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Vertebral Endplate Defect as Initiating Factor in Intervertebral Disc Degeneration; Strong Association between Endplate Defect and Disc Degeneration in the General Population

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ABSTRACT

Study design. Cross-sectional study of spine MR in a population, predominantly female, sample.

Objective. To determine the relationship between vertebral endplate defect and intervertebral disc degeneration (DD) in general population.

Summary of Background Data. Precise understanding of the mechanisms leading to DD development is lacking. In a degenerating disc, mechanical and structural changes lead to further worsening of disc integrity. Increasing attention has been paid to vertebral endplate defects as having a possible role in the etiopathogenesis of DD.

Methods. The study population comprised 831 twin volunteers from TwinsUK (mean age 54 ± 8 years, 95.8% female). Lumbar T2-weighted magnetic resonance images were coded for endplate defects from 8310 endplates into six grades. Total endplate score (TEP score) was achieved by summing both endplate defect grades from the same disc level. DD was evaluated using two different classifications; Pfirrmann grading, and a quantitative trait for DD based on a 4-point grading systems. Multivariable regression analysis was used to determine relationships between the traits of interest and the known risk factors for DD, age and body mass index (BMI). A receiver operator curve for TEP score predicting DD was generated, and survival analysis paired with Cox proportional hazards models analysis performed.

Results. There was statistically significant association between DD and age and BMI. These associations lost significance when TEP score was included as predictor in multivariable model. TEP score was strongly and independently associated at every lumbar disc level with DD (Pfirrmann $p\leq 0.001$; 4-point grading systems $p<1e-16$). A cut-off point score of 5 for TEP score was found above which there was a higher DD prevalence. Across all age subgroups, probabilities of having DD were significantly increased in those considered TEP score positive (≥ 5).

Conclusions. Our large, population-based study has shown that endplate defect was strongly and independently associated with DD at every lumbar disc level. These results provide a mechanism by which increasing age and BMI predispose to DD.

KEY WORDS: Disc degeneration, endplate, intervertebral disc, lumbar spine, magnetic resonance imaging, Pfirrmann, TEP score, total endplate score, twin, TwinsUK

Level of Evidence: 2

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INTRODUCTION

One of the specific causes of low back pain (LBP) is thought to be intervertebral disc degeneration (DD) (1-5). Aging and metabolite transport problems can predispose a disc to degeneration (6, 7), and there is some biomechanical evidence that initial damage to the annulus fibrosus or endplate can both lead to disc decompression and degeneration (8). However, it remains unclear whether a structural defect within the disc annulus or endplate can act as an initiating factor for DD in humans, and which is the more important route. Lately, increasing attention has been paid to defects in the vertebral endplate as having a possible role in the etiopathogenesis of DD. DD is usually assessed using magnetic resonance imaging (MRI) as the gold standard, with a variety of different classifications (9, 10). Pfirrmann classification (9) takes into account decrease of the disc height and signal intensity but does not assess them separately. Other DD classifications have been developed to utilize components of DD more extensively (11).

The motion segment or functional spinal unit consists of two adjacent vertebrae, the intervertebral disc and all adjacent ligaments between them, of which the vertebral body endplate is thought to be the most vulnerable structure (6). The endplate is a bilayer structure between the vertebral body and the intervertebral disc, consisting of bony and cartilaginous layers (12).

The cartilage layer helps to equalize loading between the disc and vertebral body (13) and maintains a normal hydrostatic pressure within the nucleus by opposing water loss under load (14) it also regulates metabolite transport between the disc and vertebral body (7). Damage to the endplate leads to structural change affecting the motion segment and lower intradiscal pressure in the adjacent nucleus pulposus, inducing greater compressive stresses to the annulus fibrosus (7, 15, 16). Subsequently, according to evidence from cadaveric experiments (7), organ culture (17), and animal models (15), and living humans (18), this can lead to internal disc disruption and cell-mediated DD. Endplate fracture has also been shown to lead to necrotic and apoptotic cell death in the adjacent nucleus in human subjects (17), whereas in animal models endplate perforation induced disc degeneration resembling human disc

degeneration (15). Hence, it seems reasonable to hypothesise that endplate defect could initiate disc degeneration in human lumbar spine.

Rajasekaran et al. (19) has reported that endplate defect was correlated with DD in a clinical sample of 47 patients and 26 volunteers. Endplate defect was evaluated on T1 scans and classified into six types according to severity of damage (type 1 to type 6) assessed on T1-weighted magnetic resonance scans. A Total Endplate score (TEP score) was derived from each disc by summing endplate defect scores of both rostral and caudal endplates of the disc. Strong correlation between progressive grades of endplate defect and disc degeneration was shown.

We hypothesised that endplate defect is a major initiating factor for DD not only in patients with back pain but in the general population. Accordingly, we examined existing MRI scans for endplate defects and examined the relationship between endplate defects and known risk factors for DD in TwinsUK, a large population sample highly phenotyped for medical conditions and lifestyle traits and shown to be similar to the singleton population (20). The purpose of our study was to characterise the relationship between endplate defect, other DD risk factors and DD graded by two different morphological classifications: i) Pfirrmann grading and ii) the quantitative trait for DD based on a 4-point grading system for disc height, signal change, posterior disc bulge, and anterior osteophytes in a larger population-based sample as reported previously (10).

MATERIALS AND METHODS

Study population

The study population comprised part of the TwinsUK register of King's College London (www.twinsuk.ac.uk) (21). The registry was founded in 1992 and comprises adult twins, the majority females. The baseline data and MRIs were collected between 1996 and 2000. Twins in the registry were

recruited through national media campaigns and from other twin registers and had not been selected for any particular trait(10). Subjects in the registry were invited to take part in studies that cover a wide range of traits and common medical conditions and, where possible, were not aware of the precise hypothesis being tested. Clinical and demographic information on gender, body mass index (BMI), episodes of disabling low back pain and lumbar disc degeneration have been collected previously. All subjects have signed informed consent form. The study was approved by St. Thomas' Hospital Ethics Committee.

Magnetic resonance imaging and grading

Magnetic resonance scans were performed at baseline using a Siemens (Munich, Germany) 1.0-T superconducting magnet. Sagittal images were obtained using a fast spin-echo sequence of time to recovery (TR)/time to echo (TE) 5000–4500/112 msec, with a slice thickness of 4 mm. Grading was performed on T2-weighted images. All MRI scans were performed at least 1 hour after rising in the morning, with no exercise or other rest allowed between getting up and the scan in order to avoid problems related to diurnal variation in disc height (22). Each twin pair was scanned at the same appointment.

Grading of Endplate Defects

Authors JHM and MR coded endplate defects in the baseline MRI scans from all 831 subjects (including 4155 discs and 8310 endplates). Endplate defect grade was evaluated on a scale of 1–6 according to Rajasekaran *et al.* 2008 (19) (Table 1). As in Rajasekaran *et al.* 2008 (19), total endplate scores for each disc were constructed by summing the endplate defect score of both rostral and caudal endplates in each functional spine unit. Inter-rater agreement for the coding of endplate defect was calculated using Cohen's weighted kappa and Pearson's correlation.

Agreement phase: An initial training phase was held in which an inter-rater agreement on endplate defect detection and grading of ≥ 0.85 was reached on at least 100 subjects and 1000 endplates. After the training phase, potential uncertainties were settled by discussion and consensus.

Grading of Disc Degeneration

Disc degeneration has been evaluated earlier using two different coding methods: i) 4-point grading system for disc height, signal change, posterior disc bulge, and anterior osteophytes as by (23) reported in Sambrook et al. (10) and ii) Pfirrmann classification (9).

- i) The coding process has been previously described in details (10). Briefly, the following components were assessed; 1) disc signal intensity within the nucleus pulposus; 2) disc height loss; 3) posterior disc bulge; and 4) anterior osteophytes. Every component was evaluated from 0 to 3 from every lumbar disc level utilizing standardised atlas. An overall measure of degenerative change was determined as the arithmetic sum of the grades for each feature in the lumbar spine. Thus, a summary score had range 0-12 at every lumbar disc level.
- ii) Pfirrmann classified disc degeneration progressively according to severity from 1 (disc is homogeneous with bright hyperintense white signal intensity and normal disc height) to 5 (disc is inhomogeneous with a hypointense black signal intensity and no more detectable difference between the nucleus and annulus). Consistent with other studies (19), a score equal or greater than Pfirrmann 4 was chosen to define an abnormal, degenerate disc.

Statistical analysis

Critical scores were calculated for TEP score predicting DD on the same lumbar spine level using Receiver Operating Curves (ROC)-analysis. Cumulative link mixed models and linear mixed regression models were used to analyse association between endplate defect and DD adjusted for known risk factors (age and BMI) and family structure. Kaplan-Meier survival analysis and Cox proportional hazards models analysis were carried out to assess temporal dependence (by age subgroups) between endplate

defect and DD. All calculations were done in R using packages “psych”, “survival”, “ordinal”, “lme4”, and “OptimalCutpoints”.

RESULTS

The study sample consisted of 831 subjects having mean age 54 ± 8 years, range 19-73 years 95.8% female including 4155 discs and 8310 endplates, as shown in Table 2. Inter-rater agreement for endplate defect between the two investigators showed Kappa values 0.72-0.94, with mean value of 0.86 and Pearson's correlation between the two coders was 0.864, indicating good agreement.

Disc degeneration score

Summative scores of 4-point grading system of (23) for disc height, signal change, disc bulge, and anterior osteophytes, and the Pfirrmann grading are shown in detail in Table 2.

Endplate defects and DD: Multivariable regression models revealed statistically significant associations between DD and known risk factors age ($p \leq 0.0001$) and BMI ($p \leq 0.05$) for all disc levels and by different disc codings. However, when TEP score was also included as predictor in the multivariable model, the strength of covariates such as age and BMI was mostly attenuated to non-significant, indicating endplate defect as the prevalent factor in DD. TEP score was strongly and independently associated with DD as graded with both Pfirrmann ($p \leq 0.001$) and 4-point grading system methods ($p < 1e-16$) at every lumbar disc level (Table 3).

The prevalence of DD showed a significant correlation with higher TEP score. The ROC indicated a critical TEP score (cut-off point) of 5 after which there was a higher prevalence of DD graded with Pfirrmann. The same TEP score cut-off point applied for each disc level (L1/L2, L2/L3, L3/L4, L4/L5, and L5/S1).

A survival analysis paired with Cox proportional hazards models analysis provided the probabilities of having DD by decade of age in subgroups with/without TEP score ≥ 5 , and showed that probabilities of having DD are significantly increased in TEP score positive (≥ 5) age subgroups (Figure 2).

DISCUSSION

This is the first study of a large population sample having spine MR imaging to examine the role of endplate defects in DD graded by different morphological classifications: i) Pfirrmann grading and ii) quantitative trait for DD based on a 4-point grading system for disc height, signal change, posterior disc bulge, and anterior osteophytes.

Our results showed endplate defects to be strongly and independently associated with DD graded by both Pfirrmann ($p \leq 0.001$) and 4-point grading methods ($p < 1e-16$). Although it is not possible to infer causality in a cross-sectional study such as this, the strong dose-response relationship between the two traits of interest and the evidence from other sources concerning causal mechanisms (8) suggest that endplate (micro)fracture can indeed be an initiating factor in DD. While possible, it is unlikely that the reverse is true - that DD could cause endplate damage, because degenerate discs have a very low intradiscal pressure (24) so that compressive force is transmitted through the annulus, where it is more likely to cause collapse of the anterior cortex rather than endplate damage (6).

ROC analysis demonstrated a TEP score cut-off value of 5 over which the prevalence of DD was significantly higher. The association of TEP score with DD was low until TEP score of five, and after that there was a rapid response with a great increase of likelihood of DD for each unit increase in TEP score. Of interest, the same TEP score cut-off point was found for each disc level and is similar to the cut-off of six as observed in the previous clinical study (19). One possible explanation for the minor variation of the TEP score cut-off points in these studies can be that the TwinsUK is a large population-based registry

consisting of subjects (twins) recruited through national media campaigns and from other twin registers,

who were not selected for any particular trait. The recruitment of general, asymptomatic, volunteers was meant to allow to make use of the normal situation providing normative measurements and avoid potentially confounding variables such as local patterns of referral that may occur in a symptomatic population. An additional reason may be that Rajasekaran *et al.* used T1 scans to evaluate endplate defects, which allows better assessment of cartilage features.

Our results showed that it might be enough to have a single grade 3 endplate defect (with focal disc marrow contacts, normal contour of endplate maintained and no MC associated) at a single disc level to have adjacent disc degeneration. A recent longitudinal study of 90 patients showed DD, endplate defect and Modic change (MC) to be significantly associated with each other (25). A relatively small interruption in the structural integrity of the endplate can be enough to cause significant alterations to the mechanical environment of the disc (16) as well as in diffusion patterns essential to maintain disc nutrition and hydration of the nucleus pulposus (7, 15). Also, a herniating annulus fibrosus may pull some cartilage endplate off the subchondral bone (26), giving rise to the 'erosion' type of endplate defect (27). Anaerobic bacteria also may be able to enter the disc via an endplate defect and hence lead to disc degeneration by another route (28). Moreover, oedema and changes in the vertebral bone marrow adjacent to endplate (i.e. Modic change) could be linked with endplate defect (26).

As integrity of the endplate seems to be crucial for the maintenance of mechanical environment and proper nutrition of the avascular disc, it seems reasonable to conclude that endplate defects may indeed be an initiating factor and have a precipitating role for the whole cascade of events that lead to DD, and ultimately to the clinical manifestation of severe and disabling LBP, as shown previously (29).

The finding that TEP score has a particularly great association with DD at upper lumbar levels, and a smaller, but still highly significant, association at L4/L5 (Figure 2), is consistent with experimental

findings that disc decompression following endplate damage is greatest in the upper lumbar spine and
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particularly small at L4/L5 (16). Also, disc degeneration in the lower lumbar spine may be secondary to annulus failure (8) because the wedged lower lumbar discs are particularly vulnerable to prolapse in response to loading in bending and compression (30), and there is evidence that prolapse can initiate degenerative changes in displaced disc tissue(31). Some of these prolapses may involve endplate junction failure as well as annulus rupture(32). Figure 2 suggests that there is at least one other major cause of DD because the prevalence of DD is greatest at L4/L5 (28.6%) (Figure 3), precisely where the influence of endplate damage is least. Splitting the lumbar spine into upper and lower portions, as described by Mike Adams, may reveal differences in the aetiology of DD(8). Perhaps the disc herniates more commonly through endplate junction than the annulus fibrosus than previously thought.

The limitations of this study include a study sample consisting mainly of female subjects but the previously held sex difference in DD has been questioned recently among researchers. In addition, due to missing MRI data in 10 subjects, the study population differs slightly from previous studies (29, 33). However, the generous size of the population sample can be considered a particular strength of this study. TwinsUK participants have been shown to be representative of singletons for a wide range of lifestyle and demographic traits (20). Another relevant strength is the thorough training phase undergone by the two evaluators (JHM and MR) leading to almost perfect inter-rater agreement for endplate defect: kappa value of 0.86, Pearson's correlation 0.864 (correlation and kappa were employed in conjunction to uncover non-random examiner error, as in (34)). The other main limitation is that these are cross-sectional data, and strictly speaking longitudinal studies will be required to confirm the direction of relationship between the two traits.

CONCLUSION

To conclude, this study performed on a large population based sample confirmed that endplate defects are strongly and independently associated with DD and that this relationship is evident in adults across the age spectrum and at all lumbar levels. As the endplate is positioned exactly between the disc and the vertebral body in which relevant conditions as DD and MC occur, due to its structural contiguity, it could

be that endplate defect is a major initiating factor for the whole cascade of events (that may include Modic change). A longitudinal study of twins' MR spine scans and endplate is currently under way to confirm the order of events.

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ACCEPTED

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Figure 1. Figure 1. End plate grading. A. Grade 1: Normal endplate, no breaks or defects, B. Grade 2: Focal thinning (white arrow) of the endplate, no breaks or defects, C. Grade 3: Focal disc marrow contacts (white arrow), but with maintained endplate contour, D. Grade 4: Endplate defects up to 25% of the endplate area (white arrow), E. Grade 5: Endplate defects up to 50% of the endplate area (white arrow), F. Grade 6: Extensive damaged endplates up to total destruction (white arrows).

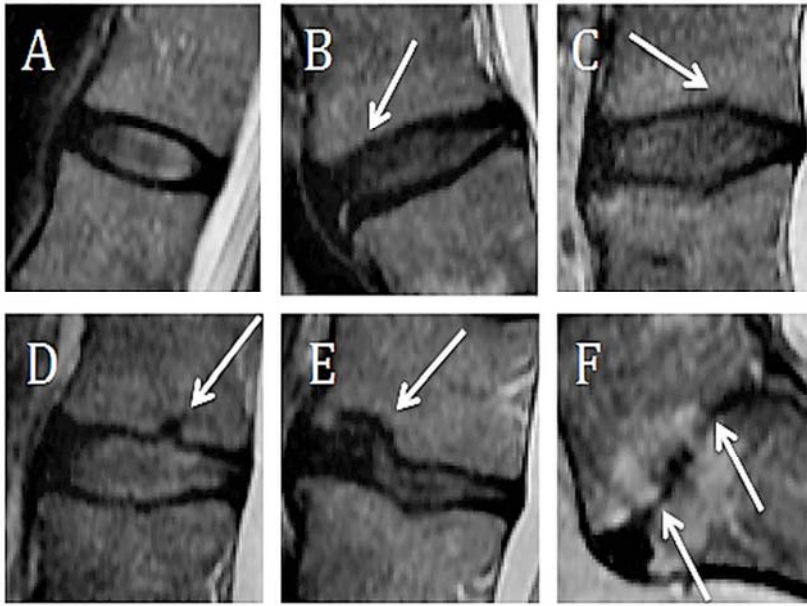


Figure 2. Survival analysis paired with Cox proportional hazards models analysis. Probabilities of having DD are significantly increased with age in TEPS positive (≥ 5) subgroups at each disc level (denoted ‘TEPS – Yes’ in the Figure). The probabilities increase with age, and the influence of endplate defect is least at L4/L5. DD = disc degeneration by Pfirrmann, HR = hazard ratio, TEPS = total endplate score.

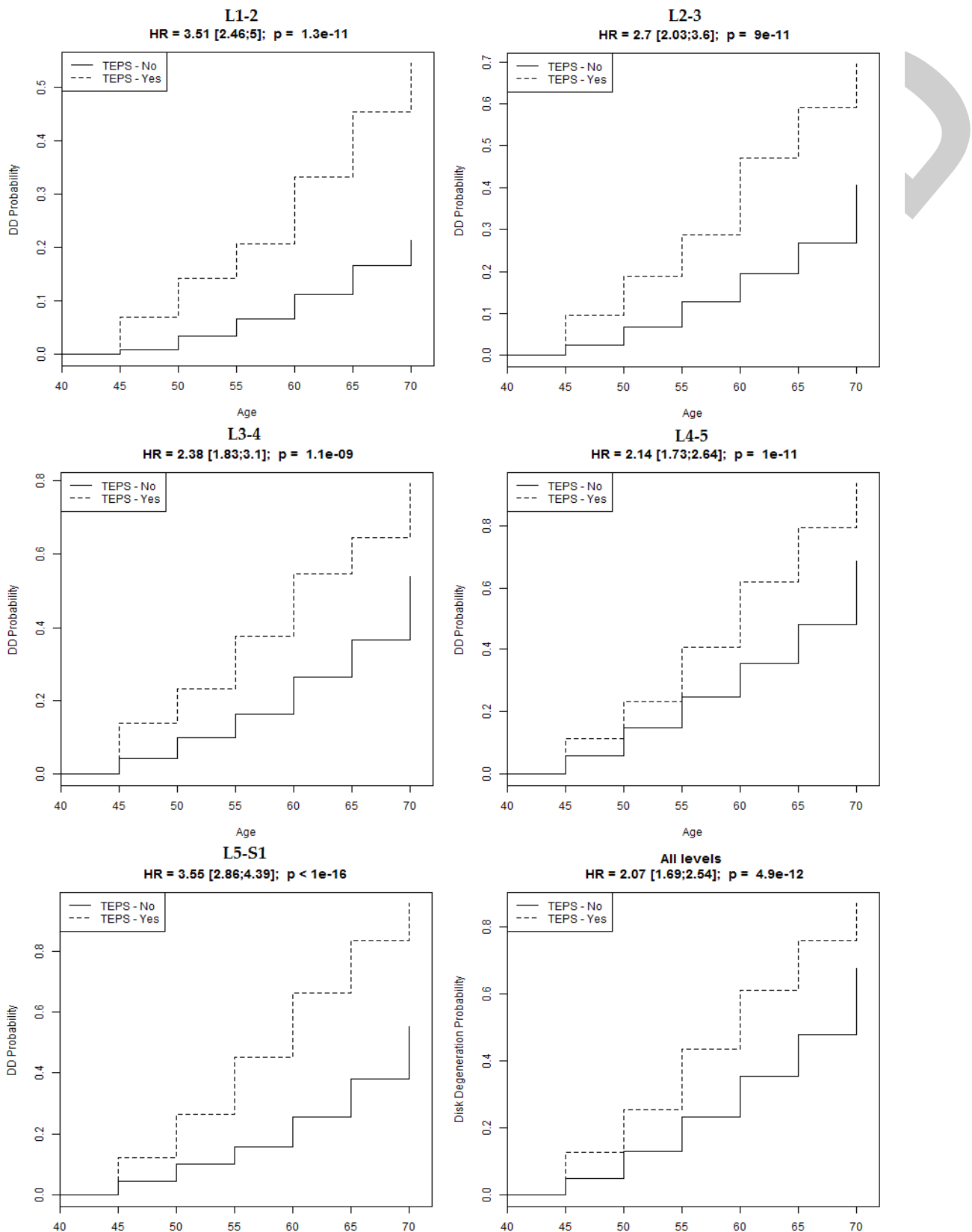


Figure 3. Prevalence of DD within the lumbar spine.

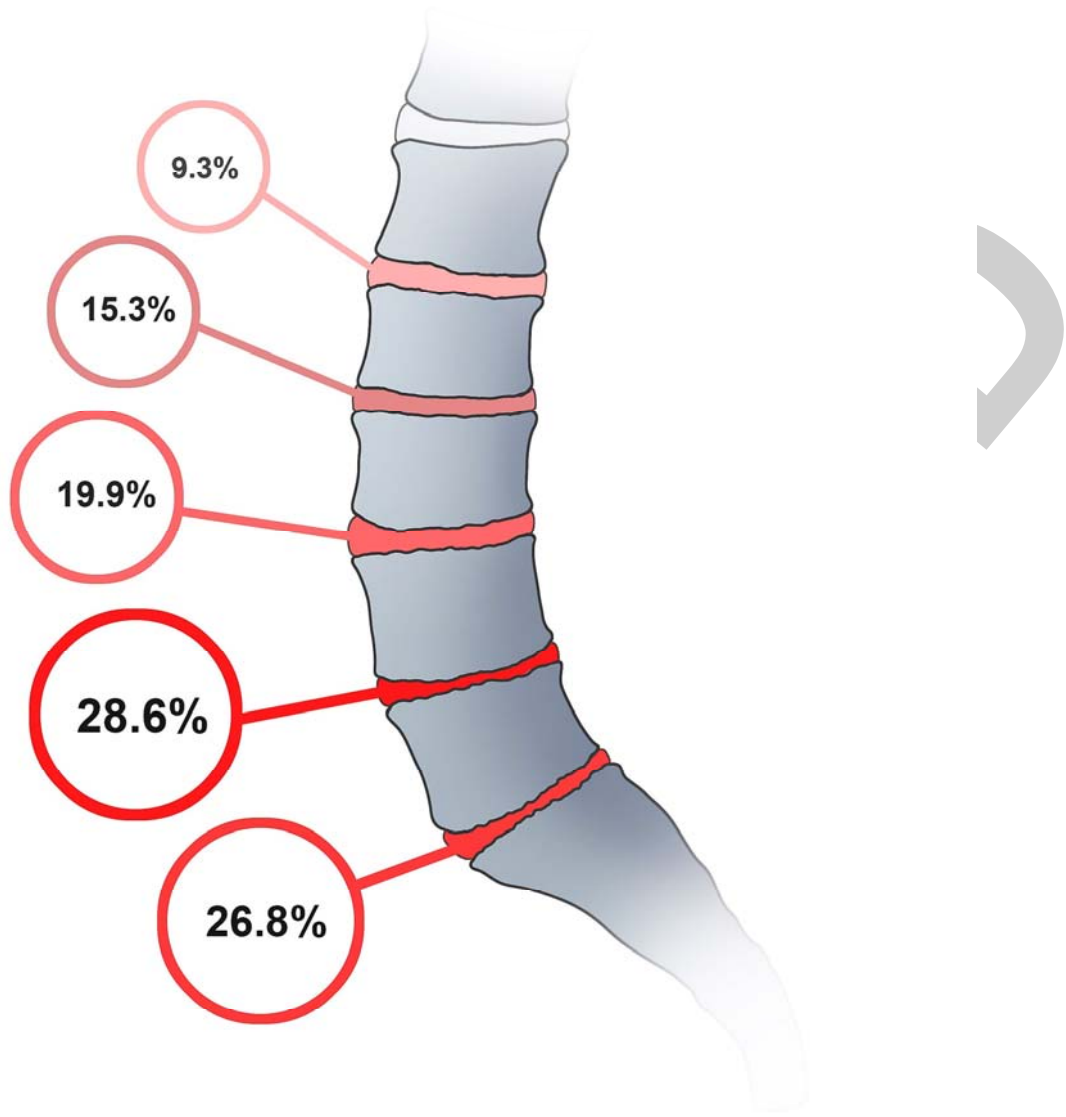


Figure 4. MRI scan showing endplate defect grade VI both at the L4/L5 rostral and caudal endplates, with associated Modic changes (MC) over both rostral and caudal bone marrows adjacent to endplates and disc degeneration evaluated as Pfirrmann grade 5 and 4-point grading system grade 10. As the endplate is a fundamental part of the vertebral body-endplate-intervertebral disc motion segment, one could consider endplate defects to be an initiating factor not only for disc degeneration, but also for MC.



Table 1. Endplate defect score

<i>Grade 1</i>	<i>Normal endplate, no breaks or defects</i>
<i>Grade 2</i>	Focal thinning of the endplate, no breaks or defects
<i>Grade 3</i>	Focal disc marrow contacts, but with maintained endplate contour
<i>Grade 4</i>	Endplate defects up to 25% of the endplate area
<i>Grade 5</i>	Endplate defects up to 50% of the endplate area
<i>Grade 6</i>	Extensive damaged endplates up to total destruction

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Table 2. Characteristics of the sample from TwinsUK.

Zygoty	N	Age (mean±SD)	Age range	Gender (F/M)	BMI (median [IQR])	4-point DD sum score (mean±SD)	Actual range (Min, Max)	Pfarrmann sum score (mean±SD)	Actual range (Min, Max)	TEPS sum score (median [IQR])	Actual range (Min, Max)
<i>MZ</i>	242	57 ± 8	32-73	238/4	24.0 (21.9, 26.5)	15.4 (7.5)	0, 45	16.2 (2.6)	10, 22	23 (20, 29)	10, 55
<i>DZ</i>	448	53 ± 8	19-71	420/28	24.2 (22.0, 27.1)	12.7 (7.6)	0, 48	15.8 (2.6)	10, 24	22 (19, 29)	10, 55
<i>Singleton</i>	141	52 ± 9	35-73	138/3	23.8 (22.1, 26.4)	12.2 (6.8)	0, 41	15.2 (2.7)	10, 21	22 (18, 27)	11, 51
<i>Total</i>	831	54 ± 8	19-73	796/35	24.1 (22.0, 26.9)	13.4 (7.5)	0, 48	15.8 (2.7)	10-24	22 (19, 29)	10-55

MZ = monozygoty, DZ = dizygoty, SD = standard deviation, F = female, M = male, BMI = body mass index, IQR = interquartile range, SUM SCORE= summary score, Min = minimum, smallest number of a set of values, Max = maximum, biggest number of a set of values

Table 3. Risk factors for disc degeneration including endplate damage, by lumbar level

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	<i>DD graded by Pfirrmann</i>				
	L1/L2	L2/L3	L3/L4	L4/L5	L5/S1
<i>TEPS</i>	2.07e-7	4.66e-7	5.26e-13	1.23e-16	1.59e-19
<i>Sex</i>	0.010	0.793	0.704	0.829	0.839
<i>Age</i>	0.656	0.894	0.785	0.805	0.726
<i>BMI</i>	0.698	0.412	0.405	0.331	0.271
	<i>DD graded by 4-point grading method</i>				
<i>TEPS</i>	$\leq 1e-16$	$\leq 1e-16$	$\leq 1e-16$	$\leq 1e-16$	$\leq 1e-16$
<i>Sex</i>	0.664	0.658	0.292	0.324	0.046
<i>Age</i>	0.538	0.535	0.723	0.128	0.054
<i>BMI</i>	0.971	0.928	0.822	0.265	0.662

Association was assessed using multivariable models with adjustment for twin pairing.
BMI = body mass index, *TEPS* = total endplate score