diagnostics and imaging	Not an RCT
Jensen et al. 2012	Rest versus exercise as treatment for patients with low back pain and Modic changes. A randomised controlled clinical trial	Not possible to elucidate association between MRI and outcome
Kaapa et al. 2012	Correlation of size and type of Modic types 1 and 2 lesions with clinical symptoms: a descriptive study in a subgroup of patients with chronic low back pain on the basis of a university hospital patient sample	Not an RCT
Kawu et al. 2011	Facet joints infiltration: a viable alternative treatment to physiotherapy in patients with low back pain due to facet joint arthropathy	Not an RCT
Kennedy et al. 2013	Multicenter randomised controlled trial comparing particulate versus nonparticulate corticosteroids via lumbar transforaminal epidural injection for acute unilateral, unilevel radicular pain due to herniated nucleus pulposus	Not possible to elucidate association between MRI and outcome

Table 7 continued

References	Title	First reason for excluding
Kerr et al. 2015	What are long-term predictors of outcomes for lumbar disc herniation? a randomised and observational study	Not possible to elucidate association between MRI and outcome
Koc 2009	Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis	Not possible to elucidate association between MRI and outcome
Koes et al. 1993	A randomised clinical trial of manual therapy and physiotherapy for persistent back and neck complaints: subgroup analysis and relationship between outcome measures	No evaluation of MRI findings
Koivisto et al. 2014	Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging	Not possible to elucidate association between MRI and outcome
Long et al. 2004	Does it matter which exercise? A randomised control trial of exercise for low back pain	No evaluation of MRI findings
Malmivaara et al. 2007	Surgical or nonoperative treatment for lumbar spinal stenosis? A randomised controlled trial	Not possible to elucidate association between MRI and outcome
Medrik-Goldberg et al. 1999	Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: a double-blind, randomised, controlled study	Not possible to elucidate association between MRI and outcome
Monro et al. 2015	Disc extrusions and bulges in nonspecific low back pain and sciatica: Exploratory randomised controlled trial comparing yoga therapy and normal medical treatment	Not possible to elucidate association between MRI and outcome
Moojen et al. 2015	IPD without bony decompression versus conventional surgical decompression for lumbar spinal stenosis: 2-year results of a double-blind randomised controlled trial	Not possible to elucidate association between MRI and outcome
Osterman et al. 2006	Effectiveness of microdiscectomy for lumbar disc herniation: a randomised controlled trial with 2 years of follow-up	Not possible to elucidate association between MRI and outcome
Peng et al. 2009	Diagnosis and surgical treatment of back pain originating from endplate	Not an RCT
Radcliff et al. 2011	Does opioid pain medication use affect the outcome of patients with lumbar disc herniation? A subgroup analysis of the SPORT study	No evaluation of MRI findings
Rajasekaran et al. 2013	Lumbar spinous process splitting decompression provides equivalent outcomes to conventional midline decompression in degenerative lumbar canal stenosis: a prospective, randomised controlled study of 51 patients	Not possible to elucidate association between MRI and outcome
Santilli et al. 2006	Chiropractic manipulation in the treatment of acute back pain and sciatica with disc protrusion: a randomised double-blind clinical trial of active and simulated spinal manipulations	Not possible to elucidate association between MRI and outcome
Sherman et al. 2009	Characteristics of patients with chronic back pain who benefit from acupuncture	No evaluation of MRI findings
Slatis et al. 2011	Long-term results of surgery for lumbar spinal stenosis: a randomised controlled trial	Not possible to elucidate association between MRI and outcome
Steenstra et al. 2009	What works best for whom? An exploratory, subgroup analysis in a randomised, controlled trial on the effectiveness of a workplace intervention in low back pain patients on return to work	Not possible to elucidate association between MRI and outcome
Styczynski et al. 2007	The effect of the grade of degenerative changes in the spine on the outcomes of surgery for lumbar discopathy with a radicular syndrome	Not an RCT
Underwood et al. 2007	Do baseline characteristics predict response to treatment for low back pain? Secondary analysis of the UK BEAM dataset	No evaluation of MRI findings
Vollenbroek-Hutten et al. 2004	Differences in outcome of a multidisciplinary treatment between subgroups of chronic low back pain patients defined using two multiaxial assessment instruments: the multidimensional pain inventory and lumbar dynamometry	No evaluation of MRI findings
Wilkens et al. 2012	No effect of 6-month intake of glucosamine sulphate on Modic changes or high intensity zones in the lumbar spine: sub-group analysis of a randomised controlled trial	Not possible to elucidate association between MRI and outcome
Zhang et al. 2014	Regression between MR findings of lumbar elements and chronic low back pain	Not an RCT
Zhuo et al. 2010	Effectiveness comparison of two surgical procedures on lumbar disc protrusion	Not an RCT

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