

# Impact of Diffuse Idiopathic Skeletal Hyperostosis on Sagittal Spinal Alignment in the General Elderly Population

A Japanese Cohort Survey Randomly Sampled from a Basic Resident Registry

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**Background:** Interest is mounting regarding diffuse idiopathic skeletal hyperostosis (DISH) as the rate in the elderly increases. Although some studies have demonstrated an effect of DISH on sagittal spinal alignment, the pathogenetic mechanism remains unknown. Random sampling from the basic resident registry of a rural town for subject selection was used to investigate the impact of DISH on sagittal spinal alignment.

**Methods:** Registered citizens who were 50 to 89 years of age were targeted for this survey. We divided the study population into 8 groups based on sex (male and female) and age (50 to 59, 60 to 69, 70 to 79, and 80 to 89 years) after random sampling from the resident registry of the town of Obuse in 2014. A total of 411 participants (202 male and 209 female) were enrolled and underwent a whole-spine lateral radiographic examination. We investigated the spinal level of DISH occurrence, measured sagittal spinal alignment parameters, and analyzed the effects of clinical factors on DISH using multivariate analysis.

**Results:** A total of 66 participants (16.1%) were identified as having DISH in our population cohort. With regard to DISH involving the thoracic spine, sagittal vertical axis, cervical sagittal vertical axis, T1 slope, thoracic kyphosis, aging, and male sex were significantly associated with DISH in the univariate analysis. Aging and male sex were also independent factors according to multivariate analysis; the odds ratio (OR) was 1.70 for aging per decade and 3.75 for male sex. Sagittal vertical axis, lumbar lordosis, sacral slope, pelvic tilt, aging, and male sex had significant associations with DISH involving the lumbar spine in univariate analysis, with decreased lumbar lordosis (OR, 1.82), aging per decade (OR, 4.35), and male sex (OR, 10.7) as independent factors in multivariate analysis.

**Conclusions:** In this study examining the impact of DISH on sagittal spinal alignment in a general population, decreased lumbar lordosis was significantly associated with DISH involving the lumbar spine in the healthy community-dwelling elderly population, and no sagittal spine parameters were significantly related to DISH affecting the thoracic spine.

**Clinical Relevance:** When there is decreased lumbar lordosis in elderly people, we should check for the existence of DISH.

Diffuse idiopathic skeletal hyperostosis (DISH) is a condition characterized by the calcification and ossification of soft tissues, mainly the ligaments and entheses<sup>1,2</sup>. The prevalence of DISH is reportedly 4% to 42%<sup>3-6</sup>. Most cases of

DISH are asymptomatic, but complications such as dysphagia, unstable spinal fracture, postsurgical heterotopic ossification, intubation difficulty, gastroscopy difficulty, aspiration pneumonia, and myelopathy sometimes occur<sup>7</sup>. The prompt diagnosis of

**Disclosure:** One author (M.U.) reported grant support from The Japan Orthopaedics and Traumatology Research Foundation, Inc. (No. 339), one author (H.K.) reported grant support from the Japanese Orthopaedic Association and the Japanese Society for Musculoskeletal Medicine, and one author (S.I.) reported grant support from the Nakatomi Foundation. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJSOA/A107>).

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fractures in patients with DISH is also important because injuries may become unstable or display union failure or severe neurological deficits even from minor trauma. The prevalence of DISH increases with age<sup>8</sup>. As the rate of elderly people reached 27% of the Japanese population in 2016<sup>9</sup>, interest is therefore mounting regarding DISH. Some studies have shown an effect of DISH on sagittal spinal alignment<sup>10,11</sup>, although the pathogenetic mechanism remains unknown.

We recently conducted an epidemiological musculo-skeletal examination in the community-dwelling elderly population. Random sampling from the basic resident registry of Obuse, a rural Japanese town, was adopted to minimize

TABLE I Cohort Characteristics			
	Group with DISH*	Group without DISH*	P Value
Age (yr)	75.6 ± 8.9	68.6 ± 11.2	<0.01
Sex			<0.01
Male	51	151	
Female	15	194	
BMI (kg/m <sup>2</sup> )	24.0 ± 3.4	22.5 ± 3.0	0.001
Sagittal vertical axis (mm)	36.2 ± 49.7	19.5 ± 42.2	0.012
Cervical sagittal vertical axis (mm)	28.8 ± 16.7	21.2 ± 13.2	<0.01
Cervical lordosis (deg)	13.3 ± 10.3	11.5 ± 9.1	0.19
T1 slope (deg)	30.3 ± 10.4	25.6 ± 9.1	<0.01
Thoracic kyphosis (deg)	32.3 ± 11.6	29.1 ± 11.1	0.048
Lumbar lordosis (deg)	41.9 ± 13.6	44.2 ± 14.5	0.21
Sacral slope (deg)	29.6 ± 8.5	31.0 ± 9.6	0.22
Pelvic tilt (deg)	18.9 ± 8.3	18.0 ± 9.3	0.42
Pelvic incidence (deg)	48.2 ± 9.0	48.7 ± 10.5	0.70

\*The values are given as the mean and the standard deviation, except for the sex category, in which the values are given as the number of patients.

TABLE II Subject Comorbidities Obtained via Detailed Interviews	
Comorbidity	No. of Patients
Hypertension	184 (44.8%)
Cancer	56 (13.6%)
Diabetes mellitus	53 (12.9%)
Osteoporosis	36 (8.8%)
Cardiovascular disease	15 (3.6%)
Cerebrovascular disease	10 (2.4%)
Pulmonary disease	7 (1.7%)
Rheumatoid arthritis	5 (1.2%)
Parkinson disease	0 (0%)

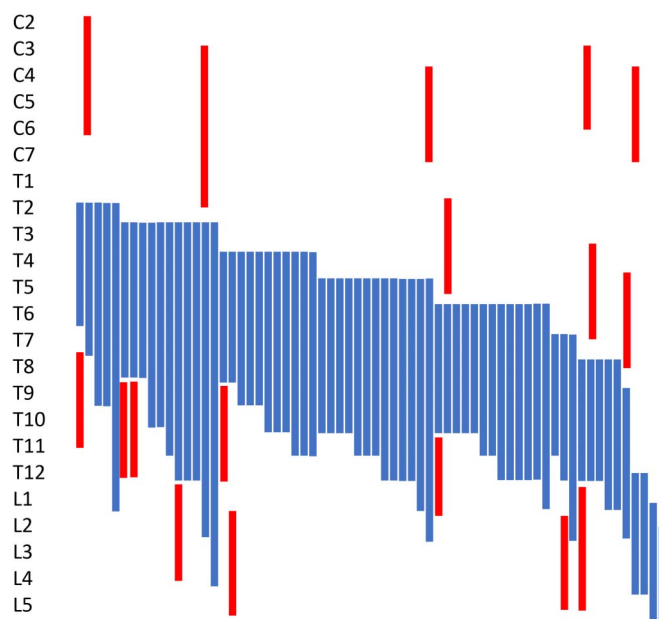


Fig. 1

Vertebral start and end levels of DISH. In most subjects, the upper end of DISH was located among the upper and middle thoracic vertebrae, and the lower end tended to situate around the thoracolumbar transition. Blue bars indicate the longest affected area. Red bars indicate shorter DISH.

selection bias and obtain a cohort representative of the general population<sup>12</sup>. The present investigation aimed to evaluate the impact of DISH on sagittal spinal alignment in the Japanese using this cohort.

## Materials and Methods

The protocol of this study was approved by the investigational review board of our hospital.

### Cohort Construction by Age and Sex

Our target survey subjects were Obuse residents who were 50 to 89 years of age. A cohort size of 400 participants was planned, which was the largest number of people who could be evaluated in terms of budget, time, and burden on volunteer subjects and research staff. First, randomly sampled study candidates from the basic resident registry of the cooperating town received an explanation about the survey and were asked to participate. Sampling was continued until the number of consenting participants surpassed 400 people. We established 8 groups by age (50 to 59 years, 60 to 69 years, 70 to 79 years, and 80 to 89 years) and sex (male and female) that were planned to contain approximately 50 participants, for a total of at least 400 subjects. We randomly selected 1,297 people from among 5,352 people between 50 and 89 years of age in the basic resident registry of the town of Obuse in 2014<sup>12</sup>. After providing written consent, 415 subjects were enrolled in this study. Four people with missing radiographic data were excluded, leaving a total of 411 participants (202 male participants and 209 female participants). The ethnicity of the subjects in our study was uniformly Japanese. The characteristics of the cohort are

**TABLE III Differences in Spinal Sagittal Alignment Between the Groups with and without T-DISH**

	Group with T-DISH*	Group without T-DISH*	P Value
Sagittal vertical axis (mm)	36.9 ± 49.7	19.5 ± 42.2	0.01
Cervical sagittal vertical axis (mm)	29.5 ± 17.0	21.2 ± 13.1	<0.01
Cervical lordosis (deg)	13.3 ± 10.4	11.6 ± 9.1	0.22
T1 slope (deg)	30.5 ± 10.7	25.7 ± 9.1	<0.01
Thoracic kyphosis (deg)	32.6 ± 11.7	29.1 ± 11.1	0.03
Lumbar lordosis (deg)	42.3 ± 13.5	44.2 ± 14.5	0.32
Sacral slope (deg)	29.9 ± 8.6	31.0 ± 9.6	0.36
Pelvic tilt (deg)	18.5 ± 8.3	18.1 ± 9.3	0.71
Pelvic incidence (deg)	48.1 ± 9.2	48.7 ± 10.5	0.67

\*The values are given as the mean and the standard deviation.

summarized in Table I. Subject comorbidities obtained via detailed interviews are presented in Table II. Scores on the Charlson Comorbidity Index<sup>13</sup> for classifying prognostic comorbidity were 0 points in 264 subjects (64%), 1 point in 75 subjects (18%), 2 points in 54 subjects (13%), 3 points in 17 subjects (4%), and 4 points in 1 subject (0.2%).

#### Evaluation of DISH

All subjects were performed whole-spine lateral radiography for the existence of DISH according to the criteria reported by Resnick and Niwayama, who defined DISH as the presence of ≥4 vertebral bodies with continuous ossification of the anterior spinal ligaments in the absence of degenerative disc disease<sup>2</sup>. We also investigated the spinal level of DISH occurrence, divided into DISH involving the cervical spine (C-DISH), thoracic spine (T-DISH), or lumbar spine (L-DISH). When DISH was found to span 2 areas, its existence was counted in each when ≥2 continuous vertebrae were affected in each area (i.e., T9-L1: T-DISH; T9-L2: T-DISH and L-DISH). The prevalence of DISH was determined by radiograph assessment by 2 spine

surgeons in a blinded manner. DISH was judged to exist upon identification by both examiners. The interrater reliability for the diagnosis of DISH was 0.83 in the cervical vertebrae, 0.95 in the thoracic vertebrae, and 0.96 in the lumbar vertebrae, indicating good agreement.

#### Measurements of Spinal Alignment

Whole-spine lateral radiography was performed with the participant in a standing position (fist on clavicle position)<sup>5</sup> for the measurement of the sagittal vertical axis as total spinal alignment; cervical sagittal vertical axis, cervical lordosis, T1 slope, and thoracic kyphosis as cervicothoracic alignment; and lumbar lordosis, sacral slope, pelvic tilt, and pelvic incidence as lumbopelvic alignment<sup>12</sup>.

The mean values of measurements by 2 spine surgeons and a trained staff member were recorded for each parameter. The interrater reliability for each parameter was as follows: 0.95 for sagittal vertical axis, 0.96 for cervical sagittal vertical axis, 0.88 for cervical lordosis, 0.88 for T1 slope, 0.92 for thoracic kyphosis, 0.89 for pelvic tilt, and 0.80 for pelvic incidence. The interrater reliability was 0.65 for lumbar lordosis and 0.48 for sacral slope, likely because of variation in the S1 end plate<sup>12</sup>.

#### Statistical Analysis

The differences in subject characteristics and sagittal spinal alignment parameters between subjects with DISH and subjects without DISH were evaluated by the Fisher exact test or the Welch t test. For statistical analysis of the impact of DISH on sagittal spinal alignment, we employed a logistic regression model with the existence of DISH as a response variable and subject-related factor candidates as explanatory variables. Obesity was defined as a body mass index (BMI) of ≥25 kg/m<sup>2</sup>. Factors selected by stepwise methods were included in subsequent multivariate analysis using EZR software (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (R Foundation for Statistical Computing). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Significance was set at  $p < 0.05$ .

**TABLE IV Influence of Patient Factors on T-DISH**

Factor	Univariate Analysis		Multivariate Analysis	
	OR*	P Value	OR*	P Value
Age (+10 years)	1.75 (1.34 to 2.28)	<0.01	1.70 (1.28 to 2.26)	<0.01
Male sex	3.92 (2.11 to 7.28)	<0.01	3.75 (1.88 to 7.48)	<0.01
Obesity† (BMI ≥ 25 kg/m <sup>2</sup> )	0.07 (-0.01 to 10.15)	0.08		
Sagittal vertical axis† (+1 cm)	1.08 (1.02 to 1.14)	<0.01		
Cervical sagittal vertical axis (+1 cm)	1.48 (1.23 to 1.79)	<0.01	1.18 (0.96 to 1.45)	0.12
T1 slope† (+10°)	1.65 (1.26 to 2.17)	<0.01		
Thoracic kyphosis (+10°)	1.30 (1.03 to 1.65)	0.03	1.22 (0.95 to 1.57)	0.12

\*The values are given as the OR, with the 95% CI in parentheses. †These factors were excluded from multivariate analysis.

**TABLE V Differences in Spinal Sagittal Alignment Between the Groups with and without L-DISH**

	Group with L-DISH*	Group without L-DISH*	P Value
Sagittal vertical axis (mm)	65.0 ± 66.8	20.7 ± 42.3	0.03
Cervical sagittal vertical axis (mm)	29.3 ± 21.7	22.2 ± 13.7	0.26
Cervical lordosis (deg)	14.7 ± 12.1	11.7 ± 9.2	0.39
T1 slope (deg)	32.0 ± 13.0	26.2 ± 9.3	0.13
Thoracic kyphosis (deg)	26.6 ± 13.9	29.7 ± 11.2	0.43
Lumbar lordosis (deg)	30.4 ± 13.7	44.3 ± 14.1	<0.01
Sacral slope (deg)	24.9 ± 7.4	31.0 ± 9.4	0.01
Pelvic tilt (deg)	26.0 ± 8.9	17.9 ± 9.1	<0.01
Pelvic incidence (deg)	50.3 ± 7.2	48.6 ± 10.4	1.43

\*The values are given as the mean and the standard deviation.

## Results

A total of 66 participants (16.1%) (51 male participants [77.3%] and 15 female participants [22.7%]) were found to have DISH among the subjects randomly selected from the basic resident registry of a rural town. The prevalence was 1.2% (5 of 411) for C-DISH, 15.1% (62 of 411) for T-DISH, and 3.2% (13 of 411) for L-DISH. Thus, the thoracic vertebrae were the most commonly affected area. There were no cases of systemic inflammation or autoimmune disease that might have caused spinal manifestations. Participants with or without DISH are summarized in Table I. There were significant differences in age, sex, BMI, sagittal vertical axis, cervical sagittal vertical axis, T1 slope, and thoracic kyphosis between the groups.

### Vertebral Start and End Levels of the Longest DISH

The vertebral start and end levels of the longest DISH were T2-6 and T2-7 in 1 subject each; T2-9 in 2 subjects; T2-L1 in 1 subject; T3-8 in 3 subjects; T3-10 in 2 subjects; T3-11 in 1 subject; T3-12 in 3 subjects; T3-L2 and T3-L4 in 1 subject

each; T4-8 in 2 subjects; T4-9, T4-10, and T4-11 in 3 subjects each; T5-10 in 4 subjects; T5-11 in 3 subjects; T5-12 in 4 subjects; T5-L1 and T5-L2 in 1 subject each; T6-10 in 5 subjects; T6-11 in 2 subjects; T6-12 in 5 subjects; T6-L1, T7-11, T7-12, and T7-L2 in 1 subject each; T8-12 in 3 subjects; T8-L1 in 2 subjects; T9-L2 in 1 subject; T12-L4 in 2 subjects; L1-5 in 1 subject; and L2-5 in 1 subject (Fig. 1).

### Effect of T-DISH on Sagittal Spinal Alignment

We observed significant differences in the sagittal vertical axis, cervical sagittal vertical axis, T1 slope, and thoracic kyphosis between subjects with and without T-DISH (Table III). In examinations of the effect of subject-related factors on DISH, sagittal vertical axis, cervical sagittal vertical axis, T1 slope, thoracic kyphosis, aging, and male sex had significant associations with DISH in univariate analysis. Aging per decade and male sex were also independent factors in multivariate testing; the odds ratio (OR) was 1.70 for aging per decade and 3.75 for male sex (Table IV).

### Effect of L-DISH on Sagittal Spinal Alignment

We noted significant differences in the sagittal vertical axis, lumbar lordosis, sacral slope, and pelvic tilt between participants with and without L-DISH (Table V). The assessment of the effect of subject-related factors on DISH revealed sagittal vertical axis, lumbar lordosis, sacral slope, pelvic tilt, aging, and male sex to be significantly associated with DISH in univariate analysis. Decreased lumbar lordosis (OR, 1.82), aging per decade (OR, 4.35), and male sex (OR, 10.7) were also independent factors in multivariate analysis (Table VI). The mean visual analog scale (VAS) score for back pain was 3.3 for patients with L-DISH and 1.7 for patients without L-DISH, which was not significantly different ( $p = 0.09$ ).

## Discussion

This study explored the impact of DISH on sagittal spinal alignment using random sampling from the basic resident registry for subject selection. Multivariate analysis revealed lumbar lordosis as an independent factor associated with

**TABLE VI Influence of Patient Factors on L-DISH**

Factor	Univariate Analysis		Multivariate Analysis	
	OR*	P Value	OR*	P Value
Age (+10 years)	5.25 (2.09 to 13.2)	<0.01	4.35 (1.69 to 11.2)	<0.01
Male sex	5.96 (1.30 to 27.2)	0.02	10.7 (1.90 to 60.7)	<0.01
Obesity† (BMI ≥ 25 kg/m <sup>2</sup> )	0.04 (−0.0003 to 0.08)	0.052		
Sagittal vertical axis† (+1 cm)	1.15 (1.06 to 1.25)	<0.01		
Lumbar lordosis (−10°)	1.87 (1.29 to 2.70)	<0.01	1.82 (1.09 to 3.05)	0.02
Sacral slope† (−10°)	1.93 (1.10 to 3.39)	0.02		
Pelvic tilt† (+10°)	2.12 (1.30 to 3.47)	<0.01		

\*The values are given as the OR, with the 95% CI in parentheses. †These factors were excluded from multivariate analysis.

L-DISH, with no sagittal spinal alignment parameters independently related to T-DISH.

The wide range of reported DISH prevalence (4% to 42%) varies depending on the study population and radiographic diagnostic criteria<sup>3-6</sup>. The prevalence of DISH increases with age and can be as high as 26% in women and 35% in men<sup>5</sup>. DISH is more prevalent in men, with sex ratios between 2:1 and 7:1<sup>4,14</sup>. Multivariate analysis in our study confirmed aging and male sex to have significant associations with the presence of DISH involving both the thoracic and lumbar spine.

Cassim et al. reported that the prevalence of DISH among black Africans (age >40 years) was 3.9%<sup>3</sup>. Weinfeld et al. showed that the prevalence of DISH among American Midwest hospital populations (age >80 years) was 28%<sup>5</sup>. Kim et al. found that the DISH prevalence among South Koreans (mean age, 64 years) was 4.1%<sup>4</sup>. In an earlier study on DISH in a Japanese population (mean age, 65 years), the prevalence of T-DISH was 8.7% as detected by chest computed tomography (CT)<sup>15</sup>. In this current Japanese population study (mean age, 69.7 years), the prevalence of DISH was 16.1%. Taking the mean ages into account, this prevalence appeared to be higher than those in other reports.

Kim et al. found that the prevalence of ossification of the posterior longitudinal ligament in patients with DISH was 37.5%<sup>16</sup>. However, this value was 7.7% according to Mori et al.<sup>15</sup>. We observed only 2 cases (0.5%) of ossification of the posterior longitudinal ligament, with concomitant DISH in 1 case (0.2%).

DISH most frequently originates in the lower thoracic spinal segments and later extends into the upper thoracic and lumbar spine<sup>2</sup>. Kagotani et al. and Hiyama et al. reported that most cases of DISH were located in the thoracic vertebrae, specifically where compressive mechanical stress at the top of the physiologic kyphosis occurred in the middle thoracic vertebrae<sup>17,18</sup>. Similarly, our study revealed the upper end of DISH to situate primarily in the upper and middle thoracic vertebrae, with the lower end around the thoracolumbar transition.

Recently, the number of patients seeking consultation for DISH-related problems and daily life disorders has been increasing, likely because of the increased elderly population and growing healthy life expectancy. After Glassman et al. reported that sagittal spinal alignment was more strongly correlated with health-related quality of life than was coronal spinal alignment<sup>19</sup>, DISH and sagittal spinal alignment have attracted considerable attention.

Several studies have addressed the effect of DISH on sagittal spinal alignment<sup>10,11</sup>. Yamada et al. found DISH to be associated with a significant decrease in lumbar lordosis, an increase in thoracic kyphosis, and decreases in sacral slope and pelvic incidence in patients with lumbar spinal stenosis<sup>10</sup>. Furthermore, they revealed that, after adjusting for age, sex, spondylolisthesis, and degenerative lumbar scoliosis, DISH involving the lumbar spine at the lowest end of the fused segment maintained a significant association with decreases in lumbar lordosis and sacral slope<sup>10</sup>. Nardo et al. reported DISH

to be associated with greater thoracic kyphosis in older individuals of 70 to 79 years<sup>11</sup>. The present study evaluated for differences in sagittal spinal alignment among the elderly population in terms of T-DISH and L-DISH. For T-DISH, sagittal vertical axis, cervical sagittal vertical axis, T1 slope, thoracic kyphosis, aging, and male sex had significant associations with DISH in univariate analysis, although no sagittal spinal alignment parameters were independent factors in multivariate analysis. For L-DISH, sagittal vertical axis, decreased lumbar lordosis, sacral slope, pelvic tilt, aging, and male sex were significantly associated with DISH in univariate analysis, with decreased lumbar lordosis remaining as an independent factor according to multivariate analysis (OR, 1.82). However, the clinical importance of any of these findings is unclear. We therefore evaluated the difference in VAS scores for back pain between patients with L-DISH (3.3 points) and patients without L-DISH (1.7 points), and these scores were not significantly different ( $p = 0.09$ ).

Lumbar lordosis was the only spinal parameter to be significantly associated with DISH in logistic regression analysis. However, there was a limitation in that the number of patients with L-DISH was small and the interrater reliability for lumbar lordosis was relatively low. In our previous study, the interrater reliability for sacral slope was also low at 0.48. In both cases, we considered that variability in the interpretation of the S1 end plate shape might have reduced reliability<sup>12</sup>. With regard to the association between lumbar lordosis and DISH, it is possible that the center of gravity moves forward as lumbar lordosis decreases and the anterior side of the vertebral bodies in the thoracic spine becomes ossified, although more study is needed.

Hyperinsulinemia has also been noted in patients with DISH<sup>20</sup>. Obesity-related hyperinsulinemia suppresses the production of insulin-like growth factor (IGF), and IGF-binding protein-1 accentuates the growth-promoting effect of IGF, which, in turn, may induce bone overgrowth<sup>21,22</sup>. Some studies concluded that, while standing, obese patients displayed hyperextension of the lumbar spine<sup>23,24</sup>. Another report revealed a tendency for slight lumbar lordosis elevation among patients with abdominal obesity<sup>25</sup>. In this study, although BMI in patients with DISH was significantly higher, univariate analysis demonstrated that obesity was not significantly associated with L-DISH (OR, 0.04 [95% confidence interval (CI), -0.0003 to 0.08];  $p = 0.052$ ) and was excluded by multivariate analysis.

The limitations of this study included a cross-sectional design and the possibility of regional and interobserver bias. We are planning longitudinal studies to investigate the prevalence of changes in DISH over time. As this was a non-compulsory survey, the proportion of people randomly sampled who ultimately participated in the study was less than one-third (i.e., two-thirds of residents approached declined to participate in the survey), suggesting an incomplete elimination of selection bias. Nevertheless, this study cohort very closely resembled the average Japanese population because of its survey design.

In conclusion, the examination of the impact of DISH on sagittal spinal alignment in a general population revealed that

lumbar lordosis was significantly associated with DISH involving the lumbar spine in the healthy community-dwelling elderly population, with no sagittal spinal parameter being notably related to DISH affecting the thoracic spine. ■

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