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Refined Phenotyping of Modic Changes

Imaging Biomarkers of Prolonged Severe Low Back Pain and Disability

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Abstract: Low back pain (LBP) is the world's most disabling condition. Modic changes (MC) are vertebral bone marrow changes adjacent to the endplates as noted on magnetic resonance imaging. The associations of specific MC types and patterns with prolonged, severe LBP and disability remain speculative. This study assessed the relationship of prolonged, severe LBP and back-related disability, with the presence and morphology of lumbar MC in a large cross-sectional population-based study of Southern Chinese.

We addressed the topographical and morphological dimensions of MC along with other magnetic resonance imaging phenotypes (eg, disc degeneration and displacement) on the basis of axial T1 and sagittal T2-weighted imaging of L1-S1. Prolonged severe LBP was defined as LBP lasting ≥ 30 days during the past year, and a visual analog scale severest pain intensity of at least 6/10. An Oswestry Disability Index score of 15% was regarded as significant disability. We also assessed subject demographics, occupation, and lifestyle factors.

In total, 1142 subjects (63% females, mean age 53 years) were assessed. Of these, 282 (24.7%) had MC (7.1% type I, 17.6% type II). MC subjects were older ($P=0.003$), had more frequent disc displacements ($P<0.001$) and greater degree of disc degeneration ($P<0.001$) than non-MC subjects. In adjusted models, any MC (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.01–2.18), MC affecting whole anterior-posterior length (OR 1.62, 95% CI 1.04–2.51), and MC affecting 2/3 posterior length (OR 2.79, 95% CI 1.17–6.65) were associated with prolonged severe LBP. Type I MC tended to associate with pain more strongly than type II MC (OR 1.80, 95% CI 0.94–3.44 vs OR 1.36, 95% CI 0.88–2.09, respectively). Any MC (OR 1.47, 95% CI 1.04–2.10), type II MC (OR 1.56, 95% CI 1.06–2.31),

MC affecting 2/3 posterior length (OR 2.96, 95% CI 1.27–6.89), and extensive MC (OR 1.95, 95% CI 1.21–3.15) were associated with disability. The strength of the associations increased with the number of MC.

This large-scale study is the first to definitively note MC types and specific morphologies to be independently associated with prolonged severe LBP and back-related disability. This proposed refined MC phenotype may have direct implications in clinical decision-making as to the development and management of LBP. Understanding of these imaging biomarkers can lead to new preventative and personalized therapeutics related to LBP.

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Abbreviations: AP = antero-posterior, BMI = body mass index, CI = confidence interval, DD = disc degeneration, FOV = field of view, IQR = interquartile range, LBP = low back pain, MC = Modic changes, MRI = magnetic resonance imaging, ODI = Oswestry Disability Index, OR = odds ratio, SN = Schmorl's nodes, T1w = T1-weighted MRI, T2w = T2-weighted MRI, TE = echo time, TR = repetition time, VAS = visual analog scale.

INTRODUCTION

Low back pain (LBP) is the world's most disabling condition, resulting in tremendous socioeconomic and healthcare costs.^{1,2} Specific LBP phenotypes have been identified, but may only represent approximately 15% of LBP conditions.³ Lumbar intervertebral disc degeneration (DD) is thought to be a significant LBP risk factor.^{4–8} Usually, in these studies, DD has been defined as disc space narrowing and disc signal intensity loss (ie, so-called “dark discs”), commonly represented in various classification schemes (eg, Pfirrmann classification).⁹ DD and other degenerative findings on magnetic resonance imaging (MRI) have also been described among asymptomatic subjects^{8,10}; therefore, more specific LBP-related MRI phenotypes would be informative.

Modic changes (MC) are one potential specific LBP phenotype.¹¹ MC are vertebral body marrow changes adjacent to the endplates that are visible on MRI,¹² and are typically characterized as 3 distinct types.^{12–14} Type I MC display decreased signal intensity on T1-weighted (T1w) and increased signal intensity on T2-weighted images (T2w), indicating marrow edema and histologically represent disruption and fissuring of the endplates and vascular granulation tissue. Type II MC present increased signal intensity on both T1w and T2w, representing histologically fatty degeneration of the adjacent vertebral marrow. Type III MC represent decreased signal intensity on both T1w and T2w, indicating relative absence of bone marrow and presence of bone sclerosis.^{12–14} When different types, usually I and II or II and III, are seen at the same adjacent vertebral body, they are called mixed types (I/II or

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II/III, respectively).^{15,16} Size and location of MC have been usually evaluated according to vertical height,¹⁷ antero-posterior (AP) length,¹⁸ or involvement in the horizontal plane stratified to 4 regions.^{16,19} However, recently, a more extensive evaluation of the MC phenotype, in particular, its topographical characteristics, has been reported.²⁰

The associations of MC with different degenerative MRI findings have largely involved DD, disc bulge or herniation, and endplate defects (ie, Schmorl's nodes [SNs]).^{12,21–27} Demographic or lifestyle factors associated with MC include age,^{16,18,28} male sex,^{24,28} higher body mass index (BMI),^{24,29} smoking,³⁰ and heavy physical work.³⁰ With the exception of age, associations of MC with different demographic or lifestyle factors remain inconclusive.

Modic changes, especially type I changes, have been associated with LBP in population samples,^{27,31} among workers,³² and in clinical populations.^{22,30,33,34} However, these studies have had at most moderate sample sizes, and insufficient assessment of spine degenerative phenotypes and confounding factors were performed. Moreover, recent studies have showed conflicting results between MC and pain,^{26,35} and between MC and back-related disability.^{36–38} Furthermore, the relation of MC with more severe LBP remains speculative. In addition, detailed MC phenotype assessment, in particular, morphological and topographical variations in relation to prolonged severe LBP and disability remains unknown. Therefore, the following study addressed the relationship of prolonged severe LBP and back-related disability with lumbar MC in a large-scale, Southern Chinese general population. More specifically, the study addressed the influence of type, location, extent, and depth of MC on pain association.

METHODS

Study Population and Design

This study was a cross-sectional cohort study from a general population that consisted of Southern Chinese volunteers who were part of the Hong Kong Disc Degeneration Population-Based Cohort Study.^{5,7,39} An informed consent was obtained from every participant and the local ethics committee approved the study. The study population was 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. Subjects underwent a nurse-lead interview, examination for lifestyle factors and demographic data, and underwent lumbar MRI. This study population has been assessed earlier to evaluate more precise phenotype of MC and their relationship to other MRI phenotypes.²⁰

Low Back Pain and Disability

Subjects reported the duration of LBP in the past year as 0 day, 1 to 7 days, 8 to 30 days, over 30 days, or daily LBP. They also marked the worst LBP experience in the past on 0 to 10-cm visual analog scale (VAS). For the analyses, LBP duration was divided into LBP under or over 30 days. Based on the results of pain severity assessment by Boonstra et al,⁴⁰ LBP severity was divided into 3 categories: no pain or mild pain (VAS <3), moderate pain (VAS 3–5.9), and severe pain (VAS ≥6). Prolonged severe LBP was defined as LBP lasting at least 30 days, with the worst LBP severity at least 6 out of 10.

Back-related disability was evaluated using Oswestry Disability Index (ODI).^{41,42} ODI takes into account back trouble

that affects everyday life such as personal care, lifting, walking, sitting, standing, and sleeping.⁴² The ODI is scored from 0% to 100%, with higher scores noting worse disability. We defined ODI scores ≥15% to note back-related disability.

Magnetic Resonance Imaging

Lumbar (L1–S1) MRIs were obtained on a 3-T scanner (Siemens or Phillips), as earlier described.²⁰ Sagittal T2-weighted MRIs consisted of the following protocol: 5 mm slice thickness, 1 mm slice gap, field of view (FOV) of 280 mm × 240 mm, and a matrix of 448 × 336. There was no fat suppression for the T2 scans. T1w axial MRIs contained the following protocol: 4 mm slice thickness, 0.4 mm slice gap, FOV of 210 mm × 210 mm, matrix of 218 × 256, and a repetition time (TR) of 500 to 800 (dependent on body size) and an echo time (TE) of 9.5 milliseconds.

Evaluation of Magnetic Resonance Imaging

Evaluation of MRIs has been described in detail in our previous study.²⁰ Briefly, lumbar MRIs were evaluated in random order by the first observer (JM), with no information of subjects' clinical status. Later, 100 MRIs were re-assessed by the first observer for intrarator reliability, and 50 MRIs by the second observer (DS) in a random order for interrator reliability. Cranial and caudal vertebral bodies and endplates were evaluated separately. MC were assessed as type I, type I/II, type II, type II/III, and Type III, as previously defined.^{12,14–16,20} The maximum vertical height of the MC was evaluated in 4 different grades, and the horizontal length in 3 zones in AP-direction (anterior, midpoint, and posterior lesions; Figures 1 and 2). MC present in only 1 sagittal slice and other small MC were excluded.

Type I MC was thought to represent an active ongoing inflammatory process, and therefore we classified type I and type I/II as “type I” group in the analyses. Similarly, we classified type II and type II/III as “type II” group.

Degree of DD was graded using the modified Pfirrmann classification⁹ as following: normal height and clear distinction of the nucleus and annulus (grades 1 and 2); normal to slightly decreased height of the intervertebral disc and unclear distinction of the nucleus and annulus (grade 3); normal to moderately decreased height of the intervertebral disc and lost distinction of nucleus and annulus (grade 4); and a collapsed disc space with lost distinction of nucleus and annulus (grade 5). DD summary score was calculated by adding all 5 lumbar levels (ie, L1–S1) and further divided into 2 categories: DD score of less than 16 was considered normal to mild degeneration, whereas a score of 16 and over was regarded as moderate to severe degeneration.²⁰ Disc displacement was noted as disc bulge, protrusion or extrusion, as earlier described,²⁰ and graded as present or absent at any level.

Lifestyle Factors

Height (meters) and weight (kg) were measured in clinical assessment and BMI was calculated as kg/m². Smoking was classified as nonsmokers and smoking ≤10 or >10 pack-years during one's lifetime. Pack-years were achieved when subjects reported years they had smoked daily in total and average amount of cigarettes smoked per day, dividing the average amount of cigarettes smoked per day by 20 and multiplying the result with years they had smoked daily in total. Physical workload was assessed from the current or past occupation as sedentary, light, medium, heavy, or very heavy, and categorized as sedentary/light, medium, and heavy/very heavy.



FIGURE 1. Sagittal T2-weighted magnetic resonance images showing a subject with (A) no modic changes (MCs), disc degeneration or history of prolonged severe low back pain (LBP); (B) another subject with MCs at L1 to L2 affecting anterior zone in cranial vertebral body, and anterior and midpoint zone in caudal vertebral body adjacent to the endplate, and history with disc degeneration, but no prolonged severe LBP; and (C) another subject with MCs at L4 to L5 affecting the whole anterior-posterior length in both cranial and caudal vertebral bodies adjacent to the endplates with disc degeneration and history of prolonged severe LBP.

Statistical Analysis

The data were collected and coded upon a spreadsheet. The descriptive statistics were calculated for all variables (Table 1), and compared among participants with and without MC using the *t* test (age, BMI), the Mann–Whitney *U* test (LBP severity, ODI score), and the chi-square test (sex, smoking, workload, LBP duration, DD, disc displacement; Table 2). Inter and intrarator reliability were evaluated using Kappa analyses. Reliability and Kappa values were considered as poor (≤ 0.69), satisfactory (≥ 0.70), and good to high (≥ 0.80).⁴³ Logistic regressions were used to analyze the associations of

LBP and ODI with type, location, extent, and depth of MC (Tables 3 and 4). First, unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the crude association between each MC variable and outcome variables. The logistic regression models were adjusted first for age and sex, then additionally for lifestyle covariates, and finally additionally for DD. After the final analyses, the influence of disc displacement on different MC variables was also assessed. Only subjects with complete data (MC, covariates, and LBP/ODI) were included to the models. In addition, linear regressions were conducted to determine the impact of number of posterior MC on

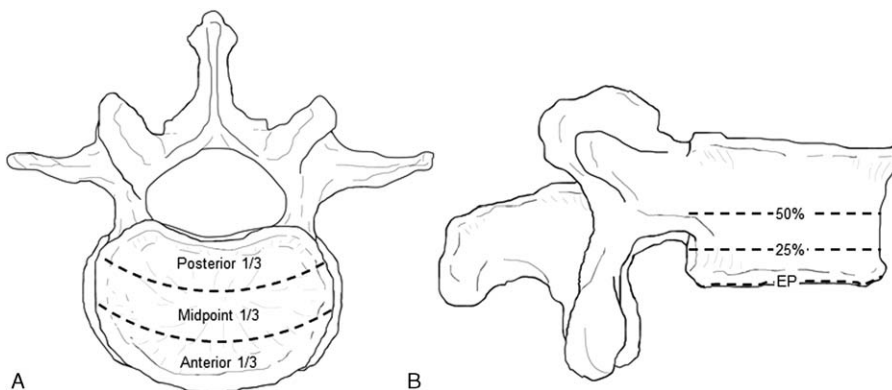


FIGURE 2. The assessment of modic changes (MCs) in the (A) horizontal and sagittal (B) plane of the vertebral body adjacent to the endplate (EP). The horizontal plane was divided into 3 zones in the anterior-posterior direction: anterior, midpoint, and posterior. The maximum vertical height was assessed to 4 different grades: MC along the EP only, MC <25%, MC 25% to 50%, and MC >50% of the relative height of the vertebra.

TABLE 1. Characteristics of the Study Population

| | n | %/Mean (SD) |
|---------------------------------------|------|-------------|
| Age* | 1142 | 52.9 (6.5) |
| Sex | | |
| Females | 717 | 62.8 |
| Males | 425 | 37.2 |
| Body mass index* | 1045 | 24.1 (3.6) |
| Smoking | | |
| No | 738 | 79.6 |
| 1–10 pack-years | 103 | 11.1 |
| >10 pack-years | 86 | 9.3 |
| Workload | | |
| Sedentary/light | 565 | 50.2 |
| Medium | 474 | 42.1 |
| Heavy/very heavy | 86 | 7.6 |
| Modic changes | | |
| No | 860 | 75.3 |
| Yes | 282 | 24.7 |
| Type I | 81 | 7.1 |
| Type II | 201 | 17.6 |
| Modic changes in different age groups | | |
| <30 yrs | 0 | 0.0 |
| 30–39 yrs | 3 | 16.7 |
| 40–49 yrs | 62 | 20.1 |
| 50–59 yrs | 185 | 26.6 |
| 60–69 yrs | 26 | 24.5 |
| 70–79 yrs | 5 | 50.0 |
| ≥80 yrs | 1 | 50.0 |
| LBP during the past year | | |
| No | 256 | 23.7 |
| Yes | 822 | 76.3 |
| 30 days | 383 | 35.5 |
| LBP intensity | | |
| No pain/mild pain (VAS < 30) | 339 | 34.4 |
| Moderate pain (VAS 30–59) | 199 | 20.2 |
| Severe pain (VAS ≥ 60) | 449 | 45.5 |
| Prolonged severe LBP† | | |
| No | 734 | 76.4 |
| Yes | 227 | 23.6 |
| ODI score | | |
| <15% | 785 | 71.2 |
| ≥15% | 318 | 28.8 |

LBP = low back pain, ODI = Oswestry Disability Index, SD = standard deviation, VAS = visual analog scale.

*Values are presented as mean (standard deviation).

†Defined as lasting for at least 30 days in the past year and severest VAS at least 6 out of 10 on a 10-cm VAS.

LBP severity or ODI score (Figure 3). In all analyses, the reference category was defined as the participants without any MC. Stata 13.1 version was used for all statistical analyses.

RESULTS

Study Population Characteristics

Magnetic resonance imaging was available for 1546 subjects. In total, 1142 (74%) subjects attended the interview and examination. There were 717 (63%) females and the mean age of the study population was 53 years (Table 1). Mean BMI was 24.1 kg/m² and 86 (9.3%) subjects had smoked more than 10

pack-years during their lifetime. Sedentary or light workload was reported by 565 (50%) subjects.

Reliability of MC Evaluation

The reliability of MC evaluation has been assessed previously.²⁰ Shortly, the intraobserver reliability of MC presence was high (kappa 0.94). The intraobserver reliability of MC height was 0.69 to 1.00 and MC width was 0.73 to 0.98, depending on the vertebral body adjacent to the endplate. Interobserver reliability was good to high regarding all MC parameters (kappa > 0.80).

Modic Changes

Modic change prevalence, horizontal and vertical locations, and sizes of MC have been previously described in detail.²⁰ Briefly, 282 (24.7%) subjects had MC (Table 1). Subjects with MC were older ($P = 0.003$), had more frequent disc displacements ($P < 0.001$), and greater DD ($P < 0.001$) than subjects without MC (Table 2). There were no significant differences regarding sex, BMI or smoking status.

Of all subjects with MC, 81 (7.1%) had “type I” and 201 (17.6%) had “type II” MC (Table 1). MC in the horizontal posterior planes were more infrequent than MC in the anterior or midpoint plane: 203 (72%) subjects had any MC in the posterior plane, 265 (94%) in the anterior plane, and 264 (94%) in the midpoint plane. Regarding MC affecting any posterior horizontal plane, 90% of those affected whole AP length. As for vertical height of MC, 127 (45.0%) subjects had at least 1 MC extending ≥ 25% of the vertebral height and 50 (17.7%) subjects 2 or more MC extending ≥ 25% of the vertebral height.

Modic Changes and Low Back Pain

Subjects with MC had experienced LBP more frequently than subjects without MC (LBP ≥ 30 days in the past year 43% vs 33%, respectively; $P = 0.005$; Table 2). Subjects with MC also reported the worst LBP episode in the history as more severe (severest LBP episode VAS median [interquartile range, IQR]: 6.7 [2.9, 8.7] vs 4.9 [1.6, 7.5], respectively; $P < 0.001$).

Table 3 presents multiple regression models between prolonged severe LBP and MC variables. In general, the associations strengthened after adjustment for age, sex, BMI, workload, and smoking, but attenuated after adjustment for DD. In the fully adjusted model, any MC was associated with prolonged severe LBP (OR 1.48, 95% CI 1.01–2.18). “Type I” MC were more strongly, but statistically nonsignificantly, associated than “type II” (OR 1.80 vs OR 1.36, respectively). MC affecting 2/3 posterior length (OR 2.79) and whole AP length (OR 1.61) were significantly associated, whereas anterior or anterior-midpoint oriented or only 1/3 posterior MC were not. The additional adjustment for disc displacement did not differ between different MC variables in AP direction ($P > 0.05$). The number of MC in the lumbar spine increased the strength of association (Table 4). These associations were similar in magnitude at both the lowermost 3 and the uppermost 2 levels of the lumbar spine. In case of LBP severity and posterior MC lesions, there was an almost linear increase in LBP severity with increasing number of posterior MC lesions after all adjustments (Figure 3A). There were no interactions between any explanatory variables in multivariable analyses, such as between sex and workload ($P > 0.05$).

TABLE 2. The Association of Modic Changes With Subject Demographics, Lifestyle, Pain Profiles and Disc Degeneration

| | n | No MC | Any MC | P |
|--------------------------------------|------|------------|------------|--------|
| Age* | 1142 | 52.6 (6.5) | 53.9 (6.3) | 0.003 |
| Male sex | 425 | 316 (36.7) | 109 (38.7) | 0.565 |
| BMI* | 1045 | 24.0 (3.8) | 24.4 (3.2) | 0.148 |
| Smoking >10 pack-years | 86 | 58 (9.4) | 28 (13.3) | 0.112 |
| Heavy workload | 86 | 58 (6.8) | 28 (10.1) | 0.075 |
| ≥30 days LBP during the past year | 383 | 267 (33.2) | 116 (42.5) | 0.005 |
| LBP intensity (VAS 0–100)† | 987 | 49 (16–75) | 67 (29–87) | <0.001 |
| ODI score (0%–100%)‡ | 1094 | 4 (0–16) | 8 (0–20) | 0.001 |
| At least moderate disc degeneration‡ | 1139 | 130 (15.2) | 126 (44.8) | <0.001 |
| Any lumbar disc displacement | 1142 | 473 (55.0) | 246 (87.2) | <0.001 |

Except when indicated otherwise, values are presented as n (percentage).

LBP = low back pain, ODI = Oswestry Disability Index, presented as percentage, VAS = visual analog scale.

*Values are presented as mean (standard deviation).

†Values are presented as median (interquartile range).

‡Moderate disc degeneration defined as summary score of at least 16.

Modic Changes and Disability

Subjects with MC had greater ODI scores than subjects without MC (median ODI [IQR]: 8 [0, 20] vs 4 [0, 16], respectively; $P=0.001$). Table 5 presents multiple regression models between back-related disability and MC variables. In general, the associations attenuated after adjustment for DD. In the fully adjusted model, MC were associated with disability (OR 1.47, 95% CI 1.04–2.10). “Type II” MC were significantly associated with disability, but “type I MC”

were not (OR 1.56 and OR 1.23, respectively). Also MC affecting 2/3 posterior length and MC affecting ≥25% of the vertebral height were significantly associated with disability (OR 2.96 and OR 1.95, respectively), whereas other horizontally located MC were not. When considering number of different MC, at least 2 MC affecting 2/3 posterior length in the lumbar spine were found to be strongly associated with disability (OR 6.60, 95% CI 1.05–41.55). When adjusting for disc displacement, there was no difference between MC

TABLE 3. Multivariate Analyses of the Association Between Prolonged Severe Low Back Pain (LBP)* and Modic Changes

| Modic Change | n (%) | | | OR, 95% CI | | |
|-----------------|------------|------------|-----------|-------------------|-------------------|-------------------|
| | All | No | Yes | Model 1 | Model 2 | Model 3 |
| Any | 199 (25.5) | 137 (23.1) | 62 (33.2) | 1.65 (1.16–2.37) | 1.72 (1.19–2.48) | 1.48 (1.01–2.18) |
| Type I | 50 (6.4) | 32 (5.4) | 18 (9.6) | 2.06 (1.12–3.79) | 2.18 (1.16–4.09) | 1.80 (0.94–3.44) |
| Type II | 149 (19.1) | 105 (17.7) | 44 (23.5) | 1.53 (1.02–2.29) | 1.56 (1.03–2.36) | 1.36 (0.88–2.09) |
| Anterior 1/3 | 21 (3.5) | 15 (3.2) | 6 (4.6) | 1.46 (0.56–3.85) | 1.46 (0.54–3.96) | 1.20 (0.43–3.33) |
| Anterior 2/3 | 60 (9.4) | 45 (9.0) | 15 (10.7) | 1.21 (0.66–2.26) | 1.25 (0.66–2.35) | 1.06 (0.55–2.03) |
| 1 | 45 (7.0) | 34 (6.8) | 11 (7.9) | 1.18 (0.68–2.40) | 1.23 (0.59–2.55) | 1.06 (0.50–2.23) |
| ≥2 | 15 (2.3) | 11 (2.2) | 4 (2.9) | 1.33 (0.42–4.25) | 1.32 (0.40–4.30) | 1.08 (0.32–3.60) |
| Midpoint 1/3 | 12 (2.0) | 9 (1.9) | 3 (2.3) | 1.22 (0.33–4.57) | 1.21 (0.32–4.65) | 0.78 (0.20–3.15) |
| Posterior 1/3 | 5 (0.9) | 4 (0.9) | 1 (0.8) | 0.91 (0.10–8.25) | 1.28 (0.14–11.76) | 0.82 (0.86–7.84) |
| Posterior 2/3 | 27 (4.5) | 16 (3.4) | 11 (8.1) | 2.51 (1.14–5.56) | 3.42 (1.47–7.95) | 2.79 (1.17–6.65) |
| 1 | 21 (3.5) | 14 (3.0) | 7 (5.2) | 1.83 (0.72–4.63) | 2.50 (0.94–6.67) | 2.13 (0.78–5.79) |
| ≥2 | 6 (1.0) | 2 (0.4) | 4 (2.9) | 7.31 (1.32–40.38) | 9.04 (1.52–53.66) | 6.48 (1.06–39.48) |
| Whole AP-length | 130 (18.3) | 85 (15.7) | 45 (26.5) | 1.94 (1.28–2.92) | 1.92 (1.26–2.92) | 1.62 (1.04–2.51) |
| 1 | 48 (6.7) | 35 (6.5) | 13 (7.7) | 1.36 (0.70–2.64) | 1.25 (0.63–2.47) | 1.11 (0.56–2.22) |
| 2 | 64 (9.0) | 40 (7.4) | 24 (14.1) | 2.19 (1.27–3.78) | 2.17 (1.24–3.78) | 1.80 (1.01–3.21) |
| ≥3 | 18 (2.5) | 10 (1.9) | 8 (4.7) | 2.92 (1.13–7.57) | 3.56 (1.31–9.72) | 2.39 (0.84–6.78) |
| Extensive† | 93 (13.8) | 62 (12.0) | 31 (19.9) | 1.83 (1.14–2.94) | 1.96 (1.20–3.19) | 1.54 (0.92–2.59) |
| 1 | 57 (8.4) | 39 (7.5) | 18 (11.5) | 1.68 (0.93–3.05) | 1.79 (0.98–3.31) | 1.51 (0.81–2.84) |
| ≥2 | 36 (5.3) | 23 (4.4) | 13 (8.3) | 2.07 (1.02–4.20) | 2.19 (1.05–4.56) | 1.55 (0.72–3.34) |

Model 1 = unadjusted; model 2 = adjusted for age, sex, BMI, workload, and smoking; model 3 = adjusted for age, sex, BMI, workload, smoking, and overall disc degeneration.

AP = antero-posterior, CI = confidence interval, OR = odds ratio, VAS = visual analog scale.

*Prolonged severe LBP defined as lasting for at least 30 days in the past year and severest VAS at least 6 out of 10 on a 10-cm VAS.

†Extensive Modic change ≥25% of the vertebral height.

TABLE 4. The Association Between Prolonged Severe Low Back Pain and a Number of Affected Cranial or Caudal Vertebral Bodies/Endplates in the Lumbar Spine

| Number of MC | n (%) | | | OR, 95% CI | | |
|--------------|-----------|-----------|-----------|------------------|-------------------|------------------|
| | All | No | Yes | Model 1 | Model 2 | Model 3 |
| 1 | 66 (8.5) | 50 (8.4) | 16 (8.6) | 1.17 (0.64–2.12) | 1.23 (0.67–2.25) | 1.17 (0.64–2.16) |
| 2 | 92 (11.8) | 65 (10.9) | 27 (14.4) | 1.52 (0.93–2.48) | 1.53 (0.92–2.52) | 1.36 (0.82–2.28) |
| 3 | 19 (2.4) | 10 (1.7) | 9 (4.8) | 3.29 (1.31–8.27) | 3.92 (1.48–10.37) | 3.11 (1.13–8.54) |
| 4 or more | 22 (2.8) | 12 (2.0) | 10 (5.4) | 3.05 (1.20–7.22) | 3.38 (1.39–8.23) | 2.47 (0.98–6.24) |

Model 1 = unadjusted; model 2 = adjusted for age, sex, BMI, workload, and smoking; model 3 = adjusted for age, sex, BMI, workload, smoking, and overall disc degeneration.

CI = confidence interval, MC = modic change, OR = odds ratio.

variables in AP direction ($P > 0.05$). A number of posterior MC lesions were associated linearly with ODI score, as shown in Figure 3B. Again, the associations between MC types, horizontal length, and vertical height of MC were essentially similar at both upper and lower levels of lumbar spine.

DISCUSSION

In our study, MC were independently associated with prolonged severe LBP and back-related disability. Type I MC were more strongly associated with prolonged severe LBP, and, on the contrary, type II MC with disability. With regards to horizontal plane, MC affecting 2/3 posterior length and whole AP length were more strongly associated with prolonged severe LBP. Additionally, MC affecting 2/3 of the posterior length were more strongly associated with both prolonged severe LBP and back-related disability than MC affecting whole AP length. Size and number of MC were also important—vertically taller MC were more strongly associated especially with disability, and ≥ 2 MC in the lumbar spine were more strongly associated with both prolonged severe LBP and disability.

The association of MC with LBP has been verified in several types of populations.^{27,31} Type I MC has been found to be associated more strongly with LBP than other MC in several studies,^{22,31–34} but there are also studies that show no association of MC with LBP at all.^{26,35} The sample size in these studies has usually been limited and they have not commonly explored association with severe LBP or disability. One recent study demonstrated MC to be independently associated with episodes of severe and disabling LBP⁴⁴ among British female twins, but otherwise the information about the relationship is scarce. In our study, we found an independent association of MC with prolonged severe LBP even after adjustments for confounding factors, including DD. We also found that both size and number of MC in the lumbar spine increased the risk to LBP severity. We believe that the current finding on an association of MC with more severe LBP, where brief episodes of LBP are excluded, strengthens the clinical relevance of MC. To our knowledge, this is the largest study to assess the relationship of distinct MC with LBP.

In our study, MC affecting the whole AP length in the horizontal plane strengthened the association with prolonged severe LBP, and there was almost a linear increase in LBP severity and ODI scores with increasing number of posterior MC lesions. Additionally, posteriorly oriented MC were more

painful than anteriorly oriented MC. Modic et al¹² already showed MC to extend from the anterior to the posterior plane. Several studies have shown MC to affect anterior plane more frequently than midpoint or posterior plane horizontally, and, moreover, MC to extend from anterior to posterior plane.^{20,28,45} Thus, one could suggest that MC extending as far as to the posterior plane horizontally could lead to more severe LBP, and MC remaining more anteriorly would not be so painful. Additionally, nerves to the lumbar vertebra and further to the endplate enter the vertebral body posteriorly and from there terminate to the endplates.^{46,47} Nerves are also found to be more densely located in the midpoint-posterior than in the anterior location.⁴⁶ These findings could suggest that the anterior location could be less innervated and thus less painful. One explanation could be posterior disc displacements as they have been associated with MC.^{22,23} Thus, one could argue that posterior MC are associated with prolonged severe and disabling LBP through posterior disc displacements. We adjusted the analyses with disc displacement and found that disc displacement was not significantly associated with MC regarding the location antero-posteriorly. Additionally, MC have been found to extend from anterior to posterior plane more frequently. To the best of our knowledge, this is the largest study analyzing the relationship of the horizontal location of MC with LBP and disability.

Interestingly, we found MC affecting 2/3 of the posterior length to be more strongly associated with both prolonged severe LBP and disability than MC affecting whole AP length. This could be due to number of reasons, for example, this may be related to the different pathomechanisms or stage of MC. The developmental pathway of MC has been studied, and the expansion of MC posteriorly has been suggested, as stated above. This could be due to flexion–extension forces from the anterior to posterior parts of the vertebra and endplate.²⁸ Some longitudinal studies have also found MC to regress,^{45,48} but the course of regression is not known. Jensen et al⁴⁵ found small MC in height to be more prone to regression than taller MC. There is still no information whether MC regress from the anterior to the posterior plane, vice versa or with some other mechanism when considering horizontal location. Thus, we cannot conclude the course of MC and we are unable to reason why MC affecting 2/3 of the posterior length are more painful than MC affecting the whole AP length. Naturally, there could be other factors than developmental pathway of MC to explain the difference.

Considering subjects with multiple MC, we included subjects with multiple analyses. Hence, one could have multiple

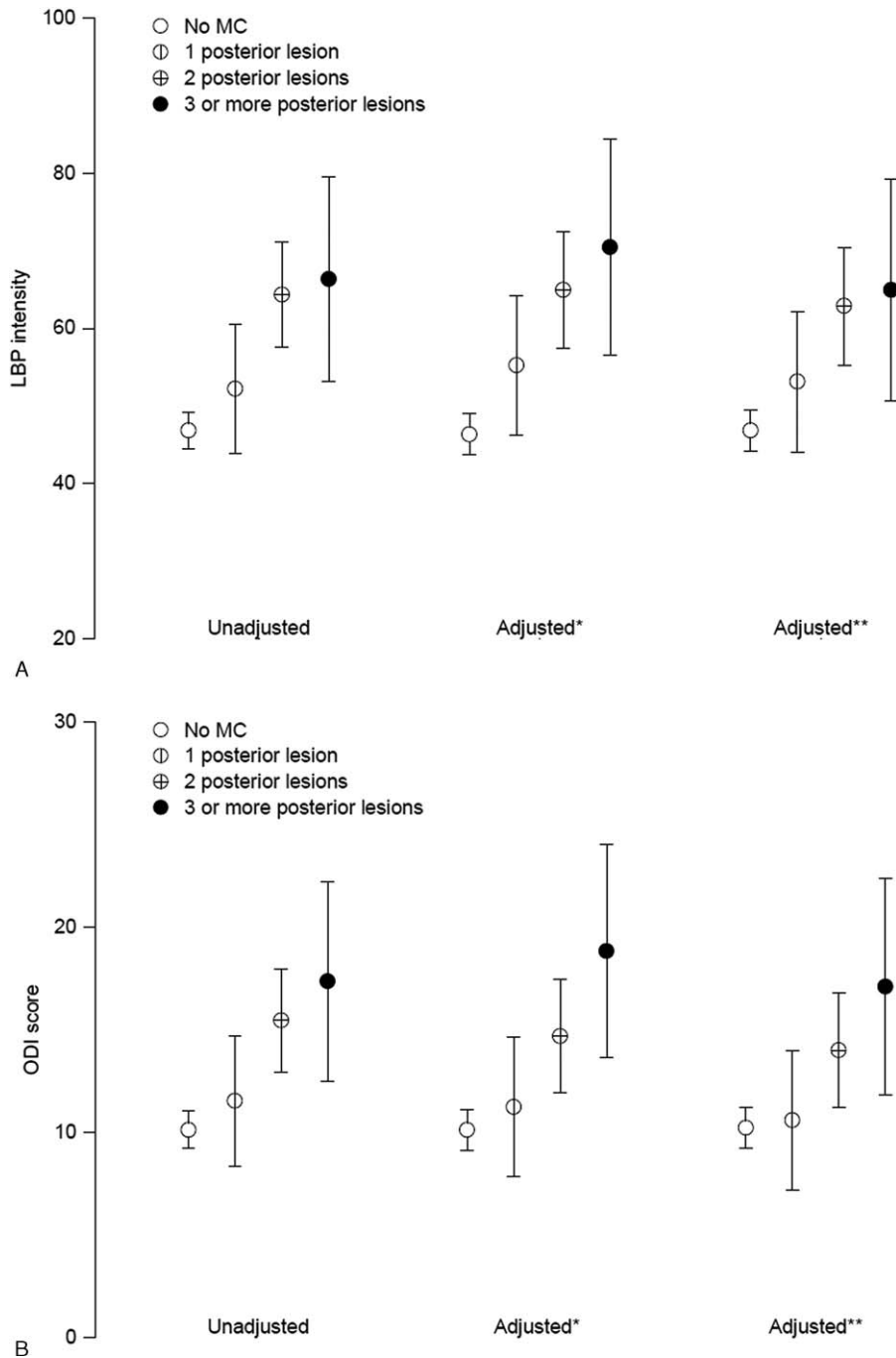


FIGURE 3. The associations of the posterior modic changes (MCs), and (A) low back pain (LBP) severity and (B) Oswestry Disability Index (ODI) score. The figures show the association of no MC, 1, 2, and 3 or more posterior MC lesions in the total lumbar spine and (A) LBP severity and (B) ODI score. Linear regression analyses were used to show the associations in unadjusted and adjusted models. In adjusted models, adjustments were made for age, sex, body mass index (BMI), workload, and smoking (Adjusted*); and age, sex, BMI, workload, smoking, and overall disc degeneration (Adjusted**).

MC with different horizontal locations. This could affect the results when evaluating the differences of horizontal locations of MC. Although our study population was quite large, we did not have enough subjects to assess all MC location possibilities separately.

Studies addressing the influence of MC on disability are rare. Järvinen et al⁴⁹ studied 64 chronic LBP patients and found that persistence of extensive type I MC was associated with higher likelihood of persistence of disability in 2-year follow-up. In the study of 85 patients with lumbar disc

TABLE 5. Multivariate Analyses of the Association Between Back-related Disability* and Modic Changes

| Modic Change | n (%) | | | OR, 95% CI | | |
|-----------------|------------|------------|-----------|-------------------|-------------------|-------------------|
| | All | No | Yes | Model 1 | Model 2 | Model 3 |
| Any | 225 (25.8) | 142 (22.8) | 83 (33.2) | 1.68 (1.22–2.32) | 1.68 (1.20–2.35) | 1.47 (1.04–2.10) |
| Type I | 62 (7.1) | 41 (6.6) | 21 (8.4) | 1.47 (0.85–2.56) | 1.49 (0.84–2.65) | 1.23 (0.67–2.24) |
| Type II | 163 (18.7) | 101 (16.2) | 62 (24.8) | 1.76 (1.23–2.53) | 1.74 (1.19–2.54) | 1.56 (1.06–2.31) |
| Anterior 1/3 | 27 (4.0) | 16 (3.2) | 11 (6.2) | 2.00 (0.90–4.34) | 1.81 (0.79–4.13) | 1.59 (0.68–3.71) |
| Anterior 2/3 | 64 (9.0) | 40 (7.7) | 24 (12.6) | 1.72 (1.01–2.95) | 1.72 (0.98–3.00) | 1.53 (0.86–2.71) |
| 1 | 46 (6.5) | 28 (5.4) | 18 (9.4) | 1.85 (1.00–3.43) | 1.90 (1.00–3.63) | 1.72 (0.89–3.32) |
| ≥2 | 18 (2.5) | 12 (2.3) | 6 (3.1) | 1.44 (0.53–3.89) | 1.35 (0.49–3.76) | 1.13 (0.40–3.22) |
| Midpoint 1/3 | 13 (2.0) | 10 (2.0) | 3 (1.8) | 0.86 (0.23–3.17) | 0.89 (0.23–3.39) | 0.67 (0.17–2.67) |
| Posterior 1/3 | 6 (0.9) | 2 (0.4) | 4 (2.3) | 5.74 (1.04–31.67) | 7.23 (1.25–41.74) | 5.58 (0.97–32.17) |
| Posterior 2/3 | 28 (4.2) | 15 (3.0) | 13 (7.2) | 2.49 (1.16–5.34) | 3.43 (1.50–7.82) | 2.96 (1.27–6.89) |
| 1 | 22 (3.3) | 13 (2.6) | 9 (5.0) | 1.99 (0.84–4.74) | 2.66 (1.04–6.81) | 2.40 (0.92–6.22) |
| ≥2 | 6 (0.9) | 2 (0.4) | 4 (2.2) | 5.75 (1.04–31.67) | 8.53 (1.40–51.90) | 6.60 (1.05–41.55) |
| Whole AP-length | 145 (18.3) | 90 (15.8) | 55 (24.8) | 1.76 (1.20–2.57) | 1.70 (1.15–2.51) | 1.44 (0.95–2.19) |
| 1 | 53 (6.7) | 39 (6.8) | 14 (6.3) | 1.03 (0.55–1.95) | 0.88 (0.45–1.69) | 0.79 (0.40–1.54) |
| 2 | 72 (9.1) | 41 (7.2) | 31 (14.0) | 2.17 (1.32–3.58) | 2.15 (1.27–3.62) | 1.85 (1.08–3.19) |
| ≥3 | 20 (2.5) | 10 (1.8) | 10 (4.5) | 2.87 (1.18–7.03) | 3.54 (1.37–9.19) | 2.58 (0.96–6.94) |
| Extensive† | 104 (13.9) | 59 (11.0) | 45 (21.2) | 2.19 (1.43–3.36) | 2.39 (1.53–3.74) | 1.95 (1.21–3.15) |
| 1 | 62 (8.3) | 39 (7.2) | 23 (10.9) | 1.70 (0.98–2.92) | 1.88 (1.07–3.33) | 1.62 (0.90–2.93) |
| ≥2 | 42 (5.6) | 20 (3.7) | 22 (10.4) | 3.16 (1.68–5.94) | 3.41 (1.75–6.63) | 2.66 (1.32–5.37) |

Model 1 = unadjusted; model 2 = adjusted for age, sex, BMI, workload, and smoking; model 3 = adjusted for age, sex, BMI, workload, smoking, and overall disc degeneration.

AP = antero-posterior, CI = confidence interval, OR = odds ratio.

*Back-related disability defined as Oswestry Disability Index of ≥15%.

†Extensive modic change ≥25% of the vertebral height.

herniation, ODI improved among patients without MC, but not among patients with MC at 6 months.³⁸ Keller et al³⁷ studied 269 chronic LBP patients and did not find any significant influence of MC on disability during the 1-year follow-up. With regards to surgery, one study with 154 chronic LBP patients who had been treated with disc prosthesis found that MC predicted better outcome at 2 years.³⁶ To the author's knowledge, there is lack of information about association of MC with disability in general population. We found MC to be associated with back-related disability, and "type II" to be more strongly associated with disability than "type I" MC.

In contrast, we found "type I" MC to be more strongly associated with prolonged severe LBP than "type II" MC. This finding is consistent with several studies and strengthens the view that type I is related to LBP more strongly than other MC types. There is a common consensus that different MC types are the same pathologic processes leading from type I to I/II or II and finally to type III.^{12,15,32} Our findings support the view that type I MC are inflammatory and more acute and thus more painful than type II MC, but type II MC are more stable and thus could be more disabling over time.

The ODI has been found to be a valuable outcome measure for spinal disorders.^{41,42} We dichotomized ODI for the analyses as scores <15% and ≥15% as we evaluated general population. The influence of ODI did not strengthen after the score of 15%. To our knowledge, there are no established cut-points to categorize ODI scores in general population.

Since MC and DD are so closely associated, one could suggest that those would affect LBP additively. The effect of

MC and DD on LBP and disability was not additive in our study, suggesting that they are related to the outcomes by common mechanisms. Indeed, this suggestion is supported by this and previous studies,^{23–25} which have found a strong association between MC and DD. A recent study from the UK Twin population⁴⁴ also found loss of disc height and disc signal intensity to be independently associated with the prevalence of MC.

Like in every study, our study also has some limitations. Our study was cross-sectional and thus we cannot conclude any causal relationships, changes in disability, or symptomatic pathway with regard to this study population. As stated previously,²⁰ volunteers have been recruited, which could overestimate people with earlier LBP history to attend the study. Nevertheless, this cohort has earlier been found to be illustrative of the general population.^{5,50} Furthermore, we have not explored the relationship between disc displacement and MC in a longitudinal design, but our aim is to evaluate this in a follow-up study more comprehensively. Theoretically, other MRI findings we have not explored in this study, such as spinal stenosis, facet arthropathy, or annular fissures, could also affect the results. The strengths of our study are the size and homogeneity of the study population, and also the ability to account for various demographic, lifestyle, and occupation factors. To our knowledge, this is the largest study to assess the relationship of specific MC and severe LBP and back-related disability. Subjects were also Southern Chinese and this increases the homogeneity of the study population and decreases the potential confounder of associated with mixed ethnicities.

CONCLUSIONS

To the best of our knowledge, our large-scale study represents one of the first to date to extensively assess the clinical relevance of distinct MC. Our results showed that MC were independently associated with prolonged severe LBP and back-related disability, and that there are specific MC phenotypes and patterns which are more significantly associated than others. These findings support the idea of MC as possible “imaging biomarkers” among LBP patients. Our study raises awareness to the need to assess specific MC phenotypes regarding morphology and extent of vertebral involvement, which may contribute to the understanding of LBP development and severity. Understanding such parameters may provide greater insight in identifying clinically relevant phenotypes for future studies (eg, genetics, biomechanical, global spinal alignment, outcome studies), and in designing preventative and personalized therapeutics addressing chronic LBP.

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REFERENCES

- Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354:581–585.
- Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163–2196.
- Deyo RA, Weinstein JN. Low back pain. *N Engl J Med*. 2001;344:363–370.
- Luoma K, Riihimäki H, Luukkonen R, et al. Low back pain in relation to lumbar disc degeneration. *Spine (Phila Pa 1976)*. 2000;25:487–492.
- Cheung KM, Karppinen J, Chan D, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine (Phila Pa 1976)*. 2009;34:934–940.
- Livshits G, Popham M, Malkin I, et al. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis*. 2011;70:1740–1745.
- Samartzis D, Karppinen J, Mok F, et al. A population-based study of juvenile disc degeneration and its association with overweight and obesity, low back pain, and diminished functional status. *J Bone Joint Surg Am*. 2011;93:662–670.
- Takatalo J, Karppinen J, Niinimäki J, et al. Does lumbar disc degeneration on magnetic resonance imaging associate with low back symptom severity in young Finnish adults? *Spine (Phila Pa 1976)*. 2011;36:2180–2189.
- Pfirrmann CW, Metzdorf A, Zanetti M, et al. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2001;26:1873–1878.
- Boden SD, Davis DO, Dina TS, et al. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am*. 1990;72:403–408.
- Albert HB, Kjaer P, Jensen TS, et al. Modic changes, possible causes and relation to low back pain. *Med Hypotheses*. 2008;70:361–368.
- Modic MT, Steinberg PM, Ross JS, et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166:193–199.
- de Roos A, Kressel H, Spritzer C, et al. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. *AJR Am J Roentgenol*. 1987;149:531–534.
- Modic MT, Masaryk TJ, Ross JS, et al. Imaging of degenerative disk disease. *Radiology*. 1988;168:177–186.
- Braithwaite I, White J, Saifuddin A, et al. Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. *Eur Spine J*. 1998;7:363–368.
- Kuisma M, Karppinen J, Niinimäki J, et al. A three-year follow-up of lumbar spine endplate (Modic) changes. *Spine (Phila Pa 1976)*. 2006;31:1714–1718.
- Jensen RK, Leboeuf-Yde C, Wedderkopp N, et al. Is the development of Modic changes associated with clinical symptoms? A 14-month cohort study with MRI. *Eur Spine J*. 2012;21:2271–2279.
- Wang Y, Videman T, Battie MC. Modic changes: prevalence, distribution patterns, and association with age in white men. *Spine J*. 2012;22:411–416.
- Jensen TS, Sorensen JS, Kjaer P. Intra- and interobserver reproducibility of vertebral endplate signal (modic) changes in the lumbar spine: the Nordic Modic Consensus Group classification. *Acta Radiol*. 2007;48:748–754.
- Määttä JH, Karppinen J, Luk KD, et al. Phenotype profiling of Modic changes of the lumbar spine and its association with other MRI phenotypes: a large-scale, population-based study. *Spine J*. 2015;25:1933–1942.
- Stäbler A, Bellan M, Weiss M, et al. MR imaging of enhancing intraosseous disk herniation (Schmorl’s nodes). *AJR Am J Roentgenol*. 1997;168:933–938.
- Albert HB, Manniche C. Modic changes following lumbar disc herniation. *Eur Spine J*. 2007;16:977–982.
- Jensen TS, Kjaer P, Korsholm L, et al. Predictors of new vertebral endplate signal (Modic) changes in the general population. *Eur Spine J*. 2010;19:129–135.
- Arana E, Kovacs FM, Royuela A, et al. Modic changes and associated features in Southern European chronic low back pain patients. *Spine J*. 2011;21:402–411.
- Kerttula L, Luoma K, Vehmas T, et al. Modic type I change may predict rapid progressive, deforming disc degeneration: a prospective 1-year follow-up study. *Eur Spine J*. 2012;21:1135–1142.
- el Barzouhi A, Vleggeert-Lankamp CL, van der Kallen BF, et al. Back pain’s association with vertebral end-plate signal changes in sciatica. *Spine J*. 2014;24:225–233.
- Mok F, Samartzis D, Karppinen J, et al. Modic changes of the lumbar spine: prevalence, risk factors and association with disc degeneration and low back pain in a large-scale population-based cohort. *Spine J*. 2016;26:32–41.
- Karchevsky M, Schweitzer ME, Carrino JA, et al. Reactive endplate marrow changes: a systematic morphologic and epidemiologic evaluation. *Skeletal Radiol*. 2005;34:125–129.
- Kuisma M, Karppinen J, Haapea M, et al. Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers. *BMC Musculoskelet Disord*. 2008;9:51.
- Kjaer P, Korsholm L, Bendix T, et al. Modic changes and their associations with clinical findings. *Eur Spine J*. 2006;15:1312–1319.
- Kjaer P, Leboeuf-Yde C, Korsholm L, et al. Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. *Spine (Phila Pa 1976)*. 2005;30:1173–1180.
- Kuisma M, Karppinen J, Niinimäki J, et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. *Spine (Phila Pa 1976)*. 2007;32:1116–1122.

33. Toyone T, Takahashi K, Kitahara H, et al. Vertebral bone-marrow changes in degenerative lumbar disc disease. An MRI study of 74 patients with low back pain. *J Bone Joint Surg Br*. 1994;76:757–764.
34. Jensen OK, Nielsen CV, Sorensen JS, et al. Type 1 Modic changes was a significant risk factor for 1-year outcome in sick-listed low back pain patients: a nested cohort study using magnetic resonance imaging of the lumbar spine. *Spine J*. 2014;14:2568–2581.
35. Kovacs FM, Arana E, Royuela A, et al. Vertebral endplate changes are not associated with chronic low back pain among Southern European subjects: a case control study. *AJNR Am J Neuroradiol*. 2012;33:1519–1524.
36. Hellum C, Johnsen LG, Gjertsen O, et al. Predictors of outcome after surgery with disc prosthesis and rehabilitation in patients with chronic low back pain and degenerative disc: 2-year follow-up. *Eur Spine J*. 2012;21:681–690.
37. Keller A, Boyle E, Skog TA, et al. Are Modic changes prognostic for recovery in a cohort of patients with non-specific low back pain? *Eur Spine J*. 2012;21:418–424.
38. Shan Z, Fan S, Xie Q, et al. Spontaneous resorption of lumbar disc herniation is less likely when modic changes are present. *Spine (Phila Pa 1976)*. 2014;39:736–744.
39. Samartzis D, Karppinen J, Chan D, et al. The association of lumbar intervertebral disc degeneration on magnetic resonance imaging with body mass index in overweight and obese adults: a population-based study. *Arthritis Rheum*. 2012;64:1488–1496.
40. Boonstra AM, Schiphorst Preuper HR, Balk GA, et al. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *Pain*. 2014;155:2545–2550.
41. Fairbank JC, Couper J, Davies JB, et al. The Oswestry low back pain disability questionnaire. *Physiotherapy*. 1980;66:271–273.
42. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)*. 2000;25:2940–2952[discussion 2952].
43. Vangeneugden T, Laenen A, Geys H, et al. Applying concepts of generalizability theory on clinical trial data to investigate sources of variation and their impact on reliability. *Biometrics*. 2005;61:295–304.
44. Määttä JH, Wadge S, MacGregor A, et al. ISSLS Prize Winner: Vertebral endplate (Modic) change is an independent risk factor for episodes of severe and disabling low back pain. *Spine (Phila Pa 1976)*. 2015;40:1187–1193.
45. Jensen TS, Bendix T, Sorensen JS, et al. Characteristics and natural course of vertebral endplate signal (Modic) changes in the Danish general population. *BMC Musculoskelet Disord*. 2009;10:81.
46. Bailey JF, Liebenberg E, Degmetich S, et al. Innervation patterns of PGP 9.5-positive nerve fibers within the human lumbar vertebra. *J Anat*. 2011;218:263–270.
47. Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral end plate in low back pain. *Global Spine J*. 2013;3:153–164.
48. Määttä JH, Kraatari M, Wolber L, et al. Vertebral endplate change as a feature of intervertebral disc degeneration: a heritability study. *Eur Spine J*. 2014;23:1856–1862.
49. Järvinen J, Karppinen J, Niinimäki J, et al. Association between changes in lumbar Modic changes and low back symptoms over a two-year period. *BMC Musculoskelet Disord*. 2015;16:98.
50. Jim JJ, Noponen-Hietala N, Cheung KM, et al. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2005;30:2735–2742.