Age and disc degeneration in low back pain: automated analysis enables a magnetic resonance imaging comparison of large cross-sectional groups of symptomatic and asymptomatic subjects.

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Abstract

Background

Degeneration of the intervertebral disc has long been associated with low back pain even though disc degeneration is seen in people who are asymptomatic. Investigations into the relationship between pain and disc degeneration in symptomatic and asymptomatic subjects are hampered by study sizes, by variations in definition of back pain and differences in MRI annotations of degeneration, study-to-study.

Methods

We compared prevalence of disc degeneration between large symptomatic (724) and asymptomatic (701) groups of anonymised female subjects, 30-80yrs. We used SpineNet, a verified automated MRI annotation system to re-annotate MRIs onto the same objective system, irrespective of their original annotation. SpineNet rapidly annotated all MRIs for disc degeneration using the Pfirrmann scale 1-5, and for other degenerative features (herniation, endplate defects, marrow signs, spinal stenosis) as binary present/absent, taking age and spinal level into account.

Findings

Severe disc degeneration (Pfirrmann 4 or 5) and degenerative features were significantly more prevalent in symptomatics than in asymptomatics in the lower (L4-S1) but not the upper (L1-L3) lumbar discs, and in subjects <60years. We showed high co-existence of several degenerative features; in both populations c.90% of marrow signs, over all ages and spinal levels, were found in discs which were severely degenerate. We also found 40-50% of the symptomatic population had no MR identified degenerative features up to *c.*60 years.

Interpretation.

The study shows that automated MRI provides a valuable means of rapidly comparing large MRI datasets. Here, it enabled us to detect age and spinal-level related differences in the prevalence of degenerative features between asymptomatic and symptomatic populations. Results also suggest that MRI, by distinguishing between symptomatics whose discs have structural defects, and symptomatics with minimal degenerative changes, could provide a means of clinical stratification, and provide a useful pathway to investigate possible pain sources.

Introduction

Chronic low back pain is common and often difficult to treat. Its causes are mostly not well understood. Even though there is strong evidence that psycho-social factors can have a major contribution[1], the role of disc degeneration is thought to be paramount. There are over 35,000 references in PubMed on the topic 'low back pain and intervertebral disc degeneration' covering areas ranging from epidemiology, biological and genetics to diagnosis and treatment. Interpretation of all this information relies on adequate definitions of the disc degeneration phenotype.

Since the advent of spinal MRI permitted *in vivo* visualisation of disc degeneration, a number of quantitative MRI grading schemes have attempted to standardise definitions[2]. These have proved vital in phenotyping and analysis of

genetic factors in disc degeneration[3,4], but less successful in demonstrating how these features relate to low back pain[5]. Many asymptomatic subjects have degenerate discs or features, which do not predict development of future back pain[6]. Balague et al., have stated a widely held view: 'Many abnormalities seen on imaging (with the possible exception of Modic signs) are equally prevalent in the asymptomatic population and merely serve as a pretext to justify overtreatment[7].

These views arise from prevalence data gathered from small sample studies where gradings of disc degeneration, the degenerative features assessed and age ranges examined, vary from study to study. Systematic reviews acknowledge the difficulties of combining or comparing data while reporting presence of degenerative change in asymptomatic people[8].

Objectives

a) to investigate relationships of MRI detected degenerative features to symptoms by comparing symptomatic back pain and asymptomatic populations. b) to investigate the effects of age on this relationship.

Study Design

We report an exploratory study comparing MRIs of large groups to provide greater insight into the prevalence of age-related disc degeneration in those with and without low back pain. We re-annotated MRI scans from two symptomatic and one population group using a rapid automated grading system (SpineNet)[9]. We compared grades of degeneration between these groups in relation to age and spinal level. We examined prevalence of degenerative change in a group of female back pain patients and in a similar sized group of female asymptomatic subjects from the TwinsUK sample. We focussed on intervertebral disc degeneration, defined by the Pfirrmann grading scheme[10], and on the pathological features disc herniation, spinal stenosis, bone marrow and endplate change, all of which have been shown to be associated with symptoms[11-14].

MATERIAL AND METHODS

Participants and settings; All subjects had been recruited with full ethical approval and consent and fully anonymised[4].

Asymptomatic cohort: (TwinsUK)- We selected 701 (69%) subjects aged 30-79 years without back symptoms in the previous 3 months (based on responses to the nurse-administered MRC Back and Neck Pain Questionnaire[4]) from the 1016 females of the TwinsUK population cohort (http://twinsuk.ac.uk) who had undergone clinical examination and MRI scans (only sagittal T2 sequence) between 1996 and 2000. Intervertebral disc degeneration was originally graded from these images on a 4-point scale.

***Symptomatic Cross-sectional Group: (OSCLMRIC*) –** We selected 763 (39%) females aged 30-79 from a total group of 1689 male and female patients with low back pain referred to a secondary-care-centre spinal pain triage service with a lumbar MRI scan. The dataset included a pain Number Rating scale, Oswestry Disability Index (v2.1a), full MR imaging and who fulfilled a criterion for chronic low back pain of >3 months duration.

Genodisc Cross-sectional Group *(https://cordis.europa.eu/project/id/201626/reporting)*

Subjects were recruited in secondary care clinics in 6 different European countries. We selected the 756 (38%) females from the 2008 male and female symptomatic subjects 18-79 years, with chronic back pain and MR imaging[9].

Sources of Bias

The symptomatic groups were recruited either at the point of referral to secondary care (OSCLMRIC), that is when primary care therapy had failed. This effectively excludes many subjects who have a natural resolution of their symptoms and those referred to pain clinics. Male subjects were excluded from the direct comparison with the asymptomatic group who were all female twins. The Genodisc group was identified in local secondary care settings after full investigation.

Study Size

The study size was constrained by the groups available. Future studies need larger datasets to calculate effect sizes.

Quantitative variables and MRI analysis

The sagittal T2 sequences of the MRIs from OSCLMRIC, Genodisc and TwinsUK were analysed by SpineNet, a rapid automated MRI analysis system, able to match the reliability of an experienced spinal radiologist in analysing degenerative features[9]. SpineNet takes ~5 seconds to analyse each spine image fully, compared to around 30 minutes for manual analysis, making re-annotation of large groups feasible. It provides a report giving Pfirrmann gradings (1-5)[10] and presence/absence of degenerative features at each disc level (https://zeus.robots.ox.ac.uk/spinenet2/). For OSCLMRIC and TwinsUK, SpineNet reported the binary characterisation of the other selected degenerative features, viz herniation, central canal stenosis, marrow signs (Modic type 2), and endplate change[9]. As indicated by the literature[15], we analysed the averages of the upper (L1/L2+ L2/L3) and lower (L4/L5+ L5/S1) lumbar intervertebral discs separately. For OSCLMRIC and TwinsUK, we calculated prevalence of none/mild (Pfirrmann grades 1 or 2) and severe degeneration (Pfirrmann Grades 4 or 5) and of degenerative features in relation to spinal level and to age group by decade. We compared prevalence in symptomatic and asymptomatic subjects both with and without relation to age and spinal level, and calculated risks of features being symptomatic as odds ratios with 95% confidence intervals[16,17].

Statistical methods

The prevalence of each feature by age and level in OSCLMRIC and TwinsUK was calculated by dividing the number of discs analyzed in each decade and spinal level with feature(s) present by the total number of discs in the same level and age group (Tables S1-S4). For marrow signs and endplate change, we calculated prevalence of the average of the rostral and caudal binary scores.

Odds ratios (OR), 95% confidence intervals (CI) and P values[17] were used to determine the probability of an individual belonging to a group with MRI features present, being symptomatic or asymptomatic. Venn diagrams were constructed in house in PowerPoint®, based on the prevalence of each feature in the lower lumbar discs, with overlaps showing the prevalence of discs containing both features.

Because of the low prevalence of degenerative features in the asymptomatic group, we found that once age and disc level were considered, the study was underpowered for regression analysis, or for refining degradative changes such as type of herniation or marrow change, degree of stenosis, or extent of endplate-defect or of marrow signs.

Role of Funding Sources

None of the funding sources have been involved in the study design, data collection, analysis or interpretation of data used in this study, the writing of the report, or the decision to submit it for publication.

RESULTS

1. Change in mean Pfirrmann score with age and spinal level.

Fig 1a,b show the age-dependence of the Pfirrmann score, averaged over the two lower (Fig 1a) and the two upper (Fig1b) lumbar discs, for two independent symptomatic groups (Genodisc, OSCLMRIC). The low rate of increase by age groups in the mean degeneration score for both groups appeared very similar. The lower two lumbar discs were already relatively degenerate in the youngest age group, 30-40yrs (Fig 1a). The upper lumbar discs were only mildly degenerate at 30-40 years, but degeneration severity increased steeply with age (Fig 1b).

Figure 1c,d compares age related Pfirrmann scores of female symptomatic (OSCLMRIC) with subjects female asymptomatic (TwinsUK). In the lower lumbar discs, the average scores of asymptomatics were distinctly lower than those of symptomatics, particularly below 60yrs (Fig 1c). In the upper lumbar discs, the age-related mean scores were similar (Fig 1d).

2. Variation with age of the prevalence of high and low Pfirrmann scores for symptomatic and asymptomatic subjects in the lower and in the upper lumbar spine.

The prevalence of severe disc degeneration (grades 4 or 5) in the lower lumbar spine, was 3-4 times higher in the symptomatics than the asymptomatics below 50yrs (OR >3·0; p<·0001; Fig 3a) and increased with age for both groups until the 7th decade, where there was no noticeable difference between them (Fig 2c). In the upper lumbar spine, the prevalence was lower and there was little difference between the symptomatic and asymptomatic groups (Fig 2d).

The prevalence of minimally degenerate discs in the lower lumbar spine was greater in asymptomatics over the whole age range; at 30-39yrs, *c.*77% of discs in the asymptomatic and *c.*43% of symptomatic groups were minimally degenerate (OR 0·29; p<·001) but prevalence fell steeply with age for both groups with no significant difference between groups by 70yrs (Table 1).

The prevalence of severely degenerate discs over the whole lumbar spine, disregarding age and spinal level, was 37% for the symptomatic and 23% for the asymptomatics. Though still showing significant differences between symptomatics and asymptomatics (OR 1·94: 95% CI:1·48-1.55, p<·0001), pooling these data loses information on the influence of age and spinal level.

3. Prevalence with age and disc level of degenerative features in symptomatic and asymptomatic subjects.
The prevalence of disc herniation (Fig 4a), central canal stenosis (Fig 4b), marrow change (Fig 4c) and endplate defect (Fig 4d) varied with age and disc level. For all features, prevalence was markedly greater in symptomatic than in asymptomatic subjects, particularly at younger age, and, apart from endplate defect, greater in the lower lumbar spine. For instance, in the lower lumbar spine at 40-49 years, nearly 50% of discs were herniated in symptomatics compared to 17% of asymptomatic discs (p <·0001, Fig 4a, Table S5(iii)). Over the same age range, marrow change was present in 32% of symptomatic compared to 11% of asymptomatic discs (p<·00001, Fig 4c; Table S5(v)); for endplate defects, prevalence was lower being 8% for symptomatic people and 3% in asymptomatic (p<·00001, Fig 4d, Table S5(vi)). For herniation, marrow change and central canal stenosis the prevalence in the upper lumbar discs was very low, <10%, and was similar in both groups (Tables S1, S2 and S4 respectively). For endplate defects, prevalence was greater in the upper spine, similar in both groups and increased with age (Table S3, Table S5(vii)).

The lower lumbar ORs were strongly age dependent (Fig 5a-d). For herniation in the lower lumbar discs for instance, the OR varied from 11·8 (95% CI 1·5-90·0; p=0·02) to 2·1 (95% CI;1·4-3·1; p<·00001) and then rose to 3·7(95%CI 2·2-6·2; p<·00001) in the 4th, 6th and 7th decades respectively (Fig 5, Table S5b (iii)); confidence intervals were wide because of the small number of herniations in asymptomatic subjects. Overall, the prevalence of degenerative features was significant (Table 1), but the effects of age and disc level were lost.

4. **Most lower lumbar discs with additional degenerative features have high Pfirrmann scores.**
The majority were of degenerative features scored here were found only in discs with Pfirrmann grades 4 or 5 (Fig 6 a-d) for both asymptomatic and symptomatic subjects, whatever the overall prevalence of the feature. >90% of marrow changes were seen in Pfirrmann 4 or 5 discs for both symptomatic and asymptomatic subjects at all ages. The low (3%) prevalence of spinal stenosis in symptomatics below 50 years, had no apparent association with disc degeneration, possibly reflecting a different pathological process such as 'developmental stenosis'[18], unlike stenosis in the older age ranges (Fig 4b. Table S5b(iv)).

5 **Co-existence of degenerative features.**
At 40-49 years, as shown by a Venn diagram (Fig 7), a relatively small proportion of either group (those with symptoms, 14·4%) or without, 12·3%) had a single degenerative feature. For instance, endplate changes or marrow (Modic) signs alone were seen in only 0.5% and 1.5% of discs respectively, and 77% of herniations were seen in discs with severe degeneration, or with EP or marrow signs. Similar co-existence of degenerative features was seen at all ages (Tables S1-S4). Note that between 30-60 years, around 40-50% of the symptomatic group had only no/mild degeneration (Pfirrmann 1 or 2), and no measured degenerative features (Table S5).

DISCUSSION
Here we show that an automated MRI analysis system (SpineNet), enabled large groups to be re-annotated rapidly onto the same grading system, independent of their original annotations, and hence compared in relation to age- and

spinal level-related degenerative changes. We found significantly higher prevalence of degenerative changes in symptomatic compared to asymptomatic subjects, particularly in the lower lumbar spine of those below 60 years, as reported elsewhere[19].

In a qualitative comparison, we found a similar age-related mean Pfirrmann grade and spread of data in two different symptomatic groups, OSCLMRIC and Genodisc (Fig 1a,b) with a mean Pfirrmann score of the lower lumbar spine already greater than 3·0 at 30-39yrs and with further slow increases in degeneration grade as age increased. In a comparison between a female asymptomatic (TwinsUK) and matched symptomatic OSCLMRIC group, in the lower but not the upper lumbar spine, the younger asymptomatic discs were markedly less degenerate than the symptomatic discs with the difference between mean Pfirrmann scores falling with increase in age (Fig 1c,d).

The differences in degenerative change between asymptomatic and symptomatic discs were shown more clearly by comparing the age-related prevalence of severe disc degeneration and the other degenerative features in asymptomatic subjects from TwinsUK with those in OSCLMRIC. In the lower, but not the upper, lumbar spine, the prevalence of highly degenerate discs (Pfirrmann grades 4 or 5) (Fig 2a,b) and of degenerative features apart from central canal stenosis (Fig 4a-d) was significantly greater in symptomatic than asymptomatic people particularly below 60 years. The odds ratios for the lower lumbar spine were highly age-dependent, falling with increase in age for marrow changes, but being highest in the youngest and oldest age groups for herniation (Fig 5). No significant difference was seen in the upper lumbar spine for any of the features examined, except for those >70y with spinal stenosis (not shown). If age and spinal level were not taken into account, the odds ratios were still significant (Table 1), but the effects of age and spinal level on their magnitude was lost.

Several degenerative changes tended to co-exist in both symptomatic and asymptomatic subjects (Fig 7a,b). More than 90% of discs with marrow signs, and a high proportion of disc with herniations or endplate defects were severely degenerate over all age ranges (Figs 6,7). The question then arises of whether degenerative features such as marrow signs or endplate changes can be usefully associated singly with symptoms[12,13], or whether all co-existing degenerative features should be considered together. Our data supports others who report much stronger associations with pain when considering several co-existing degenerative features[11,20].

We cannot ignore the findings that degeneration is also seen in asymptomatic subjects, despite associations between symptoms and degeneration seen here. Is it that the differences between features in asymptomatics and symptomatics reside in the MRIs but are not detected by current methods of analysis or by definitions of degeneration? Region specific quantitative analysis of degree of degeneration, or unbiased analyses rather than a generalised overall grading schemes, or MRI sequences other than T2, might be better able to discriminate between painful and non-painful spines[21,22]. Moreover studies, mostly small, have found that type of herniation (extruded, sequestered, with or without neural compression)[23], the degree of stenotic change[14], the type of endplate defect[24], and extent and type of different Modic signs[13] all can distinguish symptomatic from asymptomatic discs. These refinements should be investigated further. If we took age and spinal level into account, our study was underpowered to go beyond binary gradings on account of low incidence of degenerative changes in the asymptomatic group. However even advances in imaging protocols[21] may not be able to differentiate between some asymptomatic and symptomatic MRI changes; co-factors which affect other spinal structures or pain processing spinal structures but are not detected by current spinal MRIs, might trigger pain when disc degeneration is also present. The differences might also lie elsewhere other than in the spine, as shown by previous work from TwinsUK [4, 16].

The inability to relate disc degenerative changes to symptoms has hampered treatment of low back pain. There is little progress in developing condition-related therapies yet. As a result, many patients are placed into a single category such as non-specific back pain for which there is little understanding of the biology or evidence-based therapy[25]. Stratification using standard clinical MRIs has not led to progress in developing condition-related

therapies, and yet a recent attempt to stratify 'sciatica' in a primary care cohort, without use of imaging, failed to demonstrate any difference in outcome between stratified and non-stratified groups[26].

It should be noted that 40-50% of subjects with back pain at age 30-60yrs, had no apparent degeneration and no accompanying degenerative features (Table 1). As pain could be induced by different pathways in those with no evident degenerative changes, and in those with structural changes to their discs visible by imaging, spinal MRIs provide a means of stratifying between degenerative and non-degenerative low back pain, of potential clinical and research benefit.

Limitations

There are few large cohorts containing spinal MRI scans from asymptomatic people. We used the TwinsUK cohort. This population is 96% female containing both mono- and di-zygotic twin pairs with few subjects <30 years of age.

The OSCLMRIC group were early chronic back-pain patients recruited from a secondary referral centre, and subject to a poorly defined selection processes, mainly through failure to respond to interventions in primary care. This group of patients may be distinct from the totality of patients seen in general practice such as those discussed in the Lancet series[27], but was similar to those seen in Genodisc, another secondary care group. Patients recruited in other settings could differ in prevalence, gender and clinical subtypes. We used females from the OSCLMRIC group when comparing results with TwinsUK, as women are reported to have a higher incidence of low back pain than men.[28]

The prevalence of degenerative changes reported here is specific to our study. Reports of degeneration vary from study to study. For instance, in a rural farming population in Japan, the prevalence of severe disc degeneration (Pfirrmann 4 or 5) in the lower lumbar spine of asymptomatic women was ~70% at 50-69 years, and ~80% at 60-69years[29], compared to ~33% and ~45% respectively to the females in TwinsUK (Fig 2c). The prevalence of degenerative features, such as herniations in asymptomatics, also varies, with reports varying from around 63% at 20-50 years[6] to 22% at 40-49 years[5] compared to <10% over the same age ranges in our study (Fig 4a). Differences in annotation could also affect reported prevalence. Consistent annotation of large groups is critical to progressing our understanding of these complex relationships.

A limitation also lies in the imaging protocols used here. While it is reassuring to see the similarity in Pfirrmann scores of two different patient groups annotated by SpineNet, in Twins UK we had access only to Sagittal T2 exams from a single MR machine, so in the Symptomatic Group, we have reported only Sag.T2 sequences from several MR machines. Other imaging sequences and also refinement of annotations of degenerate features may provide information which is better able distinguish painful from non-painful discs[21].

Our analysis of degeneration uses 1) an average of the 1-5 categoric Pfirrmann scale (Fig 1), which conceals important information, and 2) an analysis of grades 1 or 2 versus 4 or 5 which identifies populations with either disc 'normal' or disc 'very degenerate'. It omits changes in degeneration grade in the intermediate grade 3 discs, which represent around 25% of the total discs in both groups (Tables S1a,b). However, it does not omit most of the other degenerative features which are predominantly seen in 'very abnormal' discs (Fig 6). Larger data sets would allow a sensitivity analysis in future studies.

Interpretation

Considerable challenges face experts in annotating complex imaging in large groups with difference in definitions of degenerative changes and of back pain[30]. Our results show that automated analysis can overcome most of these difficulties. Moreover, by rapidly re-annotating large groups, previously annotated by different MRI analysis systems on the same objective system, it enables data from large pre-existing groups to be compared or combined. Collection of new groups is expensive and time consuming. Automated analysis provides a way in which

epidemiological analysis could be advanced by combining and comparing data from existing groups with MRIs and information on back pain.

Here we demonstrate that an automated analysis system (SpineNet) enabled rapid re-annotation of two patient groups (Genodisc and OSCLMRIC) and a population sample drawn from the TwinsUK cohort, all previously annotated by different coding methods. We compared degenerative changes of symptomatic and asymptomatic groups and show that these differences were strongly affected by age and spinal level. Hence reporting MRI features of spinal pathology in relation to symptoms, without taking age or spinal level into account, can be very misleading. We suggest information on age and disc level should be incorporated in clinical reporting standards to maximise the value of current NHS usage of MRI scans in this population.

We also suggest further studies on larger data sets could provide useful classifications of degenerative features. This study, once age and spinal level were taken into account, did not have the power to go beyond binary classifications of features such as herniations or marrow changes even though such analyses would be possible using SpineNet.

In our study, 40-50% of patients aged 30-60 years with back pain (compared with 60-80% without back pain) had no degenerative features detectable on MRI. We suggest that spinal MRIs, by distinguishing between spines with and without structural degenerative changes, could provide a means of stratifying patients for further research into causes and treatments of low back pain.

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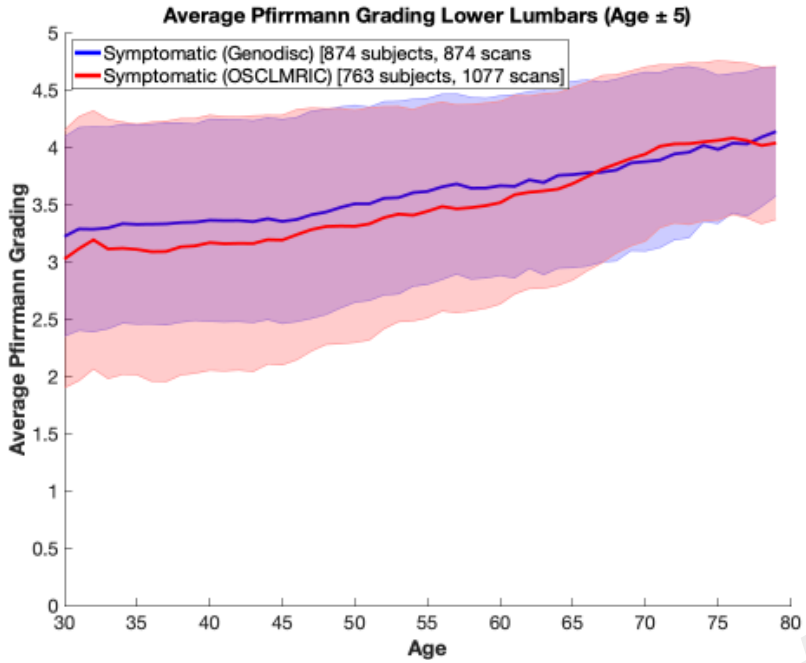
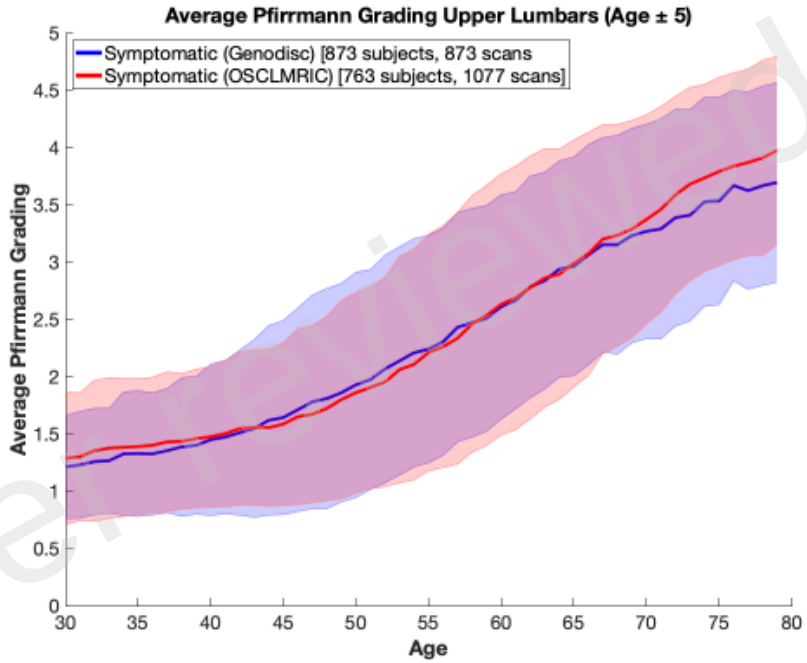
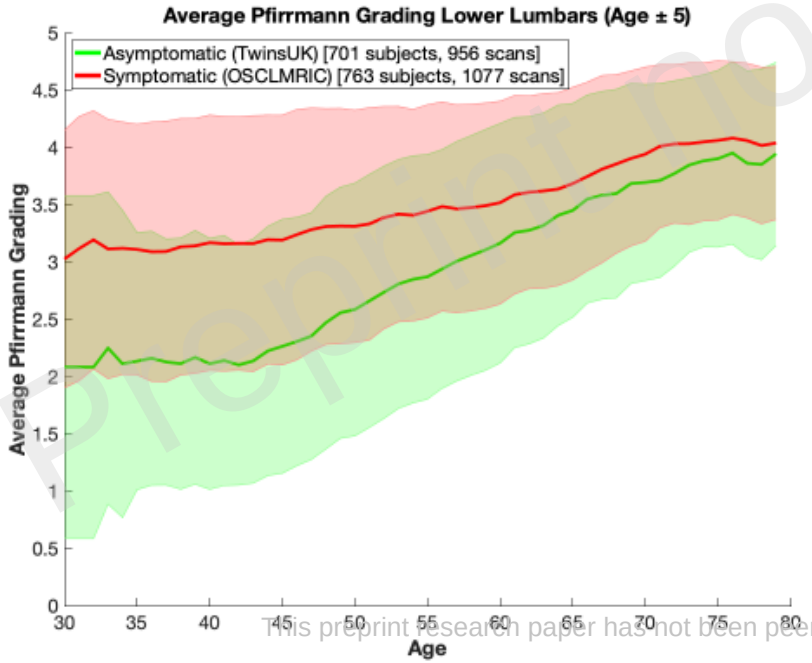
Age Range (years)	**Asymptomatic**	**Symptomatic**
30-39	77.7 (18)	43.3 (242)
40-49	75.1 (478)	50.3 (406)
50-59	60.4 (502)	43.8 (358)
60-69	47.1 (342)	32.3 (310)
70-79	22.6 (62)	18.9 (210)

Table 1; **Percentage of Discs with No Identified Degenerative Features in relation to Age; Lower lumbar Asymptomatic and Symptomatic discs.** The percentage of asymptomatic and symptomatic lower lumbar ((L4/L5) and (L5/S1)) discs which have no degenerative features identified here (viz. herniations, central canal stenosis, marrow signs, endplate defects) and only mild degeneration (Pfirrmann 1+2), with disc numbers analysed given in parentheses.

Figure 1. Average Pfirrmann Score versus age (30-79 years) lower (L4/5, L5/S1) and upper lumbar discs (L1/2, L2/3) for female subjects







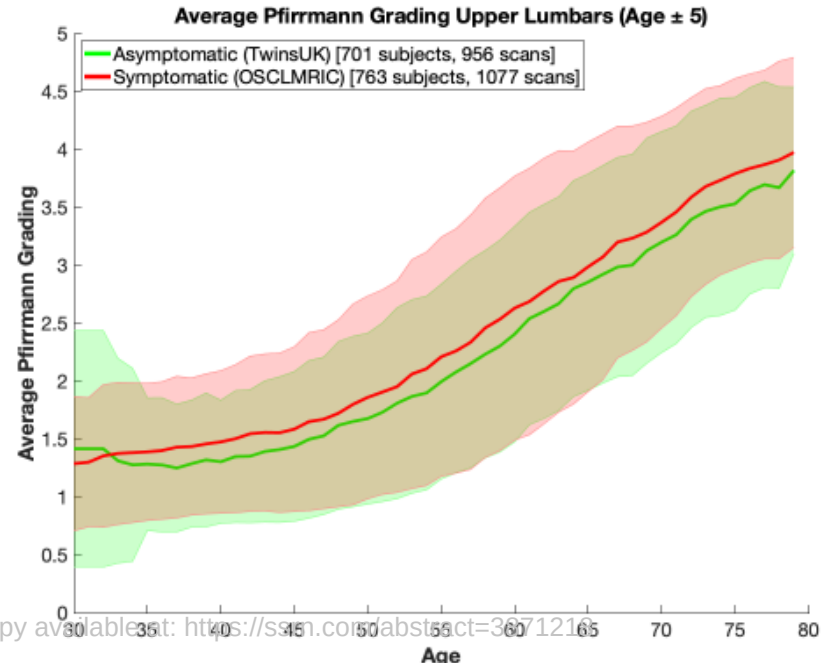


Figure 2. Variation with Age and Spinal Level in Prevalence (%) of Discs with Severe(High) and Minimal (Low) Pfirrmann Scores between Symptomatic (OSCLMRIC) and Asymptomatic (TwinsUK) Subjects

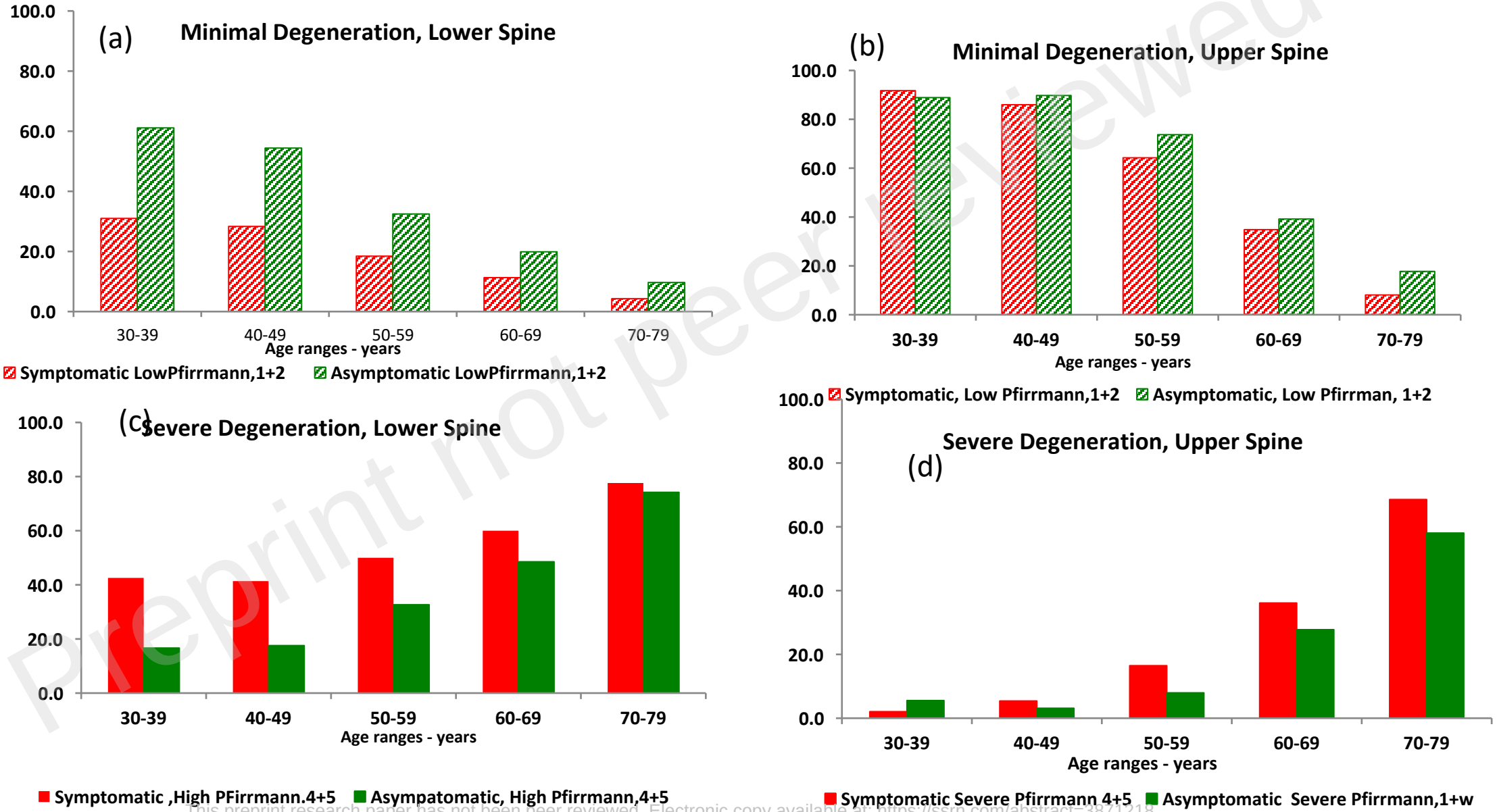
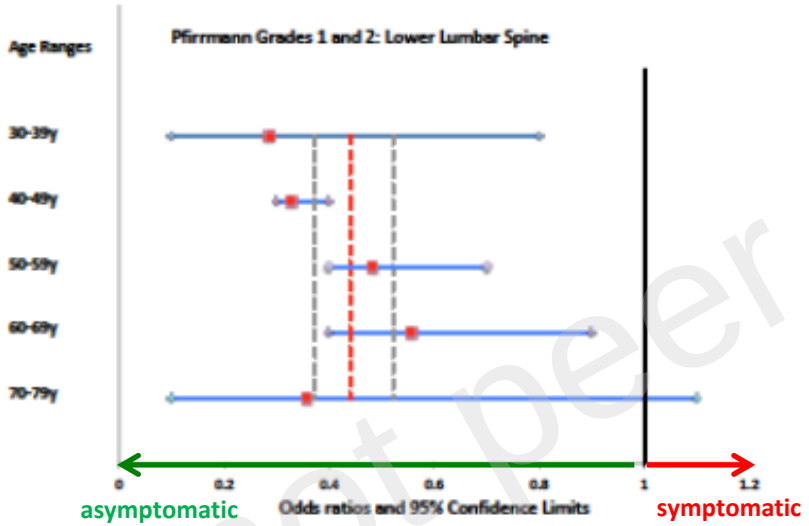


Fig 3. Odds Ratios and 95% Confidence Intervals for disc degeneration scores by age, both pooled and by decade; Symptomatic (OSCLMRIC) vs. Asymptomatic (TwinsUK) for low (a) and high (b) Pfirrmann scores in the low lumbar spine (L4/5,L5/S1)

(a)



(b)

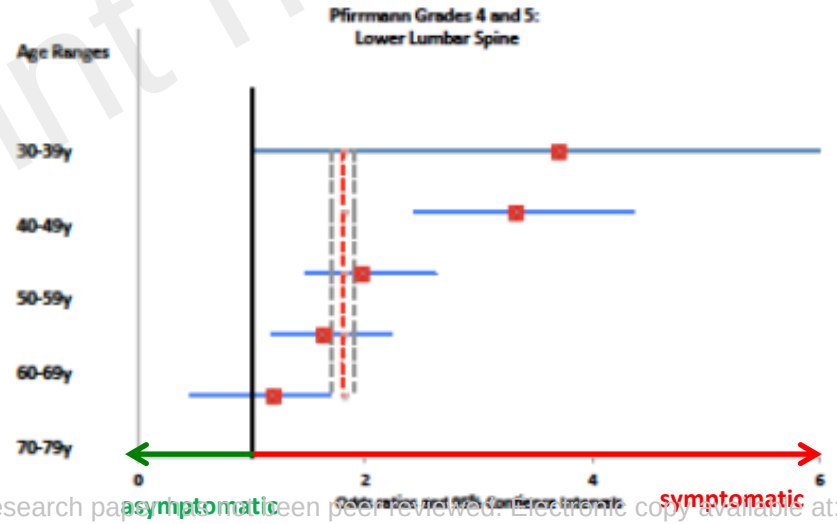


Figure 4. Prevalence of degenerative features in relation to age and spinal level in the lumbar spine, symptomatics and asymptomatics

(a) Herniations

(b) Central Canal Stenosis

(c) Marrow changes

(d) Endplate Defects

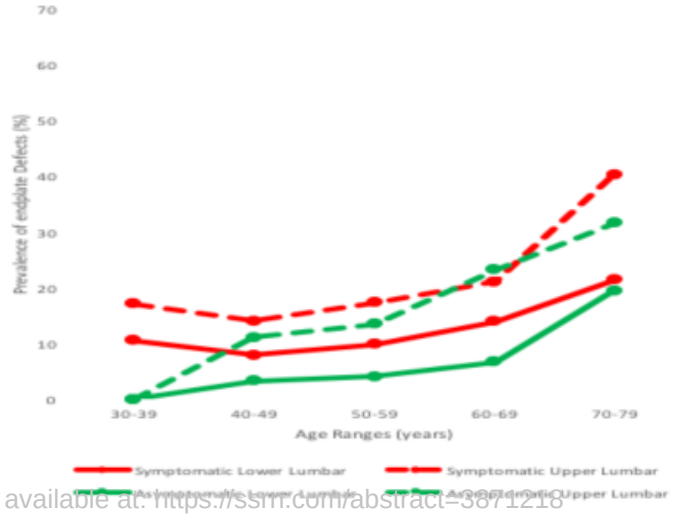
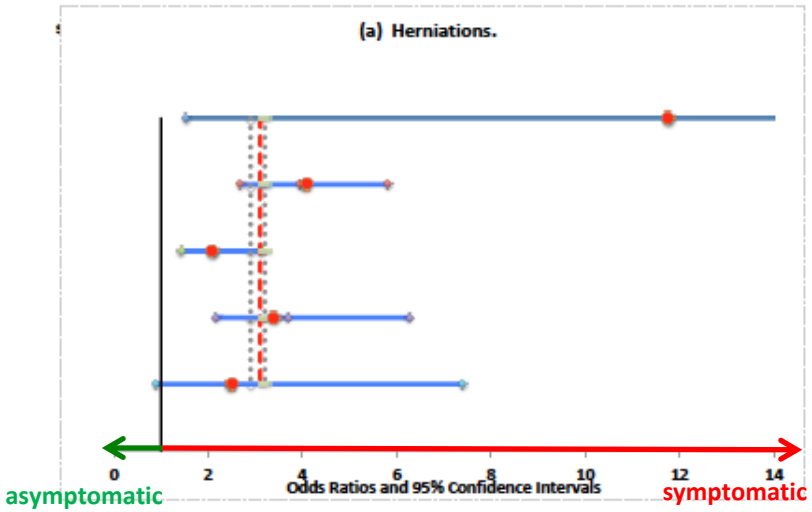
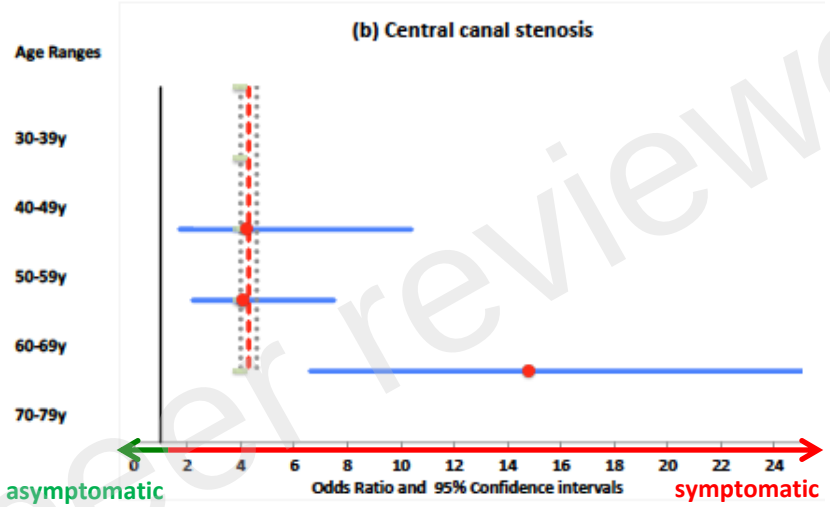
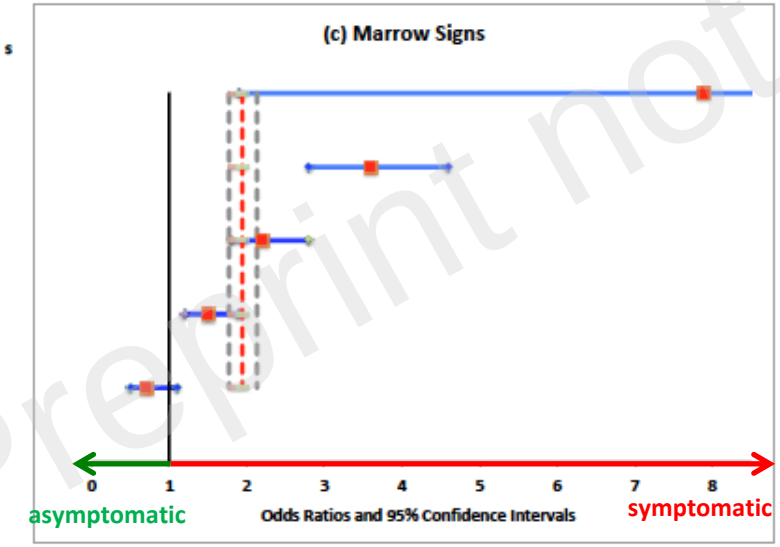


Figure 5. **Odds Ratios and Confidence Intervals for prevalence of degenerative features in relation to age, pooled and by decade; symptomatic vs asymptomatic cohorts**







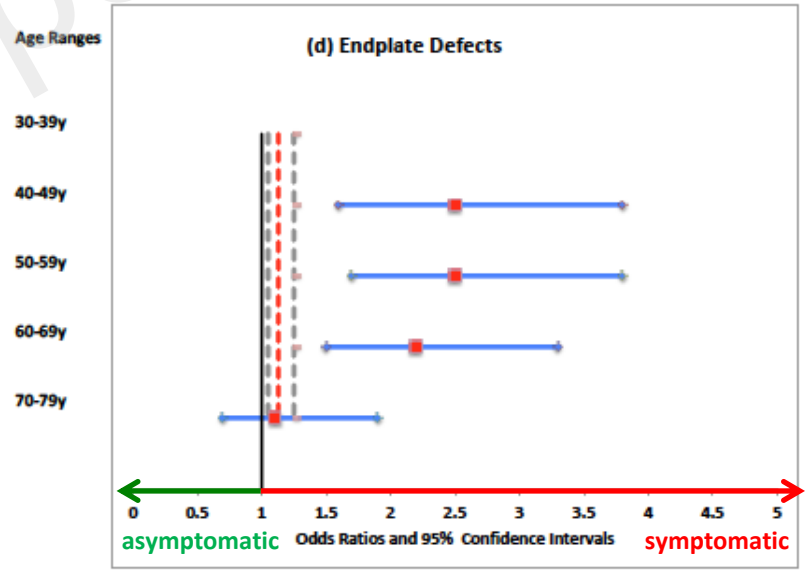


Figure 6. **Age-related Percentage of lower lumbar discs from the Symptomatic and Asymptomatic cohorts which have specific degenerative features and which are Pfirrmann Grades 4+5 in the low lumbar spine (L4/5 and L5/S1) (solid) and in the upper lumbar spine (L1/2 and L2/3) (hatched)**

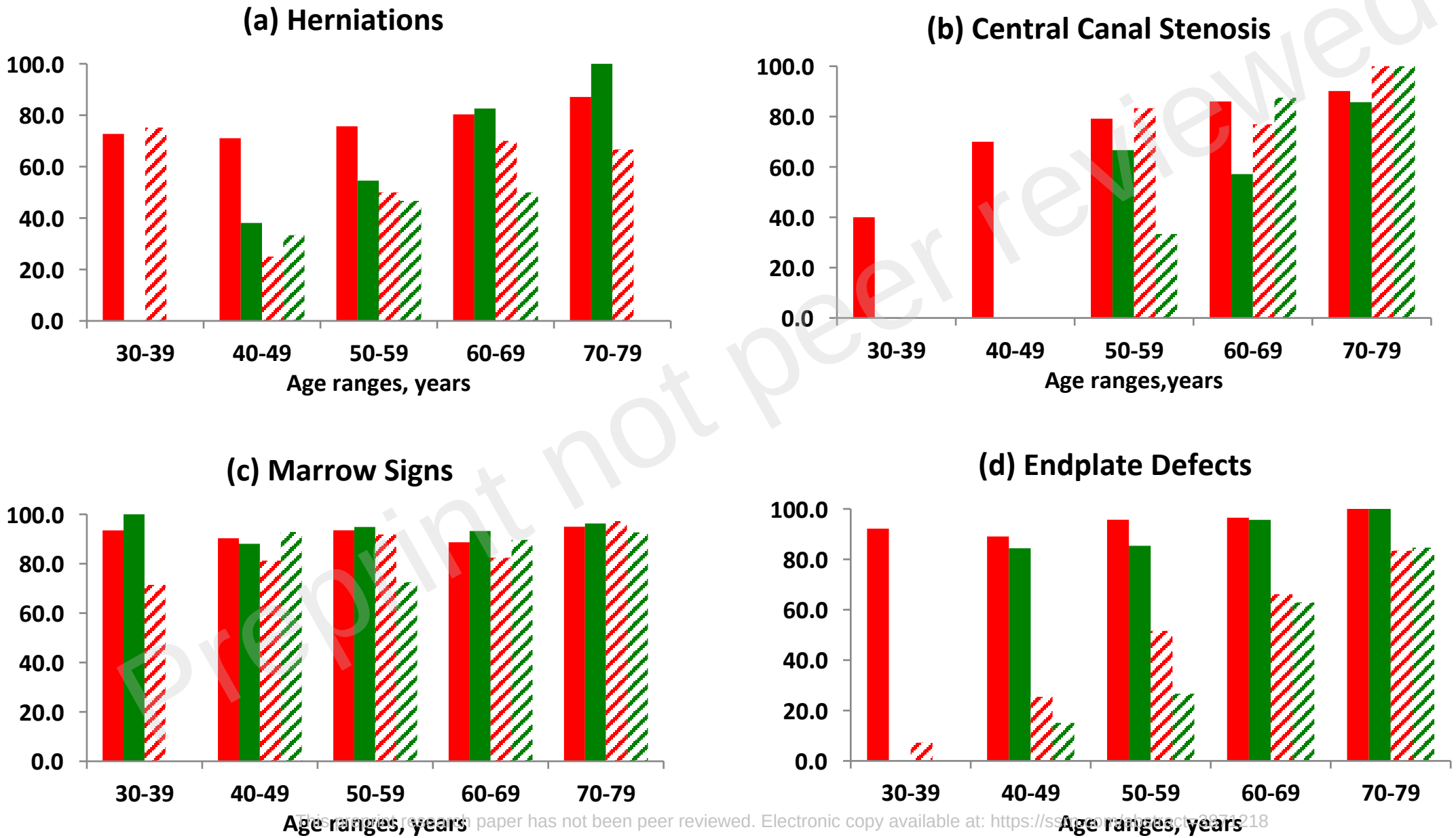
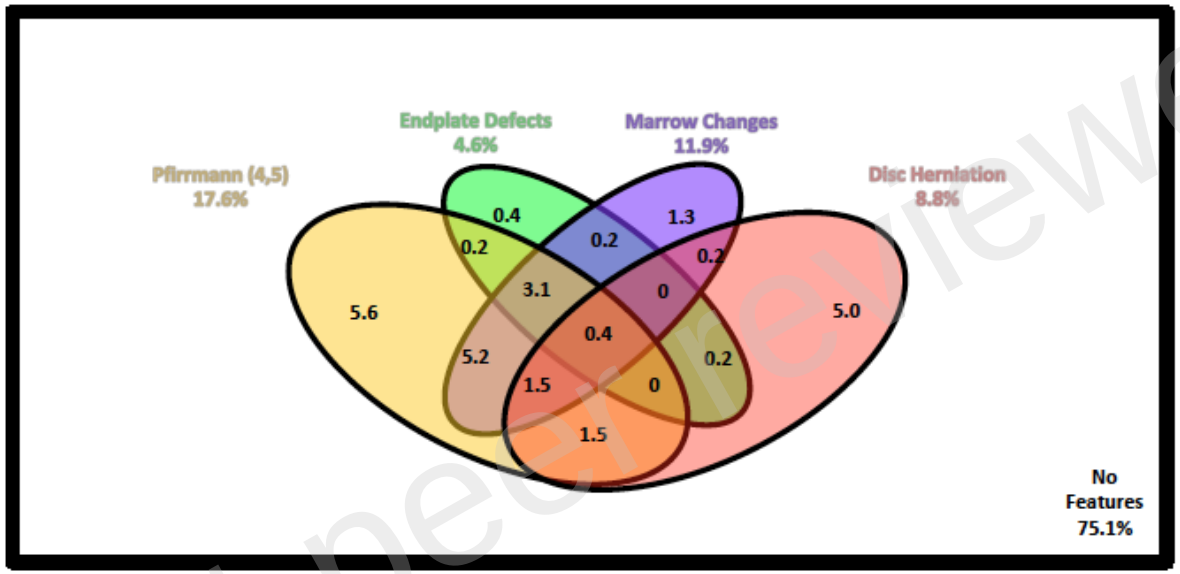


Figure 7: Venn diagrams, showing the prevalence (%) and overlap of degenerative features for Asymptomatic (a) and Symptomatic (b) Lower Lumbar discs, 40-49yrs

(a) Asymptomatic 40-49 years: Number of Subjects: 239; Number of Discs: 478

(a)



(b) Symptomatic 40-49 years: Number of Subjects: 194; Number of Discs: 388

(b)