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The Association of Modic Changes and Chronic Low Back Pain: A Systematic Review

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Abstract:	Background Modic changes (MC) have been proposed as a cause of low back pain (LBP). However, the proposition remains controversial. There is uncertainty over the existence or degree of association between the two and whether, if there is an association, if it is a causal relationship. Previous systematic reviews of the evidence have had methodological flaws. Aims The aim was to synthesize the current evidence to test the hypothesis that there is an association between MC and LBP. Methods MEDLINE, EMBASE, and CINAHL were searched for all studies up to 31 December 2018 for observational l studies. Screening, quality assessment, and data extraction were conducted by two independent reviewers. Quality was assessed using the Joanna Biggs Institute tools. The clinical heterogeneity among these studies ruled out pooling so a narrative review was undertaken. Results Fifteen studies met the inclusion criteria, varying in patient characteristics, characteristics of MC, coexisting spinal conditions, and outcomes. The quality of evidence was poor in six and moderate seven. There was wide clinical heterogeneity amongst the studies. The inclusion ages varied from early teens to over 65s, pain duration varied from under 6 weeks to over three months, and characteristics of the MC chosen for the studies also differed. The results were inconsistent across the studies: the odds ratios varied from showing an inverse relationship [Kovacs] with an odds ratio 0.31 (95% confidence interval, 0.1-0.95) to a very strong positive association 121.4 (11.21–1315.08) [Nakamae]. There was no consistency in associations for: type of MC, lumbar levels affected, position in relation to the vertebra, and presence of co-existing spinal conditions. Only one study at low risk of bias found a substantial association but it was a small study of a narrow group meaning its results may not be generalizable. Discussion The inconsistency of findings and the possibility that they were spurious means that no conclusions can be drawn about an association between MC and LBP. Future research should be designed as prospective cohort studies . Currently, clinicians should not look for the presence or absence of MC to guide their management of patients with LBP.
Response to Reviewers:	We have included a detailed table of responses to reviewer in the revision files.

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Abstract

Background

Modic changes (MC) have been proposed as a cause of low back pain (LBP). However, the proposition remains controversial. There is uncertainty over the existence or degree of association between the two and whether, if there is an association, if it is a causal relationship. Previous systematic reviews of the evidence have had methodological flaws.

Aims

The aim was to synthesize the current evidence to test the hypothesis that there is an association between MC and LBP and if there is, to evaluate the strength of the association.

Methods

MEDLINE, EMBASE, and CINAHL were searched for all studies up to 31 December 2018 for cohort, case-control, and cross-sectional studies. Screening, quality assessment, and data extraction were conducted by two independent reviewers. Quality was assessed using the Joanna Biggs Institute tools for observational studies. The clinical heterogeneity among these studies ruled out pooling so a narrative review was undertaken.

Results

Fifteen studies met the inclusion criteria, varying in patient characteristics, characteristics of MC, coexisting spinal conditions, and outcomes. The quality of evidence was poor in six and moderate seven. There was wide clinical heterogeneity amongst the studies. The inclusion ages varied from early teens to over 65s, pain duration varied from under 6 weeks to over three months, and characteristics of the MC chosen for the studies also differed. The results were inconsistent across the studies: the odds ratios varied from showing an inverse relationship [Kovacs] with an odds ratio 0.31 (95% confidence interval, 0.1-0.95) to a very strong positive association 121.4 (11.21–1315.08) [Nakamae]. There was no consistency in associations for: type of MC, lumbar levels affected, position in relation to the vertebra, and presence of co-existing spinal conditions. The associations were possibly spurious arising from potential biases suggested by incomplete reporting: publication bias, selective reporting, and post hoc analysis. Only one study at low risk of bias found a substantial association but it was a small study of a narrow group meaning its results may not be generalizable.

Discussion

The inconsistency of findings and the possibility that they were spurious means that no conclusions can be drawn about an association between MC and LBP. Future research should be designed as prospective cohort studies with adherence to reporting guidelines pertaining to observational studies and to MRI. Currently, clinicians should not look for the presence or absence of MC to guide their management of patients with LBP.

Key words: Modic change; low back pain; etiology; vertebral endplate.

Background:

The terms non-specific low back pain (LBP) and mechanical LBP have found general acceptance because the precise tissue origin of pain is unascertainable in most cases and the condition comprises several pathologies. The advent of MRI introduced new contenders for an etiological role as well as changing our understanding of the part played by such pathologies as disc disorders and spinal stenosis. Vertebral endplate changes seen on MRI were first reported by Dr Roos in 1987 [1]and are often referred to as Modic Changes (MC) after Modic who classified them into three stages according to the T weight intensity [2]. Each type represents histological changes: 1 represents bone marrow oedema and inflammation, 2 is associated with conversion of normal red hemopoietic bone marrow into yellow fatty marrow as a result of marrow ischemia and 3 represents subchondral bony sclerosis [3]. The histological finding of oedema and inflammation led to speculation that MCs identify a process in the etiology of back pain or are even a cause of LBP. [new ref Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine (Phila Pa 1976). 2006; 31(9):1026–31. https:// doi.org/10.1097/01.brs.0000215027.87102.7c PMID: 16641780.] [New reference Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. European Spine Journal. 2016 Nov;25(11):3723-34.]

The contribution of MCs to the etiology of LBP has been investigated in numerous observational studies and has been the subject of four systematic reviews [4], [5] [6] [7] The review by Zhang et al [4] had a narrow search, no quality assessment, and incomplete reporting of included studies. Jensen et al [7]looked at two outcomes: reported pain occurring in life, which we refer to as 'usual pain', and pain produced on discography. Their quality assessment tool was not referenced. Brinjikji et al [5] confined their study to the under 50s potentially excluding many relevant studies given that LBP rises with age. Their reporting was incomplete, lacking the results of their quality assessment and results of individual studies. Herlin et al [6] were not able to draw any conclusions after a review of 31 studies. Several aspects of their review itself may have led to inconclusive results. First, they included two definitions of pain, usual pain and pain on discography. The false positive rate for discography varies between 10-90% and the level of evidence for its accuracy is low [8].

Commented [KH1]: I have shortened this section which the reviewer implied was too long. I also found that Jensen was incorrectly cited as [4] on its first citation

Second, they used a quality assessment tool, QUADAS, that was inappropriate for their studies [9]. Quality assessment tools appropriate for studies of etiology, namely cohort, cross-sectional and case-control studies do exist [10]. Despite numerous studies and four systematic reviews, doubt remains over any association between MC and LBP. We concluded that the inadequacies of previous reviews justify a further systematic review meeting the criteria recommended by the Cochrane Collaboration [11] [12] . We decided to confine the question to whether there is an association between MC and presence of LBP, choosing 'usual pain' as the outcome, and to use an appropriate quality assessment tool.

Aims

This review aimed to synthesize the current best evidence to test the hypothesis that there is an association between MC and LBP with any manifestation of LBP, either acute or chronic. If an association was found and the data suitable, a further aim was to pool the results to find the strength of the association.

Methods

Our protocol was registered with PROSPERO, registration number CRD42018117676 [13]. Our report is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [14]

Search strategy

We started with the studies in Herlin et al [6] then conducted a search from the termination date of their search up to 31 December 2018. We searched MEDLINE, EMBASE, and CINAHL, using the terms:

("lumbar spine" OR "lumbar Vertebra" OR "lumbosacral region" OR "low back")

AND

("MRI" OR "Magnetic Resonance Imaging" OR "diagnostic imaging")

AND

("Modic" OR "intervertebral disc degeneration" OR "Spondylosis" OR "end plate?" OR "bone marrow" OR "edema").

The references of retrieved papers were scrutinized for further references.

Inclusion criteria

Studies were eligible for inclusion if they were cohort, case control or cross-sectional because these are the most appropriate studies for questions of association and etiology [New ref Hennekens FH and Buring JF Epidemiology in medicine, p112 ff Little Brown and Company, Boston/Ontario, 1987). All other study types and studies of back pain due to inflammation, surgery or post-trauma were excluded. Reports had to be published in peer-reviewed journals in English, French or Spanish languages. There were no age or gender limitations.

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Screening and inclusion process

Two reviewers (SS, ER) independently screened titles and abstracts for article retrieval and full text articles for inclusion/exclusion. Any disagreements were resolved by consensus, involving the third team member (KH).

Classification of study types

We found confusion in the terminology of study design so provide clarification here. Cohort studies start by identifying people with exposure, the presence of MC, and controls without exposure. The groups are observed over time to compare outcomes, LBP. Case control studies start by identifying cases, meaning people who already have the outcome, match them with controls who do not have the condition and compare their exposures. Cross-sectional studies are conducted across a sample whose exposures and outcomes are

assessed contemporaneously. Several studies incorrectly identified their study design. Määttä 2015 [15] referred to their study as a longitudinal cohort because they resampled the same population a decade apart. However, exposed and control groups were not followed up as cohorts to compare their development of back pain over time. Rather a cross-sectional study was performed on two samples separated by time so theirs is more correctly classified as two cross-sectional studies. Nakamae [16]] referred to their study as cross-sectional because it looked at patients referred by family physicians. However, they compared two groups identified by their outcomes, those with back pain (cases) and those with leg pain (controls) so it was actually a case control study. A further source of confusion is that some studies recorded outcomes separately at successive periods, such as the previous week, month and year. Such studies should still be considered case-control or cross-sectional on the basis of whether they commenced with cases or exposures.

Quality assessment and data extraction

Quality assessment and data extraction were performed independently by two reviewers (SS, ER). Disagreements were settled by consensus involving the third team member (KH). The Joanna Biggs Institute (JBI) tools for quality assessment were chosen because they provide tools for all observational studies [10]. The JBI tools require the reviewer to evaluate each aspect of the study for risk of bias (ROB) as low, moderate, or high risk and then to judge their collective impact for an overall ROB. We created Direct Acyclic Graphs (DAGs) [17] to strengthen our evaluation of confounding and collider biases (question 5 and 6 for JBI cross-sectional and case-control studies respectively). According to the model, the minimal sufficient adjustment sets for estimating the total effect of MC on LBP were Age, BMI, Deformity, Occupation, Sex, Smoking, Trauma, past LBP.

The following data were extracted. Study characteristics: study type, country, setting. Participants: male to female ratio, mean and standard deviation/range of age. Exposure: type of MRI, MC. Studies differed in the exposures they selected, for example, the presence of any MC, different degrees of MC, lumbar level of MC and presence of other pathologies such as disc degeneration. Outcomes: odds ratios (OR) for the presence of Modic changes in patients with LBP over those without. When authors did not provide ORs, we

calculated them from the original tables. Some studies that used multiple exposures and multiple outcomes. For example, Määttä [18] presented over 60 exposure-outcome results. In these cases, we extracted only those results that related to the forementioned outcome.

Analysis

The heterogeneity of studies precluded a meta-analysis, so a narrative analysis was performed. Cross-sectional and case control studies were separated to explore any effect the presence of large proportions of healthy volunteers in the former might have on the ORs. We compared all studies for the differences in types of exposure and outcomes chosen.

Results

We identified 753 citations providing 31 eligible articles after screening to which we added 14 titles from Herlin [6] (Fig 1). Three additional articles were found through searching references in retrieved articles. After full text reading, 15 studies were included in the review (Table 1). They varied in patient characteristics, type of MRI, the selected exposure (the type and position of MC and presence of other conditions), and outcomes (duration of pain, intensity, episodes). We found ten cross-sectional, five case-control and no cohort studies (table 2). Four studies were of young populations [19]– [22] and one of older patients [23]. Three studies had too few cases of MC [20]–[22] so ORs could not be extracted or calculated. They were not entered into the analysis of outcomes. Several authors did not report important outcomes, raising the possibility that selective reporting may have biased their results. We wrote to authors requesting sight of their study protocols to compare the reported outcomes and analyses with those prespecified. We received replies from only two but did not receive any protocols. We considered whether the technical specifications of MRI and the interpretation of MRI findings might influence results. MC detection and classification can be influenced by MRI resolution. It has been suggested that the poor

sensitivity of MRI may underlie the variability in association between studies [37]. However, most studies reported using the same specifications, T1w and T2w, and all stated they were using the accepted criteria for MC classification [38].

Cross-sectional studies

We found two cross-sectional studies at low, six at moderate, and two at high ROB (Table 2). The population types varied greatly: geographic areas (town, region), industrial sectors, and national twin cohorts. The range of ORs were for any MC was within the range from 1.24 (0.4–3.6) to 6.48 (1.06-39.48) (Table 3). Kuisma [22] found that while both MC1 and MC2 had an association with LBP, the association was statistically significantly greater for type 1 and at the level L5/S1. Määttä 2016 [18], at moderate ROB, also found the effect size to be greater for MC1 (OR 1.80) than for type 2 (OR 1.36) but the difference was not statistically significant. Määttä 2015 [15] found that the horizontal length of the MC had an influence. MCs affecting the posterior two thirds of the vertebral endplate had an OR of 2.79 (1.17- 6.65) rising to 6.48 (1.06-39.48) if there were two or more such lesions. However, two matters caution against concluding that horizontal position is important in etiology. First, the CI was very wide (1.06 – 39.48). Second, the large number of subgroup analyses raises the possibility of a type 1 error (false positive). They analyzed twenty-three exposure-outcome combinations using 3 separate models without any adjustment to the significance level. The lower confidence limit was very close to 1. This raises the possibility that results would be not significant had appropriate adjustment been made for multiple analyses, such as by lowering the significance level [25]. Other studies too found an association only under certain conditions. Teraguchi [27] found no association for MC alone but did find an association when both disc degeneration and Schmorl's nodes were present together. Mok [28] found an association for any MC alone with only one of its outcomes, historic back pain at lower lumbar levels (L4/L5 to L5/S1). A point of concern is that they did not report the results for other spinal levels for comparison. In contrast, Kanayama [29] found an association only for MC at the level L4/S1 but not at L5/S1

Case-control studies

We found one study at low, two at moderate, and two at high ROB (table 2). Kovacs [30] produced a surprising result against the trend of all the other studies: a statistically significant inverse association between MC and LBP, 0.31 (0.10-0.95). The authors speculated that genetic differences in the Spanish population may have caused this divergence but that is no more than a conjecture. Nakamae [23] found that larger type 1 MCs (more than half the height of a vertebral body) had a much bigger effect, than smaller ones (less than half the height), with ORs of 121.4 (11.21–1315.08) and 13.32 (1.83-96.9) respectively. They studied a select population that differed from other studies: patients aged 65 or older with degenerative lumbar scoliosis. Acar Sivas et al [19] did not describe how they recruited their subjects. They found no significant association. Hancock [31] compared young patients with acute pain against well matched patients without current back pain. Using two independent assessors of the MRI, they found an OR of 6 or 10 for any MC. Sheng-yun 2014[32] was at high ROB because the inclusion criteria for LBP and description of the subjects were missing. They found an OR 2.07 (1.41–3.04). The range of ORs excluding Nakamae [23] ranged from 0.88 (0.08-10.23) to 13.32(1.83-96.9)

Discussion

Strengths and limitations

We aimed to evaluate the evidence that addresses the question: is there an association between MC and LBP? We believe that our review is the most appropriate methodologically to date. This review has four main strengths. First, our inclusion was comprehensive. Although we limited inclusion to four languages, no studies were excluded on grounds of language alone. Second, we used quality assessment tools that are appropriate to etiological studies. Third, our outcome was usual pain. Fourth, we analyzed the study characteristics to discover why the design and reporting of studies might have produced contradictory findings. The main limitation of the review was the low quality of many studies. Observational studies can provide high quality evidence but only if designed to minimize potential bias and

if reported to accepted standards [New ref Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Strobe Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Annals of internal medicine. 2007 Oct 16;147(8):573-7.] Later we discovered that we had missed one study, Schenk [39], not present in the review by Herlin et al.

Association between MC and LBP

Despite their heterogeneity, all studies, apart from three that had insufficient numbers of MC, reported outcomes that could be extracted or calculated as ORs to demonstrate whether or not there is a significant association and its magnitude. The following positive associations were found with MC: an episode of back pain in a lifetime [29], [33], [34]; more than one-episode [25], [35]; recent pain [25]; disabling or severe pain [18], [28], [33]; acute or recent pain [25], [31], [36]; chronic pain [23], [28], [30]. The following positive associations were found with pain: any MC of whatever type [36]; only MCs affecting the posterior two thirds of the vertebral endplate [33]; only when both disc degeneration and Schmorl's nodes were present [27]; MC at levels L4/L5 to L5/S1 [28]; MC at level L4/S1 [29]; MC at the level L5/S1 [25]; size of MC type 1 [23]. Ten out of the twelve studies that had relevant ORs found an association of MC, in some form or other, and LBP, in one manifestation or other. Most ORs were in the range from 1.47 (1.13–1.87) to 13.32 (1.83-96.9).

A high proportion of studies, ten out of twelve with a statistically significant positive finding might suggest that a true association between MC and LBP exists. However, there are several reasons to doubt such a conclusion. First, the quality of most studies was poor. Only three were at low ROB [21] [25][30] and only two provided ORs. How differences between them would influence outcome was unpredictable [25] [30]. Second, several studies, including those with moderate ROB, failed to report outcomes completely and analyzed multiple outcomes without adjustment. Third, the sub-group analyses with positive associations were contradictory between studies. Schenk et al[39] found an association for MC at just one level (in their case, L5/S1) but cautioned that their finding was insufficient

evidence without adjustment for multiple testing, just as we have cautioned, The combination of incomplete reporting, multiple testing, and sub-group analyses raises the possibility several biases may have been at work to result in selective reporting of outcomes, spurious associations through post hoc analysis, and publication bias.

Relation to other reviews

The Zhang [4] review was not sufficiently systematic for a comparison. Jensen [7] concluded that there was a strong association between all vertebral endplate signal changes, including MC, and LBP with ORs varying from 0.5 to 19.9. Brinjikji [5] reported that only MC type 1 was associated with LBP. Our results support the conclusions of Herlin [6] but go further. We agree that heterogeneity could explain some of the divergence in results, but we suggest that other factors raise serious doubts about the reliability of the evidence.

Implications for research

Future research in this area needs to be improved and there are four things that could lead to improvement. First, all observational studies should be registered before data collection so to preclude post hoc analysis[40]. The researchers we have cited must have submitted protocols for funding and ethical approval. Second, researchers should use standard criteria for LBP and for chronicity as set by guidelines [41] to permit comparison. Third, they should adhere to guidelines [37] for interpreting and reporting MCs. Fourth, to demonstrate that MC has a true relation to the development of back pain, a better approach would be a prospective, cohort study with long term follow up looking to see if those individuals who develop MC go on to suffer LBP. Two researchers we have cited have already identified cohorts, one in the UK [42] and another in Hong Kong [28] but did not appear to perform longitudinal follow up of individuals

Implications for clinical practice

The only conclusion that can be drawn from the existing literature is that any association between MC and LBP may be no more than a collection of type I errors. Indeed, one of the three studies with the highest quality and a large sample, Kovacs et al, found MC was inversely associated with the presence of LBP. Based on current knowledge, MC cannot explain the causation of LBP, whether acute or chronic. Clinicians should not pay attention to MC reported on MRI to guide their management.

Disclosure statements

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How data was gathered

This systematic review searched multiple databases. Two reviewers independently assessed eligibility of studies and study quality. Two reviewers independently extracted the data from included studies.

Key messages

Previous reviews of the role of Modic changes and back pain have not assessed the quality of studies appropriately nor considered the problem of multiple analyses. The inconsistency of findings and the possibility of spurious associations means that an aetiological role for Modic changes remains unproven. Currently, clinicians have no reason to consider such changes in their management of patients with low back pain.

The Association of Modic Changes and Chronic Low Back Pain: A Systematic Review

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The Association of Modic Changes and Chronic Low Back Pain: A Systematic Review

Abstract

Background

Modic changes (MC) have been proposed as a cause of low back pain (LBP). Previous systematic reviews have not sufficiently analysed the differences between studies nor used appropriate tools for assessing their quality.

Aims

To provide an updated systematic review of the association between MC and LBP.

Methods

Commencing with results of the last systematic review, a further search was made from its termination date for observational studies. Screening, quality assessment, and data extraction were conducted by two independent reviewers. Quality was assessed using the Joanna Biggs Institute tools for observational studies. A narrative synthesis exploring the differences between studies was conducted.

Results

Fifteen studies met the inclusion criteria, varying in patient characteristics, characteristics of MC, coexisting spinal conditions, and outcomes. Six were at low and seven at moderate risk of bias. The results were inconsistent with associations reported for: type of MC,

lumbar levels affected, position in relation to the vertebra, and co-existing conditions. The associations were possibly spurious arising from potential biases suggested by incomplete reporting: publication bias, selective reporting, and post hoc analysis. Only one study at low risk of bias found a substantial association but it was a small study of a narrow group meaning its results may not be generalizable.

Discussion

The inconsistency of findings and the possibility that they were spurious means that any association between MC and LBP has not been demonstrated. Future research should be designed as prospective cohort studies with adherence to reporting guidelines pertaining to observational studies and to MRI. Currently, clinicians have no reason to consider MC in their management of patients with LBP.

Key words: Modic change; low back pain; aetiology; vertebral endplate.

Background:

The terms non-specific low back pain (LBP) and mechanical LBP have found general acceptance because the precise tissue origin of pain is unascertainable in most cases and the condition comprises several pathologies. The advent of MRI introduced new contenders for an aetiological role as well as changing our understanding of the part played by such pathologies as disc disorders and spinal stenosis. Vertebral endplate changes seen on MRI were first reported by Dr Roos in 1987 [1]and are often referred to as Modic Changes (MC) after Modic classified them into three stages according to the T weight intensity [2]. Each type represents histological changes: 1 represents bone marrow oedema and inflammation, 2 is associated with conversion of normal red hemopoietic bone marrow into yellow fatty marrow as a result of marrow ischemia and 3 represents subchondral bony sclerosis [3]

The contribution of MCs to the aetiology of LBP has been investigated in many studies and has been the subject of four systematic reviews: Zhang [4], Jensen [4], Brinjikji [5] and Herlin , [6] The review by Zhang had lacked many characteristics of a systematic review: lack of a focused question, search of only one database, incomplete reporting of inclusion and exclusion criteria, and absence of quality assessment. Jensen reviewed 10 studies of the association of MC with LBP. Their outcomes were twofold: either reported pain occurring in life, which we refer to as 'usual pain', or pain produced on discography. They used a quality assessment tool that was not referenced. Brinjikji [5] confined their study to the under 50s. Since the prevalence of LBP rises with age, this could potentially have excluded relevant studies. Their report was incomplete, lacking the results of their quality assessment and results of individual studies although providing a pooled Odds Ratio (OR).

Herlin [6] updated the review of Jensen [7], asking three questions. First, is MC associated with LBP? Second, is MC associated with activity limitation? Third, if the answer to the first or second is affirmative, what factors modify the association? They concluded that the results of studies are inconsistent for which the explanation could be the high risk of bias and the heterogeneity in study samples and clinical outcomes. Several aspects of the review itself may have led to inconclusive results. First, they included two definitions of pain, usual pain and pain on discography. The false positive rate for discography varies between 10-90% and the level of evidence for its

accuracy is low [8]. Second, activity limitation is a consequence of LBP and is influenced by psychological characteristics. Adding activity limitation as an outcome does not shed more light on the role of MC in LBP because psychological characteristics could act as confounders. Third, they used a quality assessment tool, QUADAS that was inappropriate for their studies [9]. QUADAS was designed for the assessment of cross-sectional studies of diagnostic test accuracy [9]. It does not evaluate aspects of research relevant to studies of aetiology, such as dealing with confounding and measurement of outcome. Quality assessment tools appropriate for studies of aetiology, namely cohort, cross-sectional and case-control studies do exist [10]

We concluded that the characteristics of previous reviews justify a further systematic review according to criteria recommended by the Cochrane Collaboration [11] and later confirmed in a consensus statement [12] . We decided to confine the question to whether there is an association between MC and presence of LBP, choosing 'usual pain' as the outcome, and to use an appropriate quality assessment tool. Our review aimed to clarify whether there is an association of MC with any manifestation of LBP, either acute or chronic.

Methods

Our protocol was registered with PROSPERO, registration number CRD42018117676 [13]. Our report is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [14]

Search strategy

We started with the case control and cross-sectional studies, except for discography studies, included by Herlin et al [6] then conducted a search from the termination date of their search up to 31 December 2018. We searched MEDLINE, EMBASE, and CINAHL, using the terms: ("lumbar spine" OR "lumbar Vertebra" OR "lumbosacral region" OR "low back")

AND

(“MRI” OR “Magnetic Resonance Imaging” OR “diagnostic imaging”)

AND

(“Modic” OR “intervertebral disc degeneration” OR “Spondylosis” OR “end plate?” OR “bone marrow” OR “edema”).

The references of retrieved papers were scrutinized for further references.

Inclusion criteria

Studies were eligible for inclusion if they were case control or cross-sectional. All other study types and studies of back pain due to inflammation, surgery or post-trauma were excluded. Reports had to be published in peer-reviewed journals in English, French or Spanish languages. There were no age or gender limitations.

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Screening and inclusion process

Two reviewers (SS, ER) independently screened titles and abstracts for article retrieval and full text articles for inclusion/exclusion. Any disagreements were resolved by consensus, involving the third team member (KH).

Classification of study types

We found confusion in the terminology of study design so provide clarification here. Cohort studies start by identifying people with exposure, the presence of MC, and controls without exposure. The groups are observed over time to compare outcomes, LBP. Case control studies start by identifying cases, meaning people who already have the outcome, match them with controls who do not have the condition and compare their exposures. Cross-sectional studies are conducted across a sample whose exposures and outcomes are assessed contemporaneously. Several studies incorrectly identified their study design. Määttä 2015 [15] referred to their study as a longitudinal cohort because they resampled the same population a decade apart. However, exposed and control groups were not followed

up as cohorts to compare their development of back pain over time. Rather a cross-sectional study was performed on two samples separated by time so theirs is more correctly classified as two cross-sectional studies. Nakamae [16]] referred to their study as cross-sectional because it looked at patients referred by family physicians. However, they compared two groups identified by their outcomes, those with back pain (cases) and those with leg pain (controls) so it was actually a case control study. A further source of confusion is that some studies recorded outcomes separately at successive periods, such as the previous week, month and year. Such studies should still be considered case-control or cross-sectional on the basis of whether they commenced with cases or exposures.

Quality assessment and data extraction

Quality assessment and data extraction were performed independently by two reviewers (SS, ER). Disagreements were settled by consensus involving the third team member (KH). The Joanna Biggs Institute (JBI) tools for quality assessment were chosen because they provide tools for both case control and cross-sectional studies [10]. The JBI tools require the reviewer to evaluate each aspect of the study for risk of bias (ROB) as low, moderate, or high risk and then to judge their collective impact for an overall ROB. We created Direct Acyclic Graphs (DAGs) [17] to strengthen our evaluation of confounding and collider biases (question 5 and 6 for JBI cross-sectional and case-control studies respectively). According to the model, the minimal sufficient adjustment sets for estimating the total effect of MC on LBP were Age, BMI, Deformity, Occupation, Sex, Smoking, Trauma, past LBP.

The following data were extracted. Study characteristics: study type, country, setting. Participants: male to female ratio, mean and standard deviation/range of age. Exposure: type of MRI, MC. Studies differed in the exposures they selected, for example, the presence of any MC, different degrees of MC, lumbar level of MC and presence of other pathologies such as disc degeneration. Outcomes: odds ratios (OR) for the presence of Modic changes in patients with LBP over those without. When authors did not provide ORs, we calculated them from the original tables. Some studies that used multiple exposures and multiple outcomes. For example, Määttä [18] presented over 60 exposure-outcome results. In these cases, we extracted only those results that related to the forementioned outcome.

Analysis

The heterogeneity of studies precluded a meta-analysis, so a narrative analysis was planned. Cross-sectional and case control studies were separated to explore any effect the presence of large proportions of healthy volunteers in the former might have on the ORs. We compared all studies for the differences in types of exposure and outcomes chosen.

Results

We identified 753 citations providing 31 eligible articles after screening to which we added 14 titles from Herlin [6] (Fig 1). Three additional articles were found through searching references in retrieved articles. After full text reading, 15 studies were included in the review (Table 1). They varied in patient characteristics, type of MRI, the selected exposure (the type and position of MC and presence of other conditions), and outcomes (duration of pain, intensity, episodes). We found ten cross-sectional, five case-control and no cohort studies (table 2). Four studies were of young populations [19]– [22] and one of older patients [23]. Three studies had too few cases of MC [20]–[22] so ORs could not be extracted or calculated. They were not entered into the analysis of outcomes. Several authors did not report important outcomes, raising the possibility that selective reporting may have biased their results. We wrote to authors requesting sight of their study protocols to compare the reported outcomes and analyses with those prespecified. We received replies from only two but did not receive any protocols.

Cross-sectional studies

We found two cross-sectional studies at low, six at moderate, and two at high ROB (Table 2). The population types varied greatly: geographic areas (town, region), industrial sectors, and national twin cohorts. The range of ORs were for any MC was within the range

from 1.24 (0.4–3.6) to 6.48 (1.06-39.48) (Table 3). The only one of the studies at low ROB to return an OR, Kuisma [22] found that while both MC1 and MC2 had an association with LBP, the association was statistically significantly greater for type 1 and at the level L5/S1. Määttä 2016 [18], at moderate ROB, also found the effect size to be greater for MC1 (OR 1.80) than for type 2 (OR 1.36) but the difference was not statistically significant. Määttä 2015 [15], at moderate ROB, found that the horizontal length of the MC had an influence. MCs affecting the posterior two thirds of the vertebral endplate had an OR of 2.79 (1.17- 6.65) rising to 6.48 (1.06-39.48) if there were two or more such lesions. However, two matters caution against concluding that horizontal position is important in aetiology. First, the CI was very wide (1.06 – 39.48). Second, the large number of subgroup analyses raises the possibility of a type 1 error (false positive). They analysed twenty-three exposure-outcome combinations using 3 separate models without any adjustment to the significance level. The lower confidence limit was very close to 1. This raises the possibility that results would be not significant had appropriate adjustment been made for multiple analyses, such as by lowering the significance level [25]. Other studies too found an association only under certain conditions. Teraguchi [27], at moderate low ROB, found no association for MC alone but did find an association when both disc degeneration and Schmorl's nodes were present together. Mok [28], at moderate ROB, found an association for any MC alone with only one of its outcomes, historic back pain, and only for lower lumbar levels (L4/L5 to L5/S1). A point of concern is that they did not report the results for other spinal levels for comparison. In contrast, Kanayama [29], at moderate ROB, found an association only for MC at the level L4/S1 but not at L5/S1

Case-control studies

We found one study at low, two at moderate, and two at high ROB (table 2). Kovacs [30], at low ROB and a large sample with a well-matched control group, produced a surprising result against the trend of all the other studies: a statistically significant inverse association between MC and LBP 0.31 (0.10-0.95). The authors speculated that genetic differences in the Spanish population may have caused this divergence but that is no more than conjecture. Nakamae [23] at moderate ROB, found that larger type 1 MCs (more than half the height of a vertebral body) had a much bigger effect, than smaller ones (less than half the height), with ORs of 121.4 (11.21–1315.08) and 13.32

(1.83-96.9) respectively. They studied a select population that differed from other studies: patients aged 65 or older with degenerative lumbar scoliosis. Acar Sivas et al [19], at high ROB, did not describe how they recruited their subjects. They found no significant association. Hancock [31], at moderate ROB and a small sample, compared young patients with acute pain against well matched patients without current back pain. Using two independent assessors of the MRI, they found an OR of 6 or 10 for any MC. Sheng-yun 2014[32] was at high ROB because the inclusion criteria for LBP and description of the subjects were missing. They found an OR 2.07 (1.41–3.04). The range of ORs excluding Nakamae [23] ranged from 0.88 (0.08-10.23) to 13.32(1.83-96.9)

Discussion

Our review aimed to evaluate the evidence that addresses the question, is there an association between MC and LBP? Included studies differed in their aims thus the chosen exposures and outcomes varied. In terms of exposures, all studies looked for any type of MC, but some looked for additional features such as type of MC [23], [25], [27], spinal level [25], position of MC [18]and size of MC [23]. Several also looked at the combined effect of MC and other spinal conditions, such as disc degeneration [18], [19], [21], [22], [27], [29], [31]– [33]. The outcomes varied too. Some studied acute pain in the past [27], [31], either recent or distant, while others studied chronic pain [19], [23], [30], [33]**.** The criterion for chronicity varied from 30 days to over six months. Some used episodes of pain at any point in a person's life as the outcome [22], [29]**.** Lifetime LBP prevalence is high, so it is understandable that some authors selected only more serious cases, using a cut off for severity of pain [28], pain leading to disability [33], or pain needing treatment [24]. Despite these diverse aims, all studies had in common a search for an association between MC and LBP and, apart from three that had insufficient

numbers of MC, reported outcomes that could be extracted or calculated as ORs to demonstrate whether or not there is a significant association and its magnitude.

The following positive associations were found with MC: an episode of back pain in a lifetime [29], [33], [34]; more than one-episode [25], [35]; recent pain [25]; disabling or severe pain [18], [28], [33]; acute or recent pain [25], [31], [36]; chronic pain [23], [28], [30]. The following positive associations were found with pain: any MC of whatever type [36]; only MCs affecting the posterior two thirds of the vertebral endplate [33]; only when both disc degeneration and Schmorl's nodes were present [27]; MC at levels L4/L5 to L5/S1 [28]; MC at level L4/S1 [29]; MC at the level L5/S1 [25]; size of MC type 1 [23]. Ten out of the twelve studies that had relevant ORs found an association of MC, in some form or other, and LBP, in one manifestation or other. Most ORs were in the range from 1.47 (1.13–1.87) to 13.32 (1.83-96.9).

A high proportion of studies, ten out of twelve with a statistically significant positive finding suggest confirmation of a true association between MC and LBP. However, there are several reasons to doubt such a conclusion. First, the quality of most studies was poor. Only three were at low ROB [21] [25][30] and only two provided ORs. How these differences would influence outcome was unpredictable [25] [30]. They had similar sample sizes, Kuisma [25] 228 and Kovacs et al [30] 304. Second, several studies, including those with moderate ROB, failed to report outcomes completely and analysed multiple outcomes without adjustment. Third, the sub-group analyses with positive associations were contradictory between studies. The combination of incomplete reporting, multiple testing, and sub-group analyses raises the possibility several biases may have been at work to give type I (false positive) errors: selective reporting of outcomes, spurious associations through post hoc analysis, and publication bias.

We considered whether the characteristics of the populations could explain the conflicting findings. Age varied from teenagers to the elderly. The studies that did not have enough cases of MC to report results were those with young populations Kjaer [20] (mean age 13),

Koyama [21] (19.7) and Takatalo [22] (21.2). This observation confirms what is already known, that MC changes are more common with ageing but the question of whether or not they are associated with LBP remains. Comparing the two best studies, while the size of their samples was similar, one was a cross-sectional study drawing volunteers from industry 25 while the other was a case-control study drawing patients referred for MRI 30. Nakamae [23] stand out from all other studies with a very large effect size and this may well be due to its cases, older people with lumbar scoliosis. We also considered whether the technical specifications of MRI and the interpretation of findings could explain the conflicting findings. MC detection and classification can be influenced by MRI resolution, the presence of other spinal conditions, and variability in interpretation. It has been suggested that the poor sensitivity of MRI may underlie the variability in association between studies [37]. This could explain the variability in the strength of association between our included studies. However, most studies reported using the same specifications, T1w and T2w, and all stated they were using the accepted criteria for MC classification [38].

Strengths and limitations

This review has four main strengths. First, our inclusion was comprehensive. Although we limited inclusion to four languages, no studies were excluded on grounds of language alone. Second, we used quality assessment tools that are appropriate to aetiological studies. Third, our outcome was usual pain. Fourth, we analysed the study characteristics to discover why the design and reporting of studies might have produced particular findings. No previous systematic reviews worked to all four criteria. The main limitation of the review was the low-quality of many studies. Later we discovered that we had missed one study, Schenk [39], not present in the review by Herlin [6].

Relation to other reviews

The Zhang [4] review was not sufficiently systematic for a comparison. Jensen [7] concluded that there was a strong association between all vertebral endplate signal changes, including MC, and LBP with ORs varying from 0.5 to 19.9. However, of the ten studies on which this conclusion was based, only five studied usual pain, as we have termed it, and of those, two did not compare LBP versus control, rather they followed up patients who had had an intervention (36, 37). Of the remaining three, Schenk et al [39] cautioned, as we have done, that finding an association for MC at just one level (in their case, L5/S1) is insufficient evidence without adjustment for multiple testing. Brinjikji [5] reported that only MC type 1 was associated with LBP. This conclusion was drawn by comparing the OR for all MC changes, 1.62 (0.48–5.41) with MC 1 changes 4.01 (1.10–14.55). However, we believe this conclusion to be unjustified. because there were only 5 studies in the former group and two in the latter, without any assessment of the study quality. Our results support the conclusions of Herlin [6] but go further. We agree that heterogeneity could explain some of the divergence in results, but we suggest that other factors raise serious doubts about the reliability of the evidence.

Implications for research and clinical practice

The solution to eliminate the potential biases we have identified is to implement the suggestion that all observational studies are registered before data collection [40]. The researchers we have cited must have submitted protocols for funding and ethical approval. Protocols for future observational studies of back pain should be registered publicly so that readers and reviewers can confirm that analysis and reporting were kept to protocol. Journals should demand registration as a condition for publication, as is the case for clinical trials. The widely differing eligibility criteria for enrolment between studies hinders comparison and synthesis of results. Comparison of future studies would be made easier and more reliable if standard criteria were used for eligibility. Research definitions of LBP and of the chronicity of LBP exist [41]. They should adhere to it unless there are exceptional reasons for not doing so. In such cases, researchers should be expected to justify exceptional reasons. Adherence to guidelines [37] for interpreting and reporting MCs would make comparison between studies more accurate.

Given that several cross-sectional and case control studies have failed to arrive at consensus, it is hard to envisage that future similar studies will add useful information. To demonstrate that MC has a true relation to the development of back pain, a better approach would be a prospective, cohort study with long term follows up looking for not just an association between MC and LBP but also their temporal relationship, The temporal relationships to consider include whether MC precedes LBP and whether it is linked to acute and/or chronic pain. Two researchers we have cited have already identified cohorts, one in the UK [42] and another in Hong Kong [28] but did not appear to perform longitudinal follow up of individuals. It is possible that the literature associating MC and LBP may be no more than a collection of type I errors so there is no evidence to suggest that clinicians should pay attention to these MRI findings in practice.

Disclosure statements

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Figure 1: Flow of studies selection

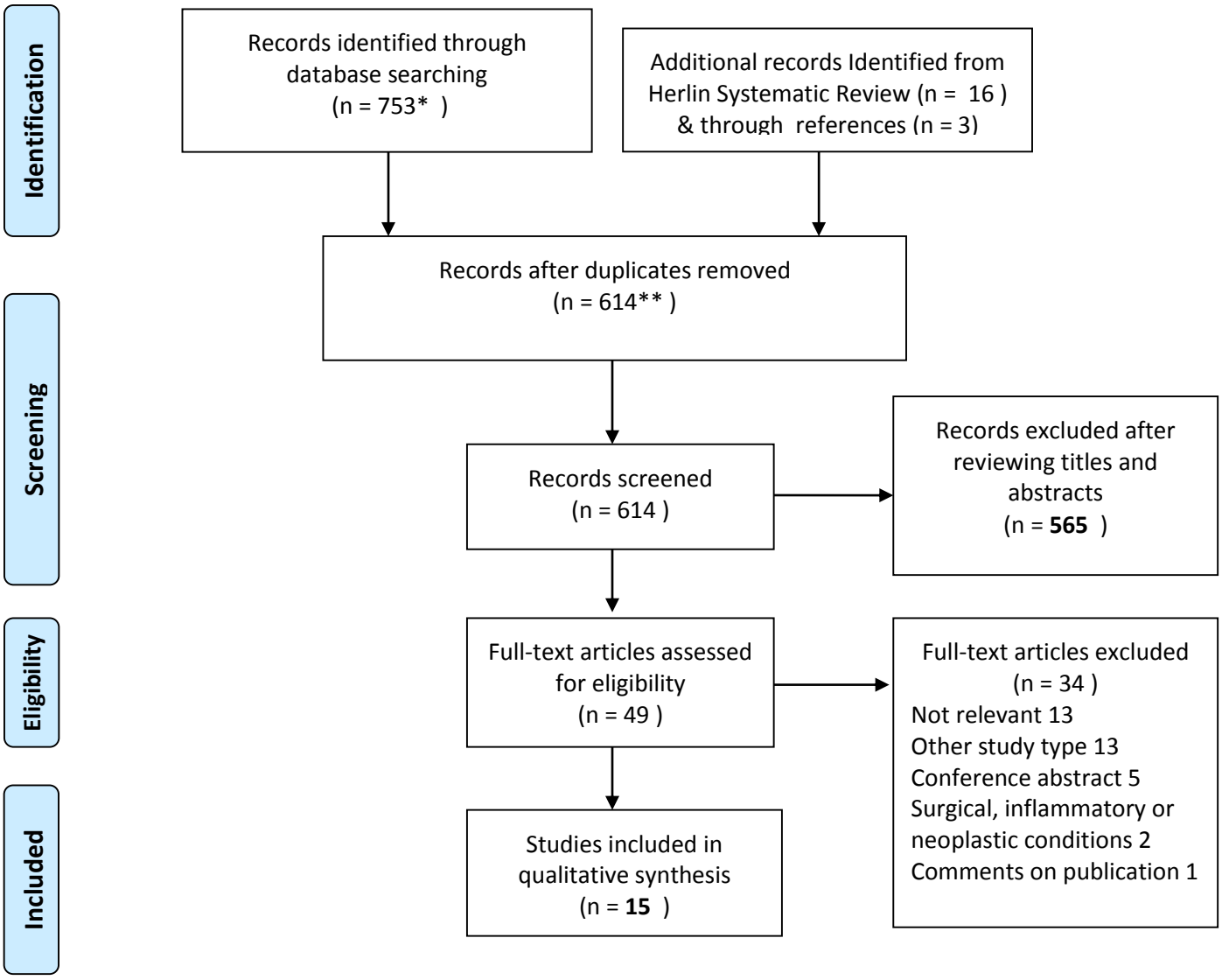

Table 1.
Characteristics of the included studies

Study	Setting	Population	MRI signal strength and sequence	N	Sex Male:Female	Age Range or SD
Cross sectional studies						
Kanayama 2009	Uncertain	Healthy volunteers excluding those with back pain requiring sick leave or any form of treatment	1.5 T. T2w	200	68:132	Mean 39.5 (Range 30-35)
Kjaer 2005a	Community single town	Randomly selected sample adults aged 40 years of age invited to participate	0.2 T. T1w, T2w	412	199:213	40
Kjaer 2005b	Community single town	Selected from previous cardiovascular study, age approximately 13	0.2 T. T1w, T2w	439	205:234	Mean 13.1 (Range 12-14)
Koyama 2013	High performing gymnasts	College gymnasts	0.3-T, T1w, T2w	104	70;34	Mean 19.7 (SD 1.0)
Kuisma 2007	Community industrial	Volunteers from railway (heavy manual) and factories (sedentary)	1.5 T. T1w, T2w, FLAIR	228 (159 train, 69 in factories)	228:0	47 (Range 36 –56)
Maatta 2015	Community National register	Twin pairs recruited from the TwinsUK register, one set from register in 1996 and a second set a decade later	1.0T, T2w	Initial sample: 823 Decade later Sample 429	1.8:98.1% 4.3:95.7%	54 (SD 8) 64 (SD7)
Maatta 2016	Community Hong Kong	Hong Kong Disc Degeneration Population-Based Cohort Study recruited by open invitation for adults with newspaper advertisements, posters, and e-mails without particularly seeking subjects with LBP. There were no exclusion criteria concerning LBP.	3.0 T. T1w, T2w	1142	37:63%	52.9 (SD 5.9)
Mok 2016	Community Hong Kong	Hong Kong Disc Degeneration Population-Based Cohort Study recruited by open invitation for adults with newspaper advertisements, posters, and e-mails without particularly seeking subjects with LBP. There were no exclusion criteria concerning LBP.	1.5T, T2w	2449	Not stated	40.4 (SD 10.9)

Takatalo 2012	Part of a longitudinal study 1986 Northern Finland Birth Cohort	Birth cohort who responded to invitation to have lumbar MRI and back pain assessment	1.5T, T1w, T2w	554	233:321	21.2 (Range 20-23)
Teraguchi 2015	Three communities from The Wakayama Spine Study (a population-based study of spinal degenerative disease)	Ambulant volunteers from communities	1.5T, T2w	975	324:651	66.4 (Range21–97)
Case control studies						
Acar Sivas 2009	Low back pain outpatient clinic	Patients referred to low back pain clinic and healthy volunteers	1.5T, T2w	71	Cases 5:22 Controls 10:38	Ranges Cases:22–30 Controls:25–30
Hancock 2012	Physiotherapy clinics	Patients referred to physiotherapy clinics with back pain < 6 weeks duration and PH ≤ 2 episodes back pain Healthy volunteers recruited from institution and matched for age, sex and PH back pain	1.5 T. T1w, T2w	60	53%:47%	Cases: 36.8 (SD 7.4) Controls: 36.6 (SD 7.4)
Kovacs 2012	Hospital radiology departments	Patients referred for lumbar MRI for back pain >90 days (cases) or cranial MRI for headache (controls)	1.5 T. T1w, T2w	304	36%: 64%	Controls 43 (Range 38–47) Controls: 45 (Range 41– 47)
Nakamae 2016	Tertiary medical centre	Patients referred by family doctors for back or leg pain aged 65 or over and suffering from degenerative lumbar scoliosis. Compared patients with back pain (cases) versus patients with leg pain (controls)	1.5 T. T1w, T2w	120	30:90	LBP 75(SD 5.3) Leg pain 76.6 (SD 5.1)
Sheng-yun 2014	Hospital	Patients seen in one year period 2011 with neck pain, back pain or other problem	1.5T, T1w, T2w	2024	1127:897	Only means for subgroups reported Overall range 22-86

Table 2.
Risk of bias assesment

Cross-sectional studies	Clear inclusion criteria	Study, subjects, & setting detailed	Exposure validly &reliably measured	Objective, standard case definition	Confounding factors identified	Confounding factors managed	Outcomes validly & reliably measured	appropriate statistical analysis			**Overall**
Kanayama 2009	○	○	○	●	◐	●	●	○			●
Kjaer 2005a	○	○	○	○	◐	◐	◐	○			◐
Kjaer 2005b	○	○	○	○	●	●	●	○			●
Koyama 2013	○	○	○	○	◐	○	○	○			○
Kuisma 2007	○	○	○	○	◐	○	○	○			○
Määttä 2015	○	○	○	○	◐	●	○	○			◐
Määttä 2016	◐	○	○	○	◐	●	○	○			◐
Mok 2016	○	○	○	○	○	◐	●	◐			◐
Takatalo 2012	○	○	○	○	◐	◐	○	○			◐
Teraguchi 2015	○	○	◐	○	◐	◐	○	○			◐

Case-Control Studies	Comparable groups	Appropriate matching	Cases & controls consistently identified	Exposure validly & reliably measured	Exposure measured consistently	Confounding factors identified	Confounding factors managed	Outcomes validly & reliably measured	Duration of exposure	Appropriate statistical analysis	Overall
Acar Sivas 2009	●	◐	○	○	○	●	●	○	◐	○	●

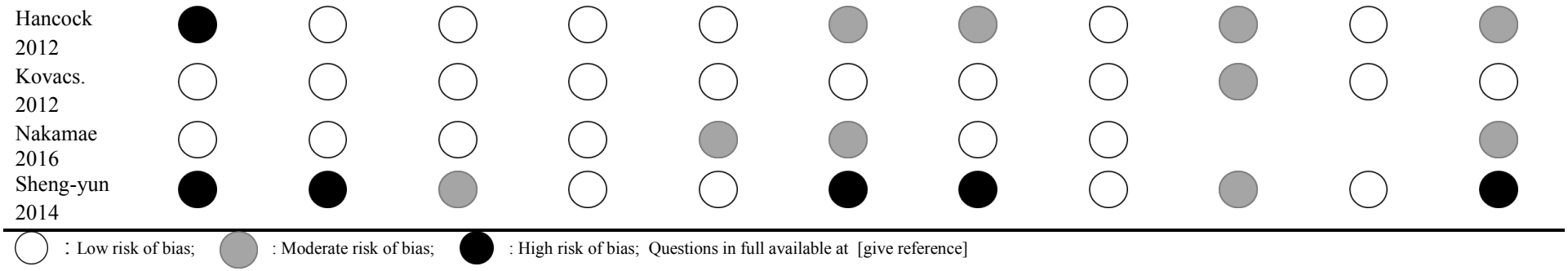
Hancock 2012
Kovacs. 2012
Nakamae 2016
Sheng-yun 2014
：Low risk of bias;
: Moderate risk of bias;
: High risk of bias; Questions in full available at [give reference]

Table 3.

Effect size of association between exposures and outcomes.

Study	Exposure	Outcome	OR (95%CI)
Cross sectional studies			
Kanayama 2009	Any MC, DD, SN, HIZ, DH, and spondylolisthesis	Episode of low back pain	3.46 (1.09-10.94)
Kjaer 2005a	Any MC, Signal intensity, Nuclear shape, Disc height, Annular Tears, HIZ, Z-joint degeneration Z-joint asymmetry Central spinal stenosis, Foraminal spinal stenosis, Anterolisthesis, Retrolisthesis	(1) low back pain in previous month, (2) previous year, (3) sought care for back pain	1.9 (1.2–3.00) 4.2 (2.2–8.2) 1.9 (1.1–3.1)
Kjaer 2005b	Any MC, Signal intensity, Nuclear shape, Disc height, Annular tears, HIZ, Disc contour, Nerve root compromise Anterolisthesis	(1) back pain in previous month (2) back pain having impact	NC
Koyama 2013	Any MC, lumbar DD, Degree of disc displacement HIZ, SN, Limbus vertebra, Spondylolisthesis	Presence of low back pain at time of study	NC
Kuisma 2007	MC at any level, MC at L1-4, L4-5, L5-S Any MC, MC 1 or 2 Extent of MC change, DD, nerve root compromise, and central spinal stenosis Results are shown here for all MC at all levels	(1) Number of episodes LBP ≥ 2w (2) Pain past week (3) Pain past three months	(1) 2.62 (1.47–3.86) (2) 1.47 (1.13–1.87) (3) 1.51 (1.17–1.90)
Määttä **2015**	Any MC	Disabling low back pain >1month (1) 1996 sample (2) 2006 sample	 (1) 2.71 (1.98-3.81) (2) 2.20 (1.42-3.39)
Määttä **2016**	Any MC, The anteroposterior length of MC in relation to the vertebral, DD (1) MC 2/3 of posterior length (2) ≥ 2 MCs of 2/3 posterior length	History of disabling back pain ≥ 1 month	(1) 2.79 (1.17 – 6.65) (2) 6.48(1.06-39.48)
Mok 2016	Any MC, SN, HIZ, Spondylolistheis	Severe prolonged LBP (VAS>6/10 and duration >30 days)	1.93 (1.05-3.54)
Takatalo 2012	Any MC, DD, DH , SN, HIZ, Spondylolisthesis	LBP (1) ever (2) past year (3) past month (4) past week (5) on the day	NC
Teraguchi 2015	MC type 1 and 2, DN, SN, Each alone and in combination	Low back pain most days in previous month	MC 1.24 (0.4–3.6) MC+DD 1.60 (1.1–2.3) MC + DD + SN 2.85

			(1.1–2.3)
Case control studies			
Acar Sivas 2009	Any MC, DD, Annular tear, Disc bulging, Disc protrusion	LBP >3 months	0.88 (0.08-10.23)
Hancock 2012	Any MC by independent assessors (1) and (2), DD, HIZ , annular tears, DH	Moderate pain < 6 weeks duration	(1) 6.00 (1.17–30.73) (2) 10.71(2.15-53.35)
Kovacs. 2012	Any MC, Severe disc changes	Back pain ≥ 90 days	0.31 (0.1-0.95)
Nakamae 2016	MC type 1 size in relation to height of vertebra: 1) less than half 2) more than half	LBP > 6 months	(1) 13.32 (1.83-96.9) (2) 121.4 (11.21–1315.08)
Sheng-yun 2014	Any MC, DD, Lumbar lordosis	LBP	2.07(1.41-3.04)

DD:disc degeneration, DH,disc herniation, HIZ=high-intensity zone, MC modic changes, SN Schmorl's node, NC not calculable, VAS=visual analogue scale.

ICMJE DISCLOSURE FORM

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Your Name: Saeed Soliman

Manuscript Title: The Association of Modic Changes and Chronic Low Back Pain: A Systematic Review

Manuscript Number (if known): JOO-S-22-00862

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Authors contribution: Kevork Hopayian: Conceptualization, Methodology, Software, Formal Analysis, Data Curation, Investigation, Visualization, Validation, Writing – Original draft, Supervision**. Eman Raslan:** Formal Analysis, Data Curation, Investigation, Writing- Reviewing and Editing. **Saeed Soliman:** Methodology, Software, Formal Analysis, Data Curation, Investigation, Visualization, Writing- Reviewing and Editing,

The Association of Modic Changes and Chronic Low Back Pain: A Systematic Review

Abstract

Background

~~Modic changes (MC) have been proposed as a cause of low back pain (LBP). Previous systematic reviews have not sufficiently analysed the differences between studies nor used appropriate tools for assessing their quality.~~ Modic changes (MC) are changes in the vertebral endplates seen on magnetic resonance imaging (MRI) that correlate with histological changes. They have been proposed as a cause of low back pain (LBP). However, the proposition remains controversial. There is uncertainty over the existence or degree of association between the two and whether, if there is an association, if it is a causal relationship. Previous systematic reviews of the evidence have had methodological flaws.

Aims

~~To~~ The aim was to synthesize the current evidence to test the hypothesis that there is an association between MC and LBP and if there is, to evaluate the strength of the association. ~~provide an updated systematic review of the association between MC and LBP.~~

Methods

MEDLINE, EMBASE, and CINAHL were searched for all studies up to 31 December 2018 for cohort, case-control, and cross-sectional studies~~Commencing with results of the last systematic review, a further search was made from its termination date for observational studies~~. Screening, quality assessment, and data extraction were conducted by two independent reviewers. Quality was assessed using

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the Joanna Biggs Institute tools for observational studies. The clinical heterogeneity among these studies ruled out pooling so a narrative review was undertaken ~~A narrative synthesis exploring the differences between studies was conducted~~.

Results

Fifteen studies met the inclusion criteria, varying in patient characteristics, characteristics of MC, coexisting spinal conditions, and outcomes. The quality of evidence was poor in six and moderate seven. There was wide clinical heterogeneity amongst the studies. The inclusion ages varied from early teens to over 65s, pain duration varied from under 6 weeks to over three months, and characteristics of the MC chosen for the studies also differed. ~~Six were at low and seven at moderate risk of bias.~~ The results were inconsistent across the studies: the odds ratios varied from showing an inverse relationship ~~with~~ [Kovacs] with an odds ratio 0.31 (95% confidence interval, 0.1-0.95) to a very strong positive association 121.4 (11.21–1315.08) [Nakamae]. There was no consistency in associations ~~associations reported~~ for: type of MC, lumbar levels affected, position in relation to the vertebra, and presence of co-existing spinal conditions. The associations were possibly spurious arising from potential biases suggested by incomplete reporting: publication bias, selective reporting, and post hoc analysis. Only one study at low risk of bias found a substantial association but it was a small study of a narrow group meaning its results may not be generalizable.

Discussion

The inconsistency of findings and the possibility that they were spurious means that no conclusions can be drawn about an~~y~~ association between MC and LBP ~~has not been demonstrated~~. Future research should be designed as prospective cohort studies with adherence to reporting guidelines pertaining to observational studies and to MRI. Currently, clinicians ~~have no reason to consider~~should not look for the presence or absence of MC ~~in~~ to guide their management of patients with LBP.

Key words: Modic change; low back pain; ~~aetiology~~etiology; vertebral endplate.

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Background:

The terms non-specific low back pain (LBP) and mechanical LBP have found general acceptance because the precise tissue origin of pain is unascertainable in most cases and the condition comprises several pathologies. The advent of MRI introduced new contenders for an ~~aetiological~~etiological role as well as changing our understanding of the part played by such pathologies as disc disorders and spinal stenosis. Vertebral endplate changes seen on MRI were first reported by Dr Roos- in 1987 [1]and are often referred to as Modic Changes (MC) after Modic who classified them into three stages according to the T weight intensity [2]. Each type represents histological changes: 1 represents bone marrow oedema and inflammation, 2 is associated with conversion of normal red hemopoietic bone marrow into yellow fatty marrow as a result of marrow ischemia and 3 represents subchondral bony sclerosis [3]. The histological finding of oedema and inflammation led to speculation that MCs identify a process in the etiology of back pain or are even a cause of LBP. [new ref Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine (Phila Pa 1976). 2006; 31(9):1026–31. https:// doi.org/10.1097/01.brs.0000215027.87102.7c PMID: 16641780.] [New reference Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. European Spine Journal. 2016 Nov;25(11):3723-34.]

The contribution of MCs to the ~~aetiology~~etiology of LBP has been investigated in ~~many~~ numerous observational studies and has been the subject of four ~~the subject of four~~ systematic reviewss~~: Zhang~~ [4], ~~Jensen [4], Brinjikji~~ [5] ~~and Herlin ,~~ [6] [7] The review by Zhang et al [4] ~~had lacked many characteristics of a systematic review: lack of a focused question,~~ had a narrow search ~~of only one database~~, no quality assessment, and incomplete reporting of included studies~~sion. and exclusion criteria, and absence of quality assessment.~~ Jensen et al [7]~~reviewed 10 studies of the association of MC with LBP. Their~~looked at two outcomes ~~were twofold~~: ~~either~~ reported pain occurring in life, which we refer to as 'usual pain', ~~or~~ and pain produced on discography. Theiry ~~used a~~ quality assessment tool ~~that~~ was not referenced. Brinjikji et al [5] confined their study to the under 50s~~. Since the prevalence of LBP rises with age, this could potentially~~

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~~have~~ potentially excluding many~~ed~~ relevant studies given that LBP rises with age. Their reporting~~t~~ was incomplete, lacking the results of their quality assessment and results of individual studies.~~s although providing a pooled Odds Ratio (OR).~~

Herlin et al [6] ~~updated the review of Jensen [7], asking three questions. First, is MC associated with LBP? Second, is MC associated with activity limitation? Third, if the answer to the first or second is affirmative, what factors modify the association? They concluded that the results of studies are inconsistent for which the explanation could be the high risk of bias and the heterogeneity in study samples and clinical outcomes~~were not able to draw any conclusions after a review of 31 studies. Several aspects of their review itself may have led to inconclusive results. First, they included two definitions of pain, usual pain and pain on discography. The false positive rate for discography varies between 10-90% and the level of evidence for its accuracy is low [8]. Second~~d, activity limitation is a consequence of LBP and is influenced by psychological characteristics. Adding activity limitation as an outcome does not shed more light on the role of MC in LBP because psychological characteristics could act as confounders. Third~~, they used a quality assessment tool, QUADAS, that was inappropriate for their studies [9]. ~~QUADAS was designed for the assessment of cross-sectional studies of diagnostic test accuracy [9]. It does not evaluate aspects of research relevant to studies of aetiology, such as dealing with confounding and measurement of outcome.~~ Quality assessment tools appropriate for studies of ~~aetiology~~etiology, namely cohort, cross-sectional and case-control studies do exist [10]. Despite numerous studies and four systematic reviews, doubt remains over any association between MC and LBP.

We concluded that the ~~characteristics~~ inadequacies of previous reviews justify a further systematic review ~~according~~ meeting the~~to~~ criteria recommended by the Cochrane Collaboration [11] ~~and later confirmed in a consensus statement~~ [12] . We decided to confine the question to whether there is an association between MC and presence of LBP, choosing 'usual pain' as the outcome, and to use an appropriate quality assessment tool. ~~Our review aimed to clarify whether there is an association of MC with any manifestation of LBP, either acute or chronic.~~

Aims

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~~Our review aimed to clarify whether there is an association of MC with any manifestation of LBP, either acute or chronic.~~

This review aimed to synthesize the current best evidence to test the hypothesis that there is an association between MC and LBP with any manifestation of LBP, either acute or chronic. If an association was found and the data suitable, a further aim was to pool the results to find the strength of the association.

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Methods

Our protocol was registered with PROSPERO, registration number CRD42018117676 [13]. Our report is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. [14]

Search strategy

We started with the ~~case control and cross sectional~~ studies in~~, except for discography studies, included by~~ Herlin et al [6] then conducted a search from the termination date of their search up to 31 December 2018. We searched MEDLINE, EMBASE, and CINAHL, using the terms:

("lumbar spine" OR "lumbar Vertebra" OR "lumbosacral region" OR "low back")

AND

("MRI" OR "Magnetic Resonance Imaging" OR "diagnostic imaging")

AND

("Modic" OR "intervertebral disc degeneration" OR "Spondylosis" OR "end plate?" OR "bone marrow" OR "edema").

The references of retrieved papers were scrutinized for further references.

Inclusion criteria

Studies were eligible for inclusion if they were cohort, case control or cross-sectional because these are the most appropriate studies for questions of association and etiology [New ref Hennekens FH and Buring JF Epidemiology in medicine, p112 ff Little Brown and Company, Boston/Ontario, 1987). All other study types and studies of back pain due to inflammation, surgery or post-trauma were excluded. Reports had to be published in peer-reviewed journals in English, French or Spanish languages. There were no age or gender limitations.

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Screening and inclusion process

Two reviewers (SS, ER) independently screened titles and abstracts for article retrieval and full text articles for inclusion/exclusion. Any disagreements were resolved by consensus, involving the third team member (KH).

Classification of study types

We found confusion in the terminology of study design so provide clarification here. Cohort studies start by identifying people with exposure, the presence of MC, and controls without exposure. The groups are observed over time to compare outcomes, LBP. Case control studies start by identifying cases, meaning people who already have the outcome, match them with controls who do not have the condition and compare their exposures. Cross-sectional studies are conducted across a sample whose exposures and outcomes are assessed contemporaneously. Several studies incorrectly identified their study design. Määttä 2015 [15] referred to their study as a longitudinal cohort because they resampled the same population a decade apart. However, exposed and control groups were not followed up as cohorts to compare their development of back pain over time. Rather a cross-sectional study was performed on two samples separated by time so theirs is more correctly classified as two cross-sectional studies. Nakamae [16]] referred to their study as cross-sectional because it looked at patients referred by family physicians. However, they compared two groups identified by their outcomes, those with back pain (cases) and those with leg pain (controls) so it was actually a case control study. A further source of confusion is

that some studies recorded outcomes separately at successive periods, such as the previous week, month and year. Such studies should still be considered case-control or cross-sectional on the basis of whether they commenced with cases or exposures.

Quality assessment and data extraction

Quality assessment and data extraction were performed independently by two reviewers (SS, ER). Disagreements were settled by consensus involving the third team member (KH). The Joanna Biggs Institute (JBI) tools for quality assessment were chosen because they provide tools for ~~both case-control and cross-sectional~~all observational studies [10]. The JBI tools require the reviewer to evaluate each aspect of the study for risk of bias (ROB) as low, moderate, or high risk and then to judge their collective impact for an overall ROB. We created Direct Acyclic Graphs (DAGs) [17] to strengthen our evaluation of confounding and collider biases (question 5 and 6 for JBI cross-sectional and case-control studies respectively). According to the model, the minimal sufficient adjustment sets for estimating the total effect of MC on LBP were Age, BMI, Deformity, Occupation, Sex, Smoking, Trauma, past LBP.

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The following data were extracted. Study characteristics: study type, country, setting. Participants: male to female ratio, mean and standard deviation/range of age. Exposure: type of MRI, MC. Studies differed in the exposures they selected, for example, the presence of any MC, different degrees of MC, lumbar level of MC and presence of other pathologies such as disc degeneration. Outcomes: odds ratios (OR) for the presence of Modic changes in patients with LBP over those without. When authors did not provide ORs, we calculated them from the original tables. Some studies that used multiple exposures and multiple outcomes. For example, Määttä [18] presented over 60 exposure-outcome results. In these cases, we extracted only those results that related to the forementioned outcome.

Analysis

The heterogeneity of studies precluded a meta-analysis, so a narrative analysis was ~~planned~~performed. Cross-sectional and case control studies were separated to explore any effect the presence of large proportions of healthy volunteers in the former might have on the ORs. We compared all studies for the differences in types of exposure and outcomes chosen.

Results

We identified 753 citations providing 31 eligible articles after screening to which we added 14 titles from Herlin [6] (Fig 1). Three additional articles were found through searching references in retrieved articles. After full text reading, 15 studies were included in the review (Table 1). They varied in patient characteristics, type of MRI, the selected exposure (the type and position of MC and presence of other conditions), and outcomes (duration of pain, intensity, episodes). We found ten cross-sectional, five case-control and no cohort studies (table 2). Four studies were of young populations [19]– [22] and one of older patients [23]. Three studies had too few cases of MC [20]–[22] so ORs could not be extracted or calculated. They were not entered into the analysis of outcomes. Several authors did not report important outcomes, raising the possibility that selective reporting may have biased their results. We wrote to authors requesting sight of their study protocols to compare the reported outcomes and analyses with those prespecified. We received replies from only two but did not receive any protocols. We considered whether the technical specifications of MRI and the interpretation of MRI findings might influence results. MC detection and classification can be influenced by MRI resolution. It has been suggested that the poor sensitivity of MRI may underlie the variability in association between studies [37]. However, most studies reported using the same specifications, T1w and T2w, and all stated they were using the accepted criteria for MC classification [38].

Cross-sectional studies

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We found two cross-sectional studies at low, six at moderate, and two at high ROB (Table 2). The population types varied greatly: geographic areas (town, region), industrial sectors, and national twin cohorts. The range of ORs were for any MC was within the range from 1.24 (0.4–3.6) to 6.48 (1.06-39.48) (Table 3). ~~The only one of the studies at low ROB to return an OR,~~ Kuisma [22] found that while both MC1 and MC2 had an association with LBP, the association was statistically significantly greater for type 1 and at the level L5/S1. Määttä 2016 [18], at moderate ROB, also found the effect size to be greater for MC1 (OR 1.80) than for type 2 (OR 1.36) but the difference was not statistically significant. Määttä 2015 [15] ~~, at moderate ROB,~~ found that the horizontal length of the MC had an influence. MCs affecting the posterior two thirds of the vertebral endplate had an OR of 2.79 (1.17- 6.65) rising to 6.48 (1.06-39.48) if there were two or more such lesions. However, two matters caution against concluding that horizontal position is important in ~~aetiology~~etiology. First, the CI was very wide (1.06 – 39.48). Second, the large number of subgroup analyses raises the possibility of a type 1 error (false positive). They ~~analysed~~analyzed twenty-three exposure-outcome combinations using 3 separate models without any adjustment to the significance level. The lower confidence limit was very close to 1. This raises the possibility that results would be not significant had appropriate adjustment been made for multiple analyses, such as by lowering the significance level [25]. Other studies too found an association only under certain conditions. Teraguchi [27] ~~, at moderate low ROB,~~ found no association for MC alone but did find an association when both disc degeneration and Schmorl's nodes were present together. Mok [28] ~~, at moderate ROB,~~ found an association for any MC alone with only one of its outcomes, historic back pain at ~~, and only for~~ lower lumbar levels (L4/L5 to L5/S1). A point of concern is that they did not report the results for other spinal levels for comparison. In contrast, Kanayama [29] ~~, at moderate ROB,~~ found an association only for MC at the level L4/S1 but not at L5/S1

Case-control studies

We found one study at low, two at moderate, and two at high ROB (table 2). Kovacs [30] ~~, at low ROB and a large sample with a well-matched control group,~~ produced a surprising result against the trend of all the other studies: a statistically significant inverse association between MC and LBP, 0.31 (0.10-0.95). The authors speculated that genetic differences in the Spanish population may have caused this

divergence but that is no more than a conjecture. Nakamae [23] ~~at moderate ROB,~~ found that larger type 1 MCs (more than half the height of a vertebral body) had a much bigger effect, than smaller ones (less than half the height), with ORs of 121.4 (11.21–1315.08) and 13.32 (1.83-96.9) respectively. They studied a select population that differed from other studies: patients aged 65 or older with degenerative lumbar scoliosis. Acar Sivas et al [19]~~, at high ROB,~~ did not describe how they recruited their subjects. They found no significant association. Hancock [31]~~, at moderate ROB and a small sample,~~ compared young patients with acute pain against well matched patients without current back pain. Using two independent assessors of the MRI, they found an OR of 6 or 10 for any MC. Sheng-yun- 2014[32] was at high ROB because the inclusion criteria for LBP and description of the subjects were missing. They found an OR 2.07 (1.41–3.04). The range of ORs excluding Nakamae [23] ranged from 0.88 (0.08-10.23) to 13.32(1.83-96.9)

Discussion

Strengths and limitations

We aimed to evaluate the evidence that addresses the question: is there an association between MC and LBP? We believe that our review is the most appropriate methodologically to date. This review has four main strengths. First, our inclusion was comprehensive. Although we limited inclusion to four languages, no studies were excluded on grounds of language alone. Second, we used quality assessment tools that are appropriate to etiological studies. Third, our outcome was usual pain. Fourth, we analyzed the study characteristics to discover why the design and reporting of studies might have produced contradictory findings. The main limitation of the review was the low quality of many studies. Observational studies can provide high quality evidence but only if designed to minimize potential bias and if reported to accepted standards [New ref Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Strobe

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Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Annals of internal medicine. 2007 Oct 16;147(8):573-7.] Later we discovered that we had missed one study, Schenk [39], not present in the review by Herlin et al.

Association between MC and LBP

~~Our review aimed to evaluate the evidence that addresses the question, is there an association between MC and LBP? Included studies differed in their aims thus the chosen exposures and outcomes varied. In terms of exposures, all studies looked for any type of MC, but some looked for additional features such as type of MC [23], [25], [27], spinal level [25], position of MC [18]and size of MC [23]. Several also looked at the combined effect of MC and other spinal conditions, such as disc degeneration [18], [19], [21], [22], [27], [29], [31] - [33]. The outcomes varied too. Some studied acute pain in the past [27], [31], either recent or distant, while others studied chronic pain [19], [23], [30], [33]. The criterion for chronicity varied from 30 days to over six months. Some used episodes of pain at any point in a person's life as the outcome [22], [29]. Lifetime LBP prevalence is high, so it is understandable that some authors selected only more serious cases, using a cut off for severity of pain [28], pain leading to disability [33], or pain needing treatment [24]. Despite these diverse aims, all studies had in common a search for an association between MC and LBP and, apart from three that had insufficient numbers of MC, reported outcomes that could be extracted or calculated as ORs to demonstrate whether or not there is a significant association and its magnitude.~~

Despite their heterogeneity, all studies, apart from three that had insufficient numbers of MC, reported outcomes that could be extracted or calculated as ORs to demonstrate whether or not there is a significant association and its magnitude.

The following positive associations were found with MC: an episode of back pain in a lifetime [29], [33], [34]; more than one-episode [25], [35]; recent pain [25]; disabling or severe pain [18], [28], [33]; acute or recent pain [25], [31], [36]; chronic pain [23], [28], [30].

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The following positive associations were found with pain: any MC of whatever type [36]; only MCs affecting the posterior two thirds of the vertebral endplate [33]; only when both disc degeneration and Schmorl's nodes were present [27]; MC at levels L4/L5 to L5/S1 [28]; MC at level L4/S1 [29]; MC at the level L5/S1 [25]; size of MC type 1 [23]. Ten out of the twelve studies that had relevant ORs found an association of MC, in some form or other, and LBP, in one manifestation or other. Most ORs were in the range from 1.47 (1.13–1.87) to 13.32 (1.83-96.9).

A high proportion of studies, ten out of twelve with a statistically significant positive finding might suggest ~~confirmation of~~that a true association between MC and LBP exists. However, there are several reasons to doubt such a conclusion. First, the quality of most studies was poor. Only three were at low ROB [21] [25][30] and only two provided ORs. How ~~these~~ differences between them would influence outcome was unpredictable [25] [30]. ~~They had similar sample sizes, Kuisma [25] 228 and Kovacs et al [30] 304.~~ Second, several studies, including those with moderate ROB, failed to report outcomes completely and ~~analysed~~analyzed multiple outcomes without adjustment. Third, the sub-group analyses with positive associations were contradictory between studies. Schenk et al[39] found an association for MC at just one level (in their case, L5/S1) but cautioned that their finding was insufficient evidence without adjustment for multiple testing, just as we have cautioned. The combination of incomplete reporting, multiple testing, and sub-group analyses raises the possibility several biases may have been at work to result in selective reporting of outcomes, spurious associations through post hoc analysis, and publication bias. ~~The combination of incomplete reporting, multiple testing, and sub-group analyses raises the possibility several biases may have been at work to give type I (false positive) errors: selective reporting of outcomes, spurious associations through post hoc analysis, and publication bias.~~

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~~We considered whether the characteristics of the populations could explain the conflicting findings. Age varied from teenagers to the elderly. The studies that did not have enough cases of MC to report results were those with young populations Kjaer [20] (mean age 13), Koyama [21] (19.7) and Takatalo [22] (21.2). This observation confirms what is already known, that MC changes are more common with~~

~~ageing but the question of whether or not they are associated with LBP remains. Comparing the two best studies, while the size of their samples was similar, one was a cross-sectional study drawing volunteers from industry 25 while the other was a case-control study drawing patients referred for MRI 30. Nakamae [23] stand out from all other studies with a very large effect size and this may well be due to its cases, older people with lumbar scoliosis. We also considered whether the technical specifications of MRI and the interpretation of findings could explain the conflicting findings. MC detection and classification can be influenced by MRI resolution, the presence of other spinal conditions, and variability in interpretation. It has been suggested that the poor sensitivity of MRI may underlie the variability in association between studies [37]. This could explain the variability in the strength of association between our included studies. However, most studies reported using the same specifications, T1w and T2w, and all stated they were using the accepted criteria for MC classification [38].~~

~~*Strengths and limitations*~~

~~This review has four main strengths. First, our inclusion was comprehensive. Although we limited inclusion to four languages, no studies were excluded on grounds of language alone. Second, we used quality assessment tools that are appropriate to aetiological studies. Third, our outcome was usual pain. Fourth, we analysed the study characteristics to discover why the design and reporting of studies might have produced particular findings. No previous systematic reviews worked to all four criteria. The main limitation of the review was the low quality of many studies. Later we discovered that we had missed one study, Schenk [39], not present in the review by Herlin [6].~~

Relation to other reviews

The Zhang [4] review was not sufficiently systematic for a comparison. Jensen [7] concluded that there was a strong association between all vertebral endplate signal changes, including MC, and LBP with ORs varying from 0.5 to 19.9. ~~However, of the ten studies on which~~

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this conclusion was based, only five studied usual pain, as we have termed it, and of those, two did not compare LBP versus control, rather they followed up patients who had had an intervention (36, 37). Of the remaining three, Schenk et al [39] cautioned, as we have done, that finding an association for MC at just one level (in their case, L5/S1) is insufficient evidence without adjustment for multiple testing. Brinjikji [5] reported that only MC type 1 was associated with LBP. This conclusion was drawn by comparing the OR for all MC changes, 1.62 (0.48–5.41) with MC 1 changes 4.01 (1.10–14.55). However, we believe this conclusion to be unjustified. because there were only 5 studies in the former group and two in the latter, without any assessment of the study quality . Our results support the conclusions of Herlin [6] but go further. We agree that heterogeneity could explain some of the divergence in results, but we suggest that other factors raise serious doubts about the reliability of the evidence.

Implications for research and clinical practice

The Fsolution to eliminate the potential biases we have identified is to implement the suggestionuture research in this area needs to be improved and there are four things that could lead to improvement. First, a that all observational studies are should be registered before data collection so to preclude post hoc analysis [40]. The researchers we have cited must have submitted protocols for funding and ethical approval. Protocols for future observational studies of back pain should be registered publicly so that readers and reviewers can confirm that analysis and reporting were kept to protocol. Second, researchers should use Journals should demand registration as a condition for publication, as is the case for clinical trials. The widely differing eligibility criteria for enrolment between studies hinders comparison and synthesis of results. Comparison of future studies would be made easier and more reliable if standard criteria were used for eligibility. Research definitions offor LBP and of thefor chronicity as set by guidelines of LBP exist [41] to permit comparison. Third, they should They should adhere to it unless there are exceptional reasons for not doing so. In such cases, researchers should be expected to justify exceptional reasons. aAdherence to guidelines [37] for interpreting and reporting MCs would make comparison between studies more accurate. Fourth,Given that several cross-sectional and case-control studies have failed to arrive at consensus, it is hard to envisage

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~~that future similar studies will add useful information~~ t~~. To~~ demonstrate that MC has a true relation to the development of back pain, a better approach would be a prospective, cohort study with long term follow~~s~~ up looking ~~for not just an association between MC and LBP but also their temporal relationship~~to see if those individuals who develop MC go on to suffer LBP~~. The temporal relationships to consider include whether MC precedes LBP and whether it is linked to acute and/or chronic pain.~~ Two researchers we have cited have already identified cohorts, one in the UK [42] and another in Hong Kong [28] but did not appear to perform longitudinal follow up of individuals

Implications for clinical practice

~~Given that several cross-sectional and case control studies have failed to arrive at consensus, it is hard to envisage that future similar studies will add useful information. To demonstrate that MC has a true relation to the development of back pain, a better approach would be a prospective, cohort study with long term follows up looking for not just an association between MC and LBP but also their temporal relationship, The temporal relationships to consider include whether MC precedes LBP and whether it is linked to acute and/or chronic pain. Two researchers we have cited have already identified cohorts, one in the UK [42] and another in Hong Kong [28] but did not appear to perform longitudinal follow up of individuals~~The only conclusion that can be drawn from ~~. It is possible that~~ the existing literature is that any association between~~ng~~ MC and LBP may be no more than a collection of type I errors. Indeed, one of the three studies with the highest quality and a large sample, Kovacs et al, found MC was inversely associated with the presence of LBP. Based on current knowledge, MC cannot explain the causation of LBP, whether acute or chronic. C~~so there is no evidence to suggest that~~ clinicians should not pay attention to ~~these~~ MC reported on MRI ~~findings in~~to guide their management~~. practice.~~

Disclosure statements

Acknowledgments

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Authors contribution: Kevork Hopayian: Conceptualization, Methodology, Software, Formal Analysis, Data Curation, Investigation, Visualization, Validation, Writing – Original draft, Supervision**. Eman Raslan:** Formal Analysis, Data Curation, Investigation, Writing-Reviewing and Editing. **Saeed Soliman:** Methodology, Software, Formal Analysis, Data Curation, Investigation, Visualization, Writing-Reviewing and Editing,

~~**Authors contribution**: provided in separate file~~

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