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# ISSLS Prize Winner: Prevalence, Determinants, and Association of Schmorl Nodes of the Lumbar Spine With Disc Degeneration

## A Population-Based Study of 2449 Individuals

Florence P. S. Mok, MSc,* Dino Samartzis, MSc, DSc, PhD (C), MRIPH, Dip EBHC,*
Jaro Karppinen, MD, PhD,† Keith D. K. Luk, MCh(Orth), FRCSE, FRCSG, FRACS, FHKAM(Orth),*
Daniel Y. T. Fong, PhD,‡ and Kenneth M. C. Cheung, MBBS, MD, FRCS, FHKCOS, FHKAM(Orth)*

**Study Design.** A cross-sectional population-based magnetic resonance imaging study of Schmorl nodes (SN) in the lumbar spine.

**Objective.** To determine the prevalence and potential determinants of SN, and their association with intervertebral disc degeneration.

**Summary of Background Data.** SN represent intravertebral disc herniation and are commonly seen in the spine. Their reported prevalence and determinants vary, and their association with disc degeneration remains uncertain. Data based on this large scale population-based study of intervertebral disc degeneration would provide important information for understanding SN and their pathomechanism.

**Methods.** Sagittal T2-weighted magnetic resonance imagings of the lumbar spine were analyzed in 2449 volunteers. Two independent observers assessed the images for the presence of SN, and scored for additional radiologic features (*e.g.*, severity of degeneration, presence of disc bulge/extrusion). Subject demographics were assessed by standardized questionnaire.

**Results.** SN were found in 16.4% (n = 401; 219 males, 182 females; mean age = 42.3) of our study population (981 males, 1468 females; mean age = 40.4), being most common at L1/2 and L2/3 (54.1%). Multivariate logistic regression revealed that males, taller and heavier individuals had an increased likelihood of SN ($P < 0.005$), but association between SN and age were not discerned. Overall presence of SN was associated with disc degeneration ($P < 0.001$), and linearly correlated ($R^2 = 0.97$) with increase in severity of degeneration. SN were particularly associated with severe disc degeneration at L1/2 and L2/3 with 22- to 15-fold increased odds, respectively ($P < 0.0001$), but less than 5-fold increased odds ($P < 0.001$) were noted in the lower lumbar spine.

**Conclusion.** In a population-based cohort, 16.4% of Southern Chinese subjects had SN at 1 or more lumbar levels. Males, taller and heavier individuals had increased likelihood of SN. Interestingly, SN were highly associated with severity of disc degeneration.

**Key words:** Schmorl nodes, lumbar, disc degeneration, magnetic resonance imaging. **Spine 2010;35: 1944–1952**

Schmorl nodes (SN) were first described in 1927 and are classically defined as intravertebral disc herniation.[1] The prevalence of SN using magnetic resonance imaging (MRI) as the examination tool varies from 9% to 38%.[2–5] Moreover, in postmortem studies, SN have been noted in 76% of the specimens.[6] The variation in prevalence could be attributed to differences in assessment methodologies, subject inclusion criteria, and presence of spinal pathologies, such as Scheuermann disease.[7–10]

Although the precise role or function of SN are not known, they may play a role in intervertebral disc degeneration.[11–14] Unlike disc degeneration, where enormous research attentions have been placed on investigating biologic factors,[15–19] biomechanical properties and mechanical loading consequences,[11,20–26] genetic factors,[27–40] and the interaction between these factors,[12,33,41–43] little has been performed on SN. An MRI study on British female twins showed that SN were strongly genetically determined with heritability over 70%, and were associated with disc degeneration.[5] However, limitations regarding subject recruitment of single gender in their study, and the lack of control of other potentially confounding factors except subjects' age and body mass index (BMI) in their analyses, still render the association of SN with disc degeneration to be questionable. In addition, another recent skeletal study on Americans with different origins reported that SN were more prevalent in males and shown to be ethnic-dependent.[44] Although different etiologies of SN have been proposed including idiopathic, traumatic, and associated with decrease in bone mineral density and neoplastic lesions,[45–53] the discrepancies in the assessment and sampling methods, and the relatively small sample sizes of the previous studies, the prevalence of SN and their determinants remain still uncertain. Therefore, as part of a large scale population-based cohort study ex-

From the *Department of Orthopaedics and Traumatology, University of Hong Kong, Pokfulam, Hong Kong, Special Administrative Region, China; †Institute of Clinical Sciences, University of Oulu, Oulu, Finland; and ‡Department of Nursing Studies, University of Hong Kong, Hong Kong, Special Administrative Region, China.
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Address correspondence and reprint requests to Kenneth M. C. Cheung, MBBS, MD, FRCS, FHKCOS, FHKAM(Orth), Department of Orthopaedics and Traumatology, Queen Mary Hospital, 102 Pokfulam Rd, Pokfulam, Hong Kong, Special Administrative Region, China; E-mail: ken-cheung@hku.hk

amining genetic factors for intervertebral disc degeneration, this study aimed to assess the prevalence, potential determinants of SN, and their association with other imaging findings.

## ■ Materials and Methods

### *Study Population*

Since 2001, a population-based cohort, involving over 3000 Southern Chinese in examining genetic factors of disc degeneration, has been started in Hong Kong.[27,30,31,35,36,40,54] The current study was a cross-sectional study conducted between May 2008 and February 2009 with 2449 subjects recruited. After approval was obtained from the local ethics committee, subjects were recruited by open invitation from a regional population of approximately 7.6 million individuals, through newspaper advertisements, and e-mails and posters (which were circulated in different universities). The inclusion criteria of this study population, as a part of the genome-wide association study cohort, only restricted to people of Southern Chinese origin but no other particular restrictions to demographics such as age were applied. Subjects with known history of spinal surgery, spinal tumors, spinal infections, and inflammatory disease of the spine were excluded. In order to minimize the potential subject recruitment bias that people with low back symptoms might be more responsive to such invitation, the partners of the symptomatic subjects were also recruited. Previously, our dataset was shown to be representative of the general population.[31,54] All subjects who met the inclusion criteria underwent MRI examination of the lumbar spine. Information on subjects' demographics was collected by standardized questionnaire. On the basis of overall presence of SN, the study population was divided into 2 groups: (1) SN group, representing those individuals who had at least 1 or more SN, and (2) non-SN group.

### *Radiographic Assessment*

Radiographic assessment was based on sagittal T2-weighted MRI of the lumbar spine. Two independent observers, blinded to the clinical history of the subjects, reviewed all the MRIs. The interobserver reliability was excellent (kappa statistic = $0.91 \pm 0.01$). Furthermore, differences in rating were settled by consensus between the 2 observers as previously reported.[30,31,36] An SN was defined as localized vertebral endplate irregularities at either the rostral or caudal endplate, or both (Figure 1). Schneiderman *et al*[55] classification scheme was used to assess the presence and the severity of disc degeneration based on the MRI signal changes. Based on such criteria, a score of 0 indicates normal signal intensity of the nucleus pulposus (bright), a score of 1 as slight decrease in signal intensity, a score of 2 as generalized hypointense nucleus pulposus with normal disc height, and a score of 3 as hypointense nucleus pulposus with disc height narrowing. The score for each disc was summated to form a degenerative disc disease (DDD) score.[30,31,35,36,40,54] As such, this overall DDD score would have a range from 0 to 15. In univariable analysis, subjects with an overall DDD score of 0 were defined as normal, while those with an overall DDD score $\geq 2$ were defined as degenerated. Subjects with an overall DDD score of 1, meaning that s/he had a very mild degeneration at only 1 disc level, were regarded to represent borderline degeneration and were not included in this analysis. While in multivariable analysis, all subjects were divided into groups of increasing in severity of degeneration based on the overall DDD score with a 2-score interval. Additional radiographic features included the presence of disc bulge/extrusions, high-intensity zones lesion, radial tear, and bone marrow changes were also assessed and scored for being "present" or "absent." Marrow changes were defined as changes in signal intensity at the endplate and vertebral body, but distinction on the type of Modic changes[56] were not possible as, due to the limitation in costs and time of this large scale study, only T2-weighted MRI images were obtained.

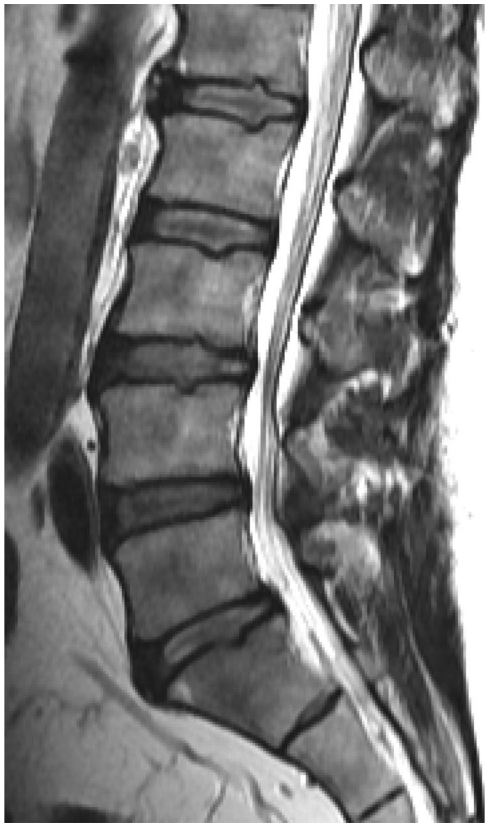

Figure 1. T2-weighted MRI scan of a 55-year-old male showing multiple Schmorl's nodes (SN) involvement and disc degeneration over the lumbar spine. In this figure, rostral and caudal SN were present at L1/2 and L3/4; Caudal SN were present at L2/3 and L5/S1. Grade 1 disc degeneration was present at L3/4 and L4/5.

### *Assessment of Subject Demographics*

Demographic data included gender, the exact age (years) with reference to the date of MRI assessment, self-reported body weight (kilogram) and height (centimeter), smoking, participation in sports, and the presence of previous lumbar spine injury. BMI was calculated ($kg/m^2$) and categorized according to the guidelines for Asians proposed by World Health Organization (WHO).[57] Smoking was noted if the subject was a current smoker or ex-smoker, and the amount and duration of cigarette smoking were accounted. Participation in sports was noted if the subject was regularly involved in any kind of exercise with a minimum frequency of twice weekly. The presence of previous lumbar spine injury was regarded as a subject who had ever sustained a blow or traumatic episode that resulted in back pain lasting 2 weeks or more.

### *Statistical Analyses*

Descriptive and frequencies statistics were carried out to all targeted variables as necessary. Univariable logistic regression analyses were conducted to evaluate the potential association

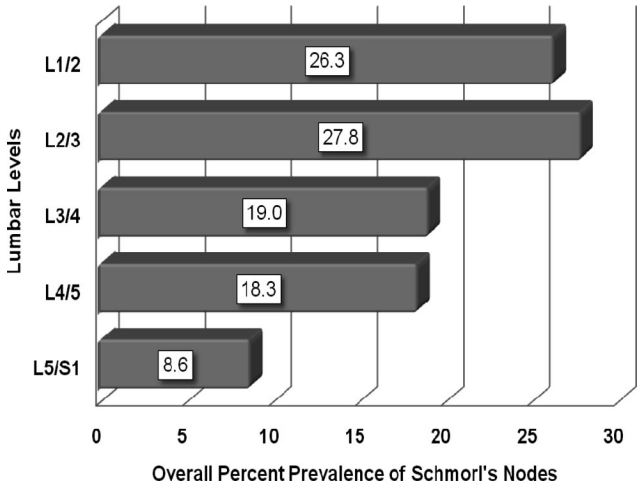


Figure 2. Bar chart showing the overall percent prevalence of Schmorl's nodes per lumbar level.

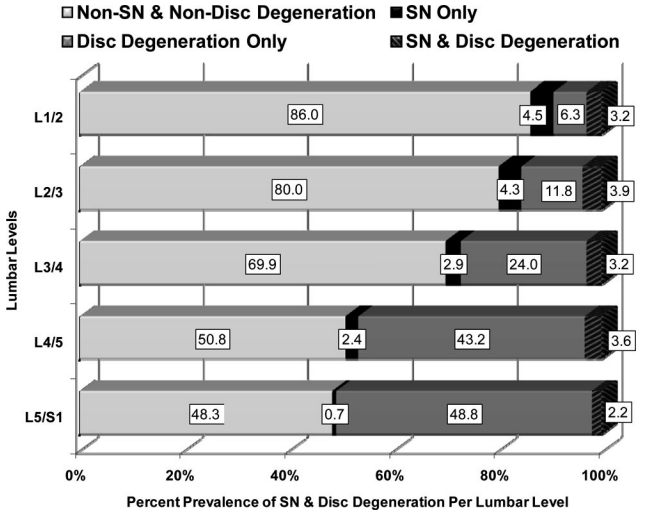


Figure 3. Bar chart showing the percent prevalence of the presence of Schmorl's nodes (SN) and disc degeneration per lumbar level. Percent values are illustrated in labels.

between various risk factors with the presence of SN. Odds ratios (OR) were assessed by using multivariable logistic regression to adjust for the effects of multiple risk factors associated with the presence of SN. Multicollinearity was checked by assessing the Variance Inflation Factor (VIF). The adequacy of all logistic regression models was examined by the Hosmer-Lemeshow goodness-of-fit test. Those variables with $P$ values equal or less than 0.20 from univariable analysis were used to test for multivariable logistic regression models. Only height and weight had high VIF (>2.5) and weight was chosen as it yields a higher Nagelkerke $R^2$. The statistical significance was set at $P < 0.05$ with 95% confidence intervals (CIs) bounds assessed for significance. The statistical analyses were performed with SPSS 16.0 (Chicago, IL) statistical software.

## Results

### Prevalence of Schmorl Nodes

Overall, there were 960 SN found in all 24,490 lumbar endplates. There were a total of 2449 subjects recruited. A total of 981 were males (40.0%) and 1468 were females (60.0%); their mean age was 40.4 years (range, 9.7–88.4 years). The non-SN group comprised 83.6% (n = 2048), of which 762 were males (31.1%) and 1286 were females (52.5%). The SN group comprised 16.4% (n = 401), of which 219 were males (8.9%) and 182 were females (7.4%). In those with SN, 49.6% (n = 199) had single lumbar level involvement, whereas 50.3% (n = 202) had multilevel involvements. SN were more prevalent in the upper 2 levels (54.1%), and L2/3 was the most common level (Figure 2). The percentage prevalence of SN and disc degeneration per lumbar levels is illustrated in Figure 3. Of note, the percentage prevalence of SN did not increase with older age in contrast to that of disc degeneration, which increased considerably with advancing age (Figure 4).

### Between Group Difference in Demographics

Demographic characteristics of all subjects and the group comparison between the SN group and non-SN group are shown in Table 1. The mean age, height, weight, and BMI of the subjects in SN group were significantly higher than that of non-SN group ($P < 0.001$). Of the 401 subjects with SN, 19 were underweight (4.7%), 157 had normal BMI (39.2%), 172 were overweight (42.9%), and 53 were obese (13.2%). Subjects in the SN group were also significantly ($P < 0.001$) more degenerated than non-SN group with an overall DDD score of 4.09 compared to 2.55.

### Determinants of Schmorl Nodes

Univariable analyses noted that male gender, increase in age, body weight, height, and BMI were associated with an increased likelihood of SN ($P < 0.001$). Smoking was also marginally associated with SN ($P = 0.035$), but neither the presence of history of lumbar injury nor participation in sports was associated with SN ($P > 0.05$). Of the radiographic features assessed, presence of disc degeneration and marrow changes increased the association with SN by more than 2-fold ($P < 0.001$), and the presence of disc bulge/extrusion was associated with a slightly higher likelihood of having SN ($P = 0.045$) (Table 2).

### Demographic and Lifestyle Factors

Males had higher odds of SN (adjusted OR: 1.54; 95% CI: 1.17–2.02; $P = 0.002$) after adjusting for demo-

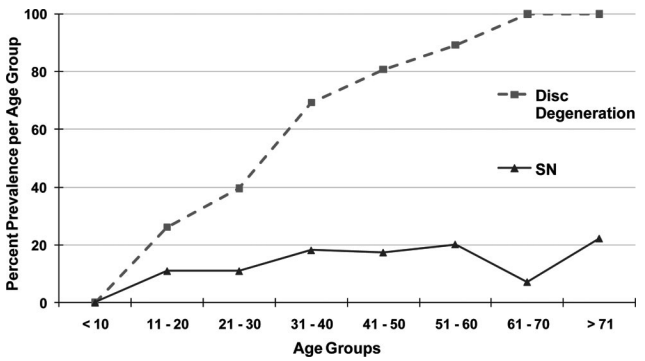


Figure 4. Graph showing the percent prevalence of the presence of Schmorl's nodes (SN) and disc degeneration per age groups.

**Table 1. Demographic Characteristics of All Subjects (N = 2449) and the Difference Between Schmorl Nodes (SN) Group (n = 401) and Non-SN Group (n = 2048)**

| | Overall Mean SD | SN Mean SD | Non-SN Mean SD | Difference (SN − Non-SN) | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Age (yr) | 40.41 ± 10.93 | 42.30 ± 10.15 | 40.04 ± 11.04 | 2.26 | 1.09–3.43 | <0.001 |
| Body weight (kg) | 60.87 ± 11.46 | 65.04 ± 11.85 | 60.06 ± 11.21 | 4.98 | 3.77–6.19 | <0.001 |
| Height (cm) | 163.11 ± 8.74 | 165.74 ± 8.95 | 162.59 ± 8.60 | 3.14 | 2.22–4.07 | <0.001 |
| BMI (kg/m$^2$) | 22.81 ± 3.53 | 23.60 ± 3.32 | 22.66 ± 3.55 | 0.94 | 0.56–1.31 | <0.001 |
| Overall DDD score | 2.80 ± 2.81 | 4.09 ± 3.11 | 2.55 ± 2.68 | 1.55 | 1.25–1.84 | <0.001 |

One-way ANOVA comparison of demographics between SN and non-SN group.
kg indicates kilograms; cm, centimeters; BMI, body mass index; SD, standard deviation; DDD score, degenerative disc disease score; CI, confidence interval.

graphic, lifestyle, and the radiographic variables in the multivariable model (Table 3). Although the mean age of SN group was significantly higher than non-SN group (Table 1), an association between age and SN was not discerned (adjusted OR: 0.99; 95% CI: 0.98–1.00; $P$ = 0.154) after adjustment for the other factors in the multivariable model. Additionally, for each kilogram increase in body weight, a 2% increase in odds of SN was observed (adjusted OR: 1.02; 95% CI: 1.01–1.03; $P$ = 0.001). Similar positive association was observed for height in centimeters, (adjusted OR: 1.03; 95% CI: 1.01–1.05; $P$ = 0.001) (data not shown in Table 3). Although per unit increase in BMI and/or BMI categories, and the presence of smoking were noted to exhibit an increased odds of SN ($P < 0.05$) in the univariable logistic regression analysis, such associations were insignificant after adjustment for other factors in the multivariable logistic model.

**Table 2. Univariable Logistic Regression on Potential Determinants of the Overall (N = 2449) Presence of Schmorl Nodes (n = 401)**

| | OR | 95% CI | *P* |
|---|---|---|---|
| Demographic variables | | | |
| Gender | | | |
| Male | 2.03 | 1.64–2.52 | <0.001 |
| Age (yr) | 1.02 | 1.01–1.03 | <0.001 |
| Body weight (kg) | 1.04 | 1.03–1.05 | <0.001 |
| Height (cm) | 1.04 | 1.03–1.06 | <0.001 |
| BMI (kg/m$^2$) | 1.07 | 1.04–1.10 | <0.001 |
| BMI (WHO–Asian category) | | | <0.001 |
| Underweight | 1 | | |
| Normal | 1.39 | 0.84–2.30 | 0.200 |
| Overweight | 2.33 | 1.41–3.86 | <0.001 |
| Obese | 2.96 | 1.68–5.21 | <0.001 |
| Lifestyle variables | | | |
| Smoking* | 1.40 | 1.02–1.91 | 0.035 |
| Participation in sports* | 1.10 | 0.87–1.38 | 0.416 |
| History of lumbar injury* | 1.14 | 0.91–1.43 | 0.255 |
| Radiographic variables | | | |
| Presence of disc degeneration* | 2.69 | 2.03–3.57 | <0.001 |
| Presence of disc bulge/extrusion* | 1.24 | 1.00–1.54 | 0.045 |
| Presence of HIZ* | 0.79 | 0.59–1.04 | 0.096 |
| Presence of radial tear* | 0.80 | 0.53–1.19 | 0.269 |
| Presence of marrow changes* | 2.35 | 1.62–3.41 | <0.001 |
| Overall DDD score group | | | <0.001 |
| 0–1 | 1 | | |
| 2–3 | 1.79 | 1.32–2.42 | <0.001 |
| 4–5 | 2.90 | 2.10–4.00 | <0.001 |
| 6–7 | 3.34 | 2.33–4.78 | <0.001 |
| 8–9 | 5.17 | 3.26–8.21 | <0.001 |
| 10–11 | 4.95 | 2.70–9.07 | <0.001 |
| ≥12 | 6.09 | 2.46–15.09 | <0.001 |

BMI categories for Asian were based on World Health Organization (WHO) guidelines[57] defining underweight <18.5, normal (18.5–23), overweight (23–27.5), and obese (>27.5).
The Hosmer-Lemeshow test with the minimal $P$ = 0.245.
*Categorical variable with reference set as "Absent."
OR indicates odds ratio; CI, confidence interval; DDD score, degenerative disc disease score; BMI, body mass index; HIZ, high-intensity zones lesion.

### *Radiographic Factors Associated With SN and the Relationship With Disc Degeneration*

After adjusting for demographics, lifestyle and other radiographic features as shown in Table 3, the overall presence of SN was noted to have a strong positive linear relationship with the increase in severity of disc degeneration ($R^2$ = 0.97) (Figure 5). On the contrary, the presence of disc bulge/extrusion, and the presence of high-intensity zone decreased the odds of SN (Table 3). In further evaluating the relationship of disc degeneration and SN at individual lumbar levels, the severity of degeneration at each lumbar level was stratified by the presence or absence of concomitant disc height narrowing, as an indicator of a more severe form of degeneration (Schneiderman Grade 3). Interestingly, SN were signifi-

**Table 3. Multivariable Logistic Regression of Potential Determinants Associated With the Overall (N = 2449) Presence of Schmorl Node (n = 401)**

| | Adjusted OR | 95% CI | *P* |
|---|---|---|---|
| Gender | | | |
| Male | 1.54 | 1.17–2.02 | 0.002 |
| Age | 0.99 | 0.98–1.00 | 0.154 |
| Body weight (kg) | 1.02 | 1.01–1.03 | <0.001 |
| Smoking | 0.95 | 0.68–1.34 | 0.781 |
| Presence of disc bulge/extrusion | 0.55 | 0.41–0.73 | <0.001 |
| Presence of HIZ | 0.59 | 0.43–0.80 | <0.001 |
| Presence of marrow changes | 1.22 | 0.81–1.83 | 0.338 |
| Overall DDD score group | | | <0.001 |
| 0–1 | 1 | | |
| 2–3 | 2.74 | 1.92–3.90 | <0.001 |
| 4–5 | 4.71 | 3.15–7.03 | <0.001 |
| 6–7 | 5.65 | 3.61–8.85 | <0.001 |
| 8–9 | 8.88 | 5.05–15.59 | <0.001 |
| 10–11 | 8.58 | 4.24–17.37 | <0.001 |
| ≥12 | 11.09 | 4.05–30.37 | <0.001 |

This multivariable logistic regression model had Nagelkerke $R^2$ = 0.124 and $P$ value by the Hosmer-Lemeshow goodness-of-fit test = 0.690.
OR indicates odds ratio; CI, confidence interval; DDD score, degenerative disc disease score; BMI, body mass index; HIZ, high-intensity zones lesion.

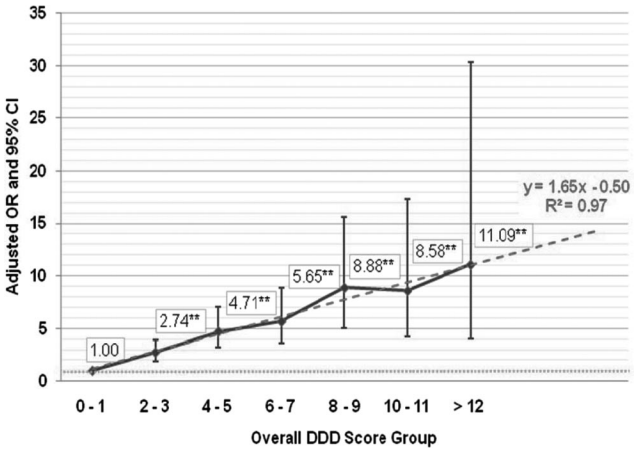


Figure 5. Graph showing the adjusted odds ratios (OR) of the overall presence of Schmorl's nodes in association with the increase in disc degeneration severity (depicted with the increase in overall DDD score groups). The OR value of individual DDD score groups and the respective width of the 95% confidence interval are illustrated in labels and bars, respectively. A dashed trendline is inserted to show the linear relationship ($R^2 = 0.97$) of disc degeneration severity and the associated risk of SN. The OR values with $P < 0.001$ are denoted with double asterisks. The dotted line represents an OR value of 1. †Cross reference to Table 3.

cantly ($P < 0.001$) associated with severe form of degeneration with disc height narrowing at all lumbar levels (Figure 6). Moreover, regional variation of such association was evident as SN were particularly associated with severe forms of disc degeneration at L1/2 and L2/3 with 22- to 15-fold increased odds, respectively, but generally less than 5-fold increased odds over lower lumbar levels (Figure 6). Furthermore, the presence of marrow changes was associated with increased odds of SN at L4/5 (adjusted OR: 3.01; 95% CI: 1.48–6.13; $P = 0.002$). Alternatively, the presence of disc bulge/extrusion showed a decreased association with SN at L5/S1 (adjusted OR: 0.40; 95% CI: 0.22–0.74; $P = 0.003$). No radiographic features were associated with SN at the upper 3 levels. Of note, the association of SN with the presence of minor form of disc degeneration (without disc height narrowing, Schneiderman Grade 1 and 2) at L4/5 did not reach statistical significance, yet with the testing of different multivariable logistic regression models by removing the potential confounding variables, results of the adjusted OR values, the *P* values and width of 95% CIs were essentially the same. Therefore, the goodness-of-fit of the chosen model was considered as adequate.

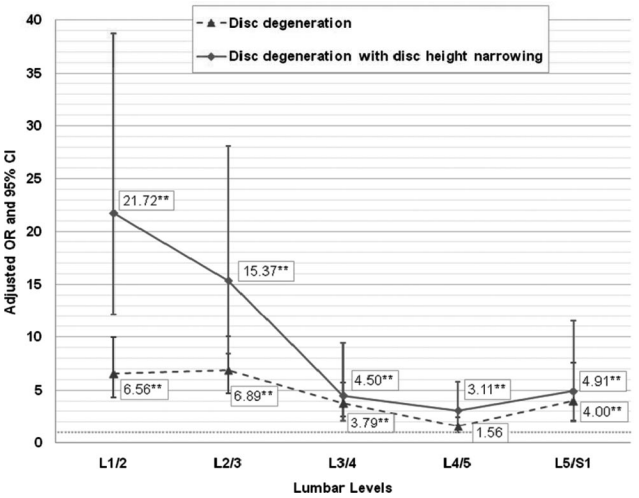


Figure 6. Graph showing the adjusted odds ratios (OR) of the overall presence of Schmorl's nodes in association with different severity of disc degeneration per lumbar levels. The OR values are assessed by multivariable logistic regression model adjusted for gender, age (year), body weight (kg), and the presence of radiographic features (*i.e.*, disc bulge/extrusion, high-intensity zone, marrow changes) at the respective levels. The OR values and the respective width of the 95% confidence interval are illustrated in labels and bars, respectively. The OR values with $P < 0.001$ are denoted with double asterisks. The dotted line represents an OR value of 1.

## ■ Discussion

To the authors' knowledge, this is the largest scale study that addressed the prevalence and potential determinants of SN using MRI assessment. It was found that 16.4% of the local population presented with SN (at 1 or more lumbar levels) in the current study. This SN prevalence seemed to be on the lower end of the reported prevalence from the reported literature.[2,4,5,44,58,59] As previously noted, this could partly be due to the nonpopulation nature of previous studies, differences in subject inclusion criteria (*e.g.*, single gender), the discrepancy in the examining methods and inclusion criteria by using MRI[2–5,59] *versus* radiographs[6,58] and direct inspection based on cadaveric specimens.[44,60] In addition, the spinal levels assessed in some of these studies varied. Oftentimes, the thoracic levels[2,4–6,44,58] were included as opposed to only lumbar spine as in our current study; therefore, such methodologic differences may explain the prevalence variations. Indeed, a recent skeletal study by Dar *et al*[44] investigating the thoracic and lumbar spines from 240 American individuals showed that the presence of SN was ethnic dependent. Their reported overall prevalence was 48.3%, but European-Americans (60.3%) were more affected than African-Americans (36.7%). Moreover, European-Americans not only significantly exhibited more SN than African-Americans (72.8% *vs.* 27.2%; $P < 0.05$) but ethnicity was also significantly associated with more multiple SN occurrences. The ethnic-dependence of SN could possibly be related to the strong genetic influence of SN,[5] nevertheless, these could explain further as to why the reported prevalence in the literatures greatly varies with the relatively "low" prevalence of SN in the current study, which is based on a Southern Chinese population.

In our study, the majority of SN presented in the upper lumbar levels with the highest prevalence in L2/3. This finding was consistent with previous reports noting that SN were more commonly located in the thoracolum-

bar region.[2,5,6,47,58] This could be due to higher mechanical stresses at the transition zone between the thoracic and lumbar spine. It has been reported that compressive loading on the posterior facet ligamentous complex of the lumbar spine increased with an increase in lordotic posture,[61] and that the average loading on the facet joints of the 3 lowest lumbar segments was higher than that of the 2 upper segments.[62] Therefore, as far as the 3-joint-complex is concerned, *i.e.*, the load sharing between the intervertebral disc and the paired facets, one would postulate that the relative compressive forces loaded onto the intervertebral disc should decrease caudally due to the increase in lumbar lordosis. In turn, it might account for the less compressive forces loaded onto the endplate, and resulting in less SN on the lower lumbar segments. However, one should also note that the overall loading onto the spine also increases caudally; therefore, if mechanical stress could account for the matter adequately, one would assume that the incidence of SN over the lower lumbar region would be the highest due to the overall high mechanical load concentrated over the area. In fact, a recent skeletal study examining the strength of endplate by indentation loading test found that in both superior and inferior endplates, there were significant differences between lumbar segments and the mechanical strength tended to increase caudad suggesting that the endplates of the upper lumbar segments were weaker than that of the lower lumbar segments.[63] Additionally, no significant difference in the strength of adjacent endplates from L1/2 and L2/3 was noted. These results not only verify the observed difference in the SN prevalence over the upper *versus* the lower lumbar levels, and the similar prevalence of SN in L1/2 and L2/3 as showed in the current study, but also hint on the importance of endplate strength in the etiology of SN.

Based on our study, the demographic determinants of SN were male gender, increase in body weight, and height. A study by Videman *et al*[64] entailing 600 Finnish twin males suggested that higher body weight, and greater lifting strength and physical activity were highly associated with disc degeneration. One could postulate that the effect of continuous loading with higher body weight could affect the function of the endplate, together with other predisposing factors (*e.g.*, genetic predisposition, endplate morphology, and size) that may affect the integrity and strength of the endplate structures. In fact, the cadaveric study by Adams *et al*[11] showed that repetitive loading in the disc with endplate damage could lead to progressive mechanical changes and initiated degeneration in the intervertebral disc. Therefore, the continuous loading with higher body weight could increase the susceptibility of endplates to failure and increase the risk of sustaining SN.[50]

In addition, as males are generally with larger physique (taller and heavier) than females, it could explain part of the reason as to why males were more associated with SN. Besides, it might also be due to the morphologic differences between gender in the height of the vertebral body and disc that render the endplates susceptible to failure under higher disc stress in males.[44] Although genetic association analysis was not the focus of the current study, it has been reported by Williams *et al* that SN were strongly genetically determined with heritability as high as 72% and 80% over the thoracic and lumbar spine, respectively, in their female twins subjects.[5] It would be interesting to know if the heritability be even higher if genders were separately analyzed. Therefore, apart from the demographic disparity between genders, genetic component might also play a role in accounting for the strong association of male gender and SN.

Although it has been documented in MRI and autopsy studies of subjects with traumatic history,[47,51,52] and in a long-term observational studies that SN may result from trauma due to vertebral fractures during childhood,[49] we did not find such association with the presence of historical lumbar injury in our subjects. One possible reason for the lack of association of previous lumbar injury and the presence of SN in our results could be due to the potential recall bias of injury incidents. Moreover, our assessment may not have been too sensitive to detect the historical presence of spinal injury. However, the effect of cumulative minor injuries, such as compressive axial loading and the effect of body weight as discussed, could indeed be a mechanism that may result in endplate damage and eventually develop SN.

The result of this study confirmed that SN were significantly associated with intervertebral disc degeneration, and this finding is consistent with previous studies.[5,6,14,58] Although the cross-sectional study design limits our conclusion in the time-course of the interaction between SN and disc degeneration, nevertheless, our study was the first to note the overall strong association between SN and severity of degeneration in a dose-dependent linear relationship, and the regional variations between the upper lumbar spine *versus* the lower lumbar spine of such an association. SN being significantly associated with severe degeneration with disc height narrowing (with 22- to 15-fold increased odds) *versus* minor disc degeneration (less than 7-fold increased odds) at L1/2 and L2/3, and *versus* generally less than 5-fold increased odds at the mid to lower lumbar levels regardless of the severity of degeneration. As shown in our findings, disc degeneration was most common in the lower lumbar spine (almost 50% affected) but was relatively rare in the upper lumbar (less than 14%). On the contrary, more than 50% of SN were present in the upper 2 lumbar levels but much less at L5/S1 (8.6%). Additionally, the presence of disc bulge/extrusion significantly decreased the association of SN, especially over L5/S1 by 60%. If one maintains that SN are herniation of the disc material into the adjacent endplate, one might assume that SN would act similar to disc herniations, at least to some extent, in reducing disc pressure. As such, the reduced disc pressure with disc bulge/extrusion would decrease the likelihood of having SN and *vice*

*versa*. In fact, it has been shown in cadaveric models that the pressure in the nucleus pulposus (NP) could be reduced by 25% ± 27% with minor endplate damage.[11] While the association of disc herniation with degeneration is not surprising, experimental study in sheep discs has suggested that peripheral tear in the anulus fibrosis would lead to progressive biochemical degradation of the intervertebral disc.[65] Nevertheless, cadaveric study by Przybyla *et al*[66] using human lumbar discs found that endplate fracture produced an immediate effect by significantly reducing the nucleus pressure by 37% ($P$ = 0.004), whereas the outer anulus tear produced only negligible effect (1%) in decreasing the nucleus pressure. This clearly indicates the more important role of endplate fracture over peripheral anulus tear in the etiology of intervertebral disc degeneration. Therefore, the presence of SN might warrant more attention being that such lesions could eventually lead to a degenerative cascade of the intervertebral disc.

The presence of endplate defect as a detrimental factor in maintaining the normal nutritional pathway, and the overall integrity of the disc was highlighted by the diffusion studies by Rajasekaran *et al*.[13,67,68] Our observation of a linear dose-dependent association between SN and degeneration severity are in line with their findings. Furthermore, Peng *et al*,[50] based on their investigation of the histologic findings of surgical specimens from patients with severe low back pain, suggested that the pathogenesis of SN is due to the ischemic osteonecrosis beneath the cartilaginous endplate. Apart from the potential determinants in demographic, lifestyle and radiographic factors in association with SN as mentioned above, and the genetic influence on SN as suggested by Williams *et al*,[5] the authors also found the unique pattern of SN characteristics and their interesting associations with the endplates (Mok *et al* unpublished) by using a proposed standardized classification of SN. In addition, while disc degeneration is correlated with aging,[15] and we found SN being significantly associated with disc degeneration, our results did not show the prevalence of SN nor the likelihood of SN to increase with advancing age. Therefore, we believe that SN are indeed a radiographic marker being attributed by multiple factors and the interactions between these factors, such that the genetic role in controlling the endplate defect with SN might indeed share a common pathway with degenerative changes in the disc.

Although our study elaborated on the prevalence, potential determinants of SN, and their interesting association with disc degeneration, there are several limitations that should be noted. First, due to financial cost involved in scanning all subjects in this large cohort, the radiographic assessment was limited to sagittal T2-weighted MRI, and additional assessments such as axial or T1-weighted images were not performed. Yet, sagittal T2-weighted MRIs have showed to be reliable in assessing intervertebral disc conditions of the lumbar spine.[55,69,70] Second, bone mineral density was not assessed in the current study. However, the potential factors associated with the manifestations of osteoporosis such as age, gender (females), and lifestyles variables such as smoking, and regular participation to sports activities were taken into account in the univariable and multivariable analyses (Tables 2, 3). In fact, our results showed that these potential factors of osteoporosis did not seem to increase the likelihood of SN. Moreover, radiographic[45] nor cadaveric[48] studies did not find such an association between SN and osteoporosis or low bone mineral content. Third, the cross-sectional study design based on Southern Chinese also limited suggestions regarding causal inferences between SN and disc degeneration. Additionally, given the recently proposed ethnic-dependency of SN,[44] caution must be paid when generalizing our results to other populations.

Regardless, based on this largest population-based cohort covering a wide age-range from 10 to 88 years, our study provided important information on the various potential determinants associated with SN over other studies. More importantly, the dose-dependent linear association of SN with disc degeneration severity and its regional variations, which has not been addressed before, provide insights for further understanding of intervertebral disc pathology.

## ■ Conclusion

In conclusion, the prevalence of SN on the lumbar spine was 16.4% in Southern Chinese and most common at the upper 2 lumbar levels. Demographically, male gender, height, and weight were associated with an increased likelihood of having SN. More importantly, our results showed that the overall presence of SN is strongly associated with severity of disc degeneration in a dose-dependent linear relationship. The upper 2 lumbar levels were associated with 15- to 22-fold increased odds of SN with severe disc degeneration as compared to less than 5-fold in other levels. The regional variation in SN prevalence and the association between SN and disc degeneration of the lumbar spine may further stress the importance of the endplate on the pathomechanism of disc-related changes.

### ■ Key Points

- The prevalence of SN was 16.4%, and they were most common at the upper 2 lumbar levels.
- Male gender, height, and weight were significantly associated with SN, whereas age was not.
- SN were strongly associated with severity of disc degeneration in a dose-dependent linear relationship.
- SN were particularly associated with severe disc degeneration at L1/2 and L2/3.

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