Aus dem Julius Wolff Institut
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

The effect of age and sex on spinal shape and mobility in asymptomatic adults – systematic reviews and meta-analyses

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Table of contents

List of figures and tables

List of abbreviations

20s	20–29 years old
30s	30–39 years old
40s	40–49 years old
50s	50–59 years old
60s	60–69 years old
GDP	Gross Domestic Product
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoF	Range of Flexion
RoE	Range of Extension
RoFE	Range of Flexion *plus* Extension
RoLB	Range of Lateral Bending
RoAR	Range of Axial Rotation
SD	Standard Deviation

Zusammenfassung

Einleitung

Rückenschmerzen zählen zu den Hauptbeschwerden der heutigen Gesellschaft. Bei Patienten mit Rückenschmerzen ist die Untersuchung der Wirbelsäulenform und ihrer Beweglichkeit ein grundlegender Bestandteil der körperlichen Untersuchung. Es wird allgemein angenommen, dass die Korrektur der Wirbelsäulenform und die Behebung von Bewegungseinschränkungen Schmerzen lindern und die Lebensqualität verbessern kann. Hierfür sind jedoch grundlegende physiologische Referenzwerte von asymptomatischen Probanden nötig. Obwohl bekannt ist, dass die Wirbelsäulenform und ihre Beweglichkeit von Alter und Geschlecht abhängig sind, bleiben die Details dieser Veränderungen immer noch unklar. Eine evidenzbasierte Beschreibung dieser Unterschiede aufgrund von Alter und Geschlecht ist daher für eine Therapieverbesserung unerlässlich.

Methodik

Es wurden drei systematische Reviews erstellt um den Einfluss von Alter und Geschlecht auf die Form und Beweglichkeit der Hals-, Brust- und Lendenwirbelsäule bei asymptomatischen Erwachsenen zu ermitteln. Für die Hals- und Lendenwirbelsäule wurden zusätzlich Meta-Analysen durchgeführt. Zur Bewertung der Qualität der Arbeiten wurde das *quality assessment tool for quantitative studies* verwendet.

Ergebnisse

Die Literaturrecherche ergab 4037, 897 und 2372 Arbeiten zum Thema Form und Beweglichkeit von Hals-, Brust- bzw. Lendenwirbelsäule. Davon erfüllten 34, 45 bzw. 65 Studien die Einschlusskriterien und wurden für die systematischen Reviews herangezogen. Die meisten Arbeiten waren Querschnittsstudien mit einer moderaten Studiendesignqualität. In elf Arbeiten aus dem Halswirbelsäulen- und zwölf aus dem Lendenwirbelsäulenbereich wurden ähnliche Altersbeschreibungen verwendet und in die Meta-Analysen einbezogen. Aufgrund unzureichender Homogenität der Daten konnte für die Brustwirbelsäule keine Meta-Analyse durchgeführt werden.

Mit jeder Lebensdekade zwischen den 20er bis zu den 60er Jahren nahm die Brustwirbelsäulenkyphose zu. Die Lendenwirbelsäulenlordose änderte sich in diesen

Altersabschnitten uneinheitlich und war bei Frauen in jeder Altersgruppe im Durchschnitt größer als bei Männern. Die zervikale, thorakale und lumbale Beweglichkeit nahm mit zunehmendem Alter richtungsabhängig nicht monoton ab. Die Auswirkungen des Geschlechts auf die Mobilität der Wirbelsäule waren in jedem Jahrzehnt uneinheitlich und unterschieden sich in den verschiedenen Wirbelsäulenregionen sowie in den verschiedenen anatomischen Richtungen.

Schlussfolgerung

In dieser Arbeit wurden die quantitativen Auswirkungen von Alter und Geschlecht auf die Wirbelsäulenform und ihre Mobilität bei asymptomatischen Erwachsenen statistisch ausgewertet. Die Ergebnisse ermöglichen es, besser zwischen Funktionsstörungen, die durch Wirbelsäulenerkrankungen und solchen, die durch physiologische Anpassungsprozesse während des Alterns verursacht werden, zu unterscheiden. Für einen umfassenden Vergleich, der auch symptomatische Veränderungen umfasst, sind weitere Langzeitstudien mit Langzeit-Follow-up an Patienten mit Rückenschmerzen erforderlich.

Abstract

Introduction

Spinal pain is one of the leading causes of disability in modern societies. In patients with spinal pain, observation of spinal shape and mobility is a basic component of the physical examination, which is due to a common belief that correcting spinal shape and mobility aberrations can alleviate pain and improve the quality of life. When clinicians aim to normalize dysfunctional spinal shape or mobility, a fundamental basis of physiological reference values in asymptomatic individuals is a prerequisite. Although there is a general understanding that the spinal shape and mobility alter with age and sex, the details of these variations remain lacking. Therefore, an evidence-based description of these differences because of age and sex is essential for an improved treatment.

Methods

Three systematic reviews were performed to investigate the effect of age and sex on cervical, thoracic and lumbar spinal shape and mobility in asymptomatic adults. Meta-analyzes were additionally performed for the cervical and lumbar spine. The *quality assessment tool for quantitative studies* was applied to assess the methodological quality.

Results

The literature search yielded 4037, 897 and 2372 hits for cervical, thoracic and lumbar spinal shape and mobility, respectively. Among these, 34, 45 and 65 studies, respectively, met the inclusion criteria and were included in the systematic reviews. Most were cross-sectional studies with a moderate study design quality. Eleven studies for the cervical and twelve for lumbar spine with similar age descriptions were included in the meta-analyses. Insufficient homogeneous data did not allow a meta-analysis for the thoracic spine.

With one-decade age increments from the 20s to 60s, there was an increasing tendency for thoracic kyphosis. Lumbar lordosis changed inconsistently with aging from the 20s to 60s and was greater in females than in males in each age range. Cervical, thoracic and lumbar mobility decreased non-monotonically with aging in each anatomical direction. The effect of sex on spinal mobility was inconsistent in each decade age range and differed among different spinal regions as well among different anatomical directions.

Conclusions

Quantitative effects of age and sex on spinal shape and mobility in asymptomatic adults were statistically evaluated. These findings allow better discrimination between functional deficits caused by spinal disorders and by physiological adaptive processes during aging. Further longitudinal studies with long-term follow-up including subjects with spinal pain need to be conducted to ensure an extensive comparison between symptomatic and asymptomatic individuals.

1. Introduction

Cervical, thoracic and lumbar pain are among the most serious public health problems worldwide. Numerous epidemiological studies demonstrated their extraordinary level of lifetime incidence and high prevalence [1-7]. A review of different cross-sectional studies indicated that approximately 70–85% of the population experience spinal pain at some point in their life [8]. This exceptionally high number of individuals involved and the serious consequences, including the loss of labor productivity and high rates of hospital admission, result in tremendous direct and indirect costs for societies' healthcare systems and economies. In 2009, the total spinal pain costs were estimated to €48.96 billion for Germany, which equated to 2.2% of the Gross Domestic Product (GDP) [9]. In China, the years lived with disability for back pain was 16.347 million in 2013, which was the leading cause for disability [10]. Because of the demographic changes of an aging society, this socio-economic burden will increase further in future. Although spinal pain can arise through various reasons, most patients suffer without specific anatomic and/or neurophysiological changes [8]. However, observation of spinal shape and mobility is a basic component of the physical examination in patients with spinal pain, which is partly due to a common belief that identifying and correcting spinal shape and mobility aberrations can reduce pain and improve the quality of life [11-13]. When clinicians aim to normalize dysfunctional shape or mobility, an empirical basis of normal values for reference is required.

Although spinal shape and mobility are important parameters for a patient-specific diagnosis and therapy planning, the reported values vary considerably because of multiple factors, among which age and sex are the two most significant. However, the current findings remain inconclusive. For cervical mobility, some studies found a tendency for reduction with aging [1, 14-17], whereas others failed to detect a significant age effect [18, 19]. An increasing tendency with aging was reported for thoracic kyphosis [20, 21]; however, the age-dependent effect has not yet been quantified or clarified in detail. The influence of sex on thoracic kyphosis has been described as contradictory in the literature [22-26]. Multiple studies demonstrated that thoracic mobility was greater at a younger age than at an older age [27-29]; nevertheless, the effect of sex is unclear [25]. Age and sex also caused temporal and spatial variation in lumbar lordosis and mobility in the asymptomatic population [21, 30-32]. Previously, a systematic review and meta-analysis was conducted to understand the differences in the lumbar mobility because of aging [33]. However, the analysis was based on limited available datasets and the sex-dependent difference was unclear. Therefore, an evidence-based understanding of these differences because of age and sex is necessary.

In the clinical setting, X-ray is the gold standard for the assessment of spinal shape with direct exposure of anatomical structures [21, 32]. However, a frequent use of this technology brings ethical problems in both spinal pain patients for closed-meshed monitoring of a treatment success and in asymptomatic individuals for collecting normative reference data. Functional X-rays have long been used to determine functional deficits to provide reliable spinal mobility results [34, 35]. Nevertheless, the ethical radiation problem remains, and the spinal mobility in the axial plane cannot be measured. Several simple physical examinations have been developed to evaluate spinal mobility during medical consultation or in the laboratory, like the Schober test and the Finger-Floor-Distance [36]. The disadvantage is that there is no significant difference between subjects with or without back pain in these tests [36, 37]. Moreover, the Finger-Floor-Distance is unable to differentiate between spinal and pelvic movements and, therefore, cannot discriminate whether a change in mobility is caused by spinal or pelvic motion. Clinicians also evaluate the spinal shape or mobility by visual inspection, which is not quantified and with low reliability. Because of the limitations of the aforementioned methods, multiple non-radiological devices have been developed in recent years, including goniometer, inclinometer, electromagnetic, ultrasonic, and optoelectronic systems [4, 15, 38-41]. To avoid the need for radiation exposure, non-radiological devices can be utilized for multiple spinal shape and mobility determinations in both symptomatic and asymptomatic subjects. Here, the question arises, whether these multiple non-radiological measurement instruments can lead to comparable results for spinal shape and mobility as determined radiologically.

Because systematic reviews and meta-analyses can provide a complete and exhaustive summary of the current evidence on the relevant topics, three systematic reviews, two of which in combination with a meta-analysis, were performed to determine the effect of age and sex on cervical (study 1), thoracic (study 2) and lumbar (study 3) spinal shape and mobility. The potential difference between radiological and non-radiological results was further investigated. The results were documented and summarized in three scientific publications [42-44].

2. Methods

Three systematic reviews, two of which in combination with a meta-analysis, concerning cervical (study 1), thoracic (study 2) and lumbar (study 3) spinal shape and mobility were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [45], which improves the reporting of systematic reviews and meta-analyses.

2.1. Search strategy

For all three systematic reviews and both meta-analyses, only studies with asymptomatic adult subjects (age > 18ys) and measuring active spinal mobility (motion controlled by subjects) were included.

2.1.1. Cervical spine (study 1)

The terms in Figure 1 were combined with logical operators (AND, OR and NOT) and searched in three electronic databases (PubMed, EmBase and Web of Science) from their inception to April 2018.

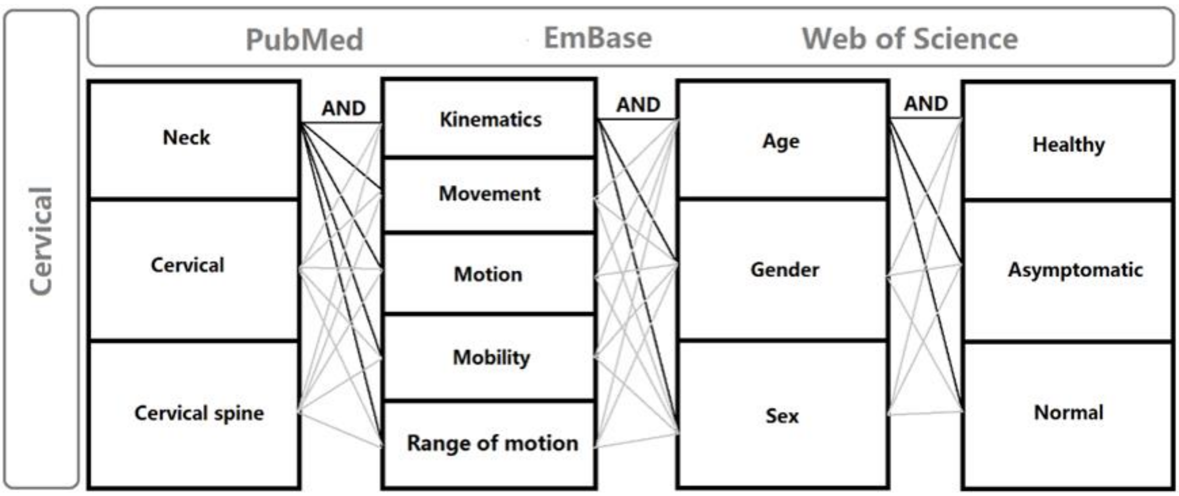

Figure 1. Search strategy on cervical mobility.

2.1.2. Thoracic spine (study 2)

The search strategy included the terms in Figure 2 with logical operators (AND, OR and NOT) and was searched in PubMed with the time limitation from their inception to April 2018.

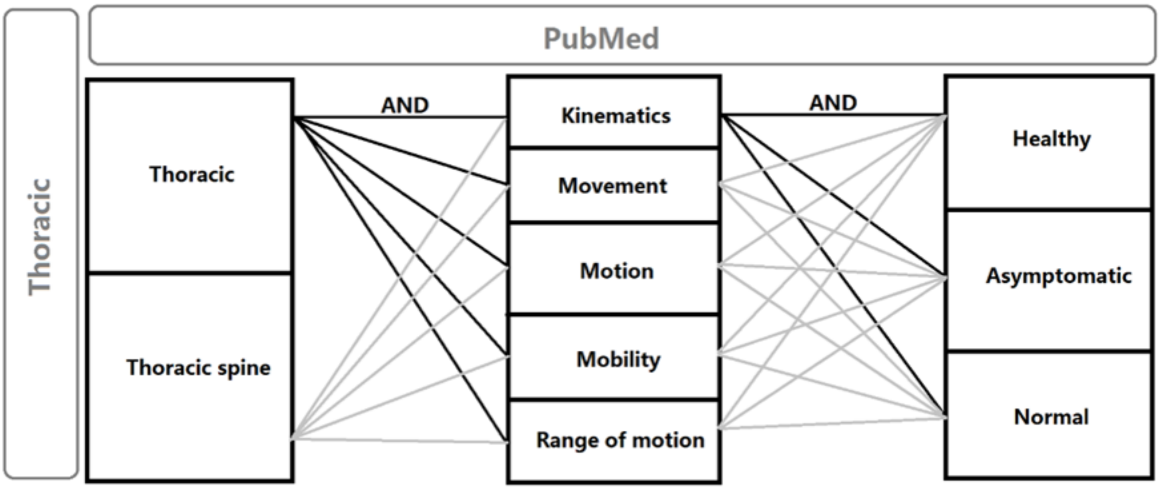

Figure 2. Search strategy on thoracic mobility.

2.1.3. Lumbar spine (study 3)

Similar to the cervical spine, three electronic databases were used with the terms shown in Figure 3 with logical operators (AND, OR and NOT) from their inception to March 2018.

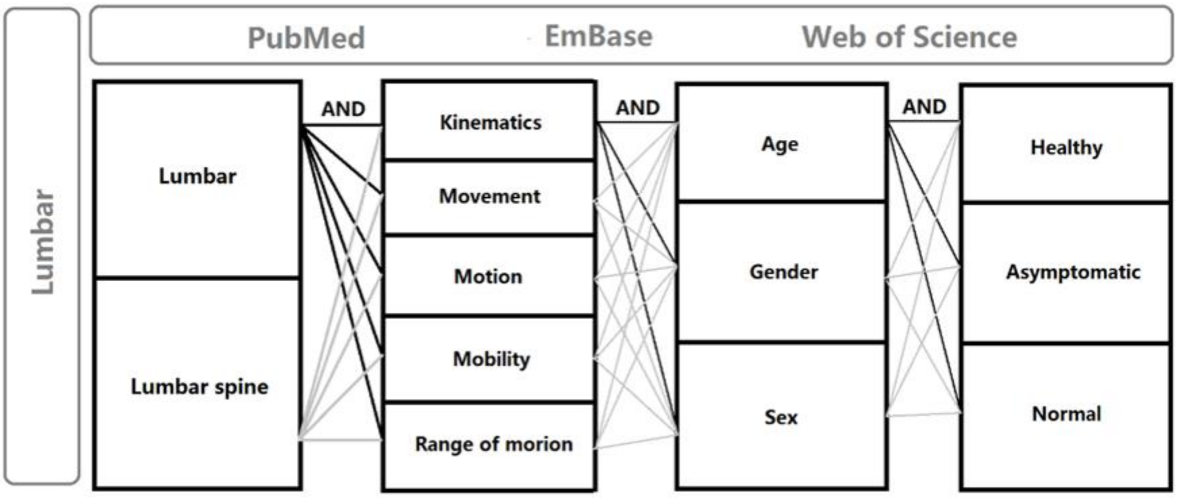

Figure 3. Search strategy on lumbar mobility.

Additionally, a manual search of references was performed to further include possible studies that were absent from the database search.

2.2. Methodological assessment

The quality of the included studies was assessed using the *quality assessment tool for quantitative studies*, which was developed by the Effective Public Health Practice 2003, Canada [46]. This tool evaluates the quality of the following items: study design, confounders, blinding of participants and examiners, data collection methods, withdrawals and drop-outs of participants, measurement integrity and statistical analysis suitability. The quality of each item, except statistical analysis, is classified into three levels: strong, moderate and low. The suitability of statistical analysis is evaluated as Yes or No.

2.3. Data extraction and management

Data for means and standard deviations (SDs) of the spinal shape and mobility, and sample size for each age and sex group were extracted from reported values or figures in selected studies. “Half-cycle” spinal mobility represents the range of flexion (RoF), extension (RoE), left or right lateral bending (RoLB) and left or right axial rotation (RoAR) separately. “Full-cycle” spinal mobility represents the range of flexion *plus* extension (RoFE), two-side RoLB or two-side RoAR. When there existed sufficient studies (at least three) with similar age descriptions (e.g., 20s, 30s, 40s, 50s and 60s) and separate sexes, a meta-analysis was conducted, otherwise, only descriptive data synthesis was performed.

2.4. Data synthesis and meta-analysis

For meta-analysis, mean values and SDs as well as the sample size in each age and sex group were pooled using the Review Manager Software (RevMan5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). A random-effect model was adopted because of the heterogeneity among the studies. Statistical heterogeneity among studies was evaluated based on the inconsistency (I^2) index, which estimates the percentage of total variation across studies that is ascribed to heterogeneity; <25% indicates low, 25% to 75% medium and >75% high heterogeneity [47]. Mean pooled differences ± 95% confidence intervals in the spinal shape and mobility between different age and sex groups were presented, with statistical significance defined as $p<0.05$.

3. Results

3.1. Cervical spine (study 1)

Thirty-four studies were included in the systematic review. All were cross-sectional cohort studies with a moderate study design quality. The differences of the age descriptions were substantial. Eleven studies with non-radiological results and same-age descriptions (20s, 30s, 40s, 50s and 60s) were included for meta-analysis; among these, results were pooled from four studies [15, 41, 48, 49] for "full-cycle" cervical mobility determined non-radiologically in different age and sex groups (Table 1). Different pooled results between two age groups or sexes led to different degrees of heterogeneity (I^2) ranging from 0 to 96%.

Table 1. Mean ± 95% confidence interval of cervical mobility (°) in each age and sex group.

Plane	Parameter	Sex	20s	30s	40s	50s	60s
Non-radiological Measurements							
Sagittal	RoFE	Males	129.42 ± 27.70	118.73 ± 32.23	116.38 ± 10.26	120.48 ± 10.96	106.82 ± 6.43
		Females	133.24 ± 10.37	127.43 ± 26.89	119.80 ± 17.18	115.44 ± 13.37	114.11 ± 4.54
Coronal	Two-side RoLB	Males	91.27 ± 4.72	82.08 ± 16.39	78.65 ± 4.40	72.50 ± 5.43	66.61 ± 4.45
		Females	91.47 ± 4.06	89.67 ± 5.57	85.20 ± 4.39	69.64 ± 5.57	67.06 ± 6.09
Axial	Two-side RoAR	Males	155.16 ± 14.13	148.70 ± 18.75	141.40 ± 7.88	141.74 ± 9.00	134.97 ± 8.36
		Females	161.08 ± 9.33	154.51 ± 12.67	145.66 ± 11.90	137.11 ± 16.93	128.94 ± 18.42

RoFE – Range of Flexion plus Extension; RoLB – Range of Lateral Bending; RoAR – Range of Axial Rotation.

3.1.1. Effect of age and sex on cervical lordosis

No results are available in study 1 [43].

3.1.2. Effect of age and sex on cervical mobility

When determined non-radiologically, males displayed a significant decrease in the cervical RoFE from the 20s to 30s and from the 50s to 60s ($p<0.05$); females displayed a significant decrease from the 30s to 40s and from the 40s to 50s ($p<0.05$). For the two-side RoLB, males displayed a significant decrease from the 50s to 60s ($p<0.05$); however, females displayed a significant decrease from the 30s to 40s and from the 40s to 50s ($p<0.05$). For the two-side RoAR, both males and females displayed a significant decrease with a one-decade age increase ($p<0.05$), except in males from the 30s to 40s and from the 40s to 50s. For the effect of sex, females displayed a greater RoFE and two-side RoAR than males in the 30s and 40s (p<0.05); in the 60s, females displayed a greater RoFE than males (p<0.05).

3.1.3. Comparison of measurement techniques

Radiological devices were normally used to measure cervical mobility from C2–7 in the sagittal plane while non-radiological devices were normally used for cervical mobility from the head to thorax in all three anatomical planes. Cervical mobility determined non-radiologically was greater than determined radiologically in each age and sex group (Figure 4).

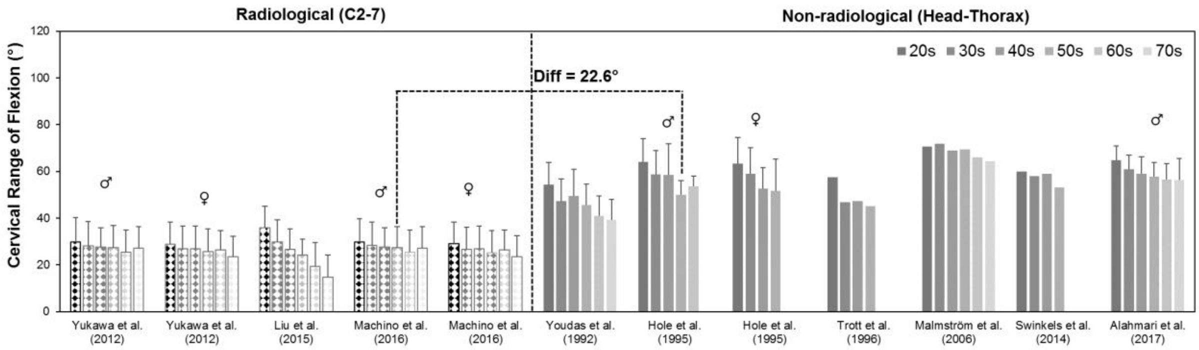

Figure 4. Difference of cervical range of flexion between radiological and non-radiological results in each age and sex group (mean ± standard deviation). ♂ Males; ♀ Females.

3.2. Thoracic spine (study 2)

Forty-five studies were included in the systematic review. Three were prospective while 42 were cross-sectional. Twenty-five studies reported the validity or reliability of the results, whereas 20 did not. Because the studies displayed a large heterogeneity, only descriptive data syntheses were conducted.

3.2.1. Effect of age and sex on thoracic kyphosis

There was an increasing tendency for thoracic kyphosis with aging when determined both radiologically and non-radiologically (Figure 5). The increase of thoracic kyphosis with aging occurred in the lower level rather than in the upper level [21].

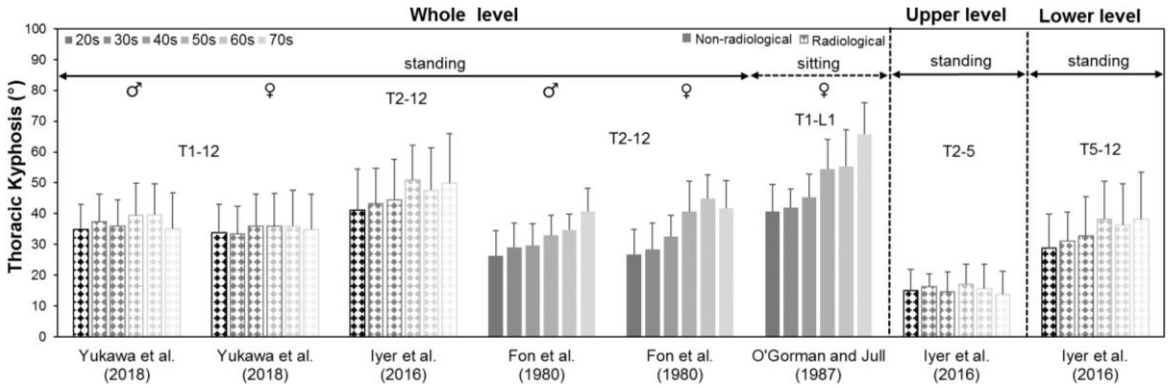

Figure 5. The effect of age on thoracic kyphosis (mean ± standard deviation). ♂ Males; ♀ Females.

3.2.2. Effect of age and sex on thoracic mobility

One non-radiological study [29] reported a decreasing tendency for thoracic mobility with a one-decade age increase in all three planes during sitting in females (Figure 6). The decrease of thoracic mobility with aging mainly occurred in the lower level rather than in the upper level [27, 50].

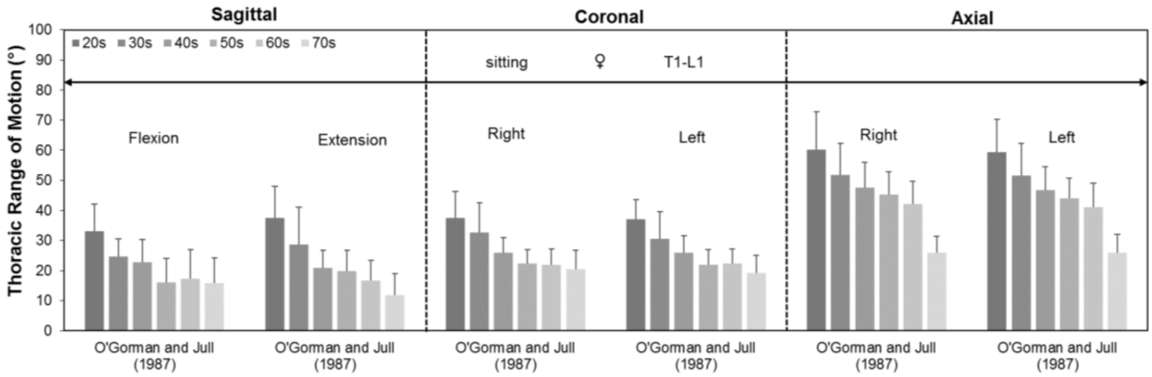

Figure 6. The effect of age on thoracic mobility (mean ± standard deviation). ♂ Males; ♀ Females.

3.3.3. Comparison of measurement techniques

During standing, the thoracic kyphosis over T1–12 ranged from 29 to 45° (mean=34°, Figure 7) when determined non-radiologically [51-56] and approximately 40° when determined radiologically [22, 57].

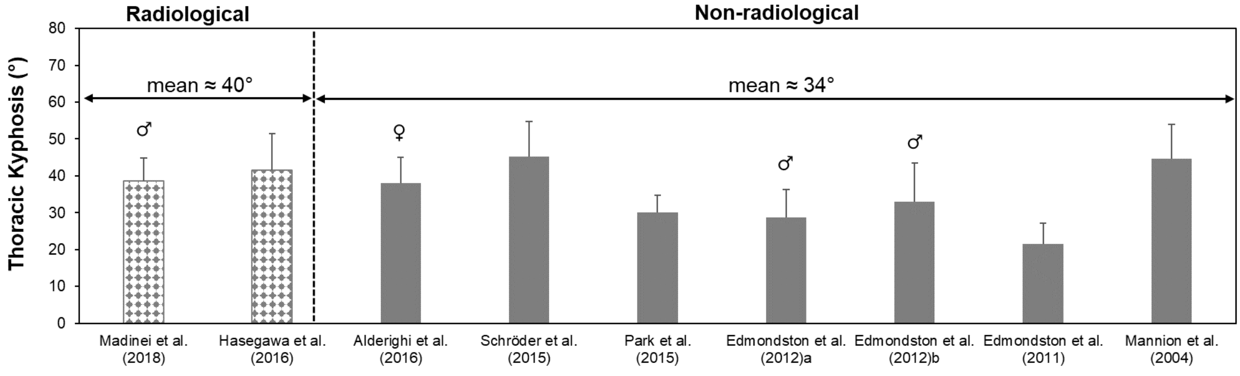

Figure 7. Difference of thoracic kyphosis between radiological and non-radiological results measured during standing over T1–12 (mean ± standard deviation). ♂ Males; ♀ Females.

3.3. Lumbar spine (study 3)

Sixty-five studies were included in the systematic review. Six showed a strong study design quality, 58 a moderate quality and one a weak quality. The differences of the age descriptions were substantial. Twelve studies [20, 21, 30, 32, 58-65] with same age descriptions (20s, 30s, 40s, 50s and 60s) were included for meta-analysis to investigate the effect of age and sex on lumbar lordosis determined radiologically, and mobility determined non-radiologically (Table 2). The studies selected for meta-analysis were cross-sectional cohort studies with a moderate study design quality. Different pooled results between two age groups or sexes led to different degrees of heterogeneity (I^2) ranging from 0 to 96%.

Table 2. Mean ± 95% confidence interval of lumbar lordosis and mobility (°) in each age and sex group.

Plane	Parameter	Sex	20s	30s	40s	50s	60s
Radiological Measurements							
Sagittal	Lumbar lordosis	Males	45.37 ± 6.70	43.33 ± 7.87	50.65 ± 6.93	47.24 ± 5.73	53.14 ± 8.20
		Females	49.28 ± 6.77	50.93 ± 5.43	54.76 ± 4.10	53.78 ± 3.35	54.94 ± 5.93
Non-radiological Measurements							
Sagittal	RoF	Males	62.61± 9.91	60.66 ± 9.75	58.91 ± 11.92	57.11 ± 9.42	55.63 ± 10.21
		Females	57.10 ± 4.39	60.54 ± 6.77	55.64 ± 4.80	56.17 ± 9.02	51.99 ± 6.44
	RoE	Males	28.81 ± 8.60	26.40 ± 7.36	22.72 ± 6.38	20.78 ± 6.00	17.56 ± 6.06
		Females	32.29 ± 4.84	29.32 ± 7.89	26.27 ± 6.01	22.77 ± 6.67	18.72 ± 4.49
Coronal	Right RoLB	Males	33.90 ± 3.45	31.53 ± 5.35	28.19 ± 2.92	27.66 ± 3.37	22.59 ± 8.50
		Females	32.25 ± 5.44	31.13 ± 5.48	28.52 ± 4.86	27.49 ± 3.48	24.29 ± 4.59
	Left RoLB	Males	33.77 ± 3.69	31.72 ± 4.68	27.53 ± 4.75	26.89 ± 5.53	22.48 ± 8.28
		Females	30.67 ± 5.42	31.40 ± 5.25	27.32 ± 7.10	26.62 ± 3.16	23.70 ± 3.64
Axial	Right RoAR	Males	20.83 ± 15.78	16.32 ± 14.11	18.65 ± 11.47	18.76 ± 14.60	19.57 ± 9.70
		Females	24.38 ± 11.27	22.55 ± 13.82	20.42 ± 14.11	20.24 ± 11.76	18.00 ± 10.18
	Left RoAR	Males	21.36 ± 13.62	17.89 ± 11.76	17.83 ± 12.15	19.12 ± 15.39	17.22 ± 12.45
		Females	24.67 ± 11.86	24.50 ± 12.94	22.43 ± 13.33	21.09 ± 12.54	19.77 ± 10.47

RoF – Range of Flexion; RoE – Range of Extension; RoLB – Range of Lateral Bending; RoAR – Range of Axial Rotation.

3.3.1. Effect of age and sex on lumbar lordosis

When determined radiologically, males in their 30s displayed a smaller lumbar lordosis than in their 40s and 50s ($p<0.05$). Females in their 20s and 30s displayed a smaller lumbar lordosis than in their 40s and 50s ($p<0.05$). In their 40s, both males and females displayed a greater lumbar lordosis than in their 50s ($p<0.05$). For the effect of sex, females in their 20s, 30s, 40s and 50s displayed a greater lumbar lordosis than males in the same age range ($p<0.05$).

3.3.2. Effect of age and sex on lumbar mobility

When determined non-radiologically, males displayed a significant decrease in the lumbar RoF from the 50s to 60s ($p<0.05$); in contrast, females displayed a significant decrease from the 30s to 40s ($p<0.05$). Both males and females displayed a significant decrease in the lumbar RoE with a one-decade age increase ($p<0.05$), except in females from the 20s to 30s. Males displayed a significant decrease in both the left and right lumbar RoLB ($p<0.05$), except from the 40s to 50s; females displayed a significant decrease ($p<0.05$), except from the 20s to 30s. No significant decrease in the RoAR was detected with a one-decade age increase, except in males for the right RoAR from the 20s to 30s ($p<0.05$). For the effect of sex, males displayed a greater lumbar RoF than females in the 20s ($p<0.05$). In the 40s, females displayed a greater left RoAR than males; in the 50s, females displayed a greater right RoAR than males ($p<0.05$).

3.3.3. Comparison of measurement techniques

Radiological devices measured the lumbar curvature while non-radiological devices measured the dorsal skin curvature. Lumbar lordosis determined radiologically was mostly greater than lordosis determined non-radiologically when incorporating age and sex (Figure 8).

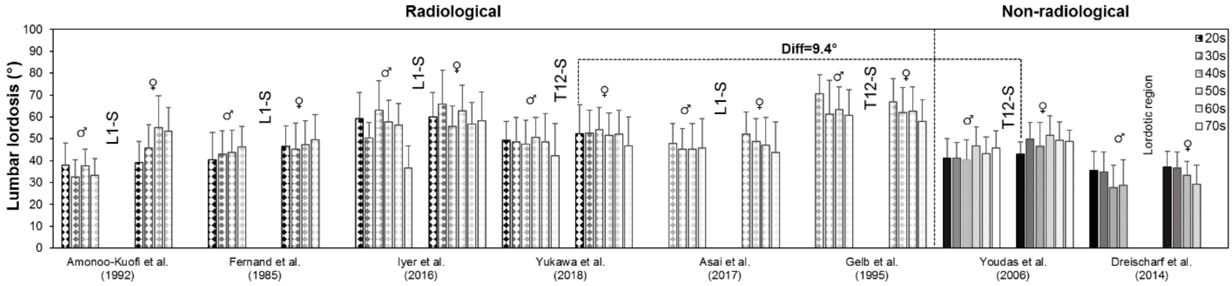

Figure 8. Difference of lumbar lordosis between radiological and non-radiological results (mean ± standard deviation). ♂ Males; ♀ Females.

4. Discussion

4.1. Cervical spine (study 1)

Study 1 performed a systematic review and meta-analysis on cervical mobility in asymptomatic adults, with a specific focus on the effect of age and sex, as well as different measurement techniques.

Radiological devices normally measured cervical mobility in the sagittal plane from C2–7, whereas non-radiological devices could measure cervical mobility in all three anatomical planes, but normally from the head to thorax. Therefore, the cervical mobility determined radiologically were much less than the mobility determined non-radiologically. These differences prompt researchers and clinicians to develop a standard protocol (e.g., similar device and measuring level) to determine cervical mobility and make the results comparable. Therefore, it is essential to note that when applying the non-radiological results in the clinic, different reference values should be adopted than for radiological examination.

In the meta-analysis, the results of cervical mobility measured non-radiologically from the head to thorax with separate sexes were pooled. Consequently, the cervical RoFE and two-side RoLB decreased non-monotonically and the two-side RoAR decreased monotonically with aging. The decrease in cervical mobility might arise from spinal degeneration with aging [35, 66-68]. However, the patterns of decrease differed between the sexes. This difference might result from a variety of factors, including different occupational patterns (e.g., females on average work fewer hours than males) [69], daily activities (e.g., males spend more time than females in moderate and vigorous physical activity) [70] and anatomical structures (e.g., males have greater a cervical lordosis than females) [71]. The current results can serve to distinguish between pathological and aging degeneration for the evaluation of impairment and for the assessment of treatment success as well as for developing spinal implants.

There was no significant sex-dependent difference in cervical mobility in the 20s age group, because the youngest age group can normally perform the greatest mobility. Females displayed a greater cervical RoFE and two-side RoAR than males in the age range of the 30s and 40s. Although not significant, females in their 50s displayed less mobility than males. This might be because females undergo the menopause process during this age range, which could influence the cervical mobility [72, 73]. Once in their

60s, females again displayed greater cervical mobility than males. However, the actual mechanism causing these differences still needs to be investigated.

4.2. Thoracic spine (study 2)

Study 2 performed a systematic review to investigate the effect of age and sex on thoracic kyphosis and mobility in asymptomatic adults, as well as the influence of different measuring devices. However, because of the large heterogeneity among the studies, a meta-analysis was impossible and only a descriptive synthesis was conducted.

Radiological devices normally measured thoracic kyphosis from T4–12 for exposure of the spinal markers. Without an exposure problem, non-radiological devices measured thoracic kyphosis from C7 or T1 to T12. Because a kyphosis angle greater than 40° (determined radiologically from T4–12 during standing) is defined as hyper-kyphosis [26], it is essential to measure the thoracic kyphosis under a similar protocol (e.g., consistent technology, segments and posture). We compared the radiological and non-radiological results when measuring thoracic kyphosis from T1–12 during standing, and found a difference of approximately 6°. The soft-tissue artefacts might cause this difference. However, there is a lack of sufficient data to determine whether or not this level of difference is significant.

With one-decade age increments, Yukawa et al. [32] found no significant change in thoracic kyphosis measured by X-ray. By contrast, another radiological study [21] and two non-radiological studies [26, 29] demonstrated that there was an increasing tendency for thoracic kyphosis with aging. Because of insufficient data, it was impossible to perform a meta-analysis to quantify the age effect. However, these results emphasize that hyper-kyphosis of the thoracic spine is partly derived from a natural adaptive aging process. Iyer et al. [21] measured the thoracic kyphosis in the upper (T2–5) and lower (T5–12) levels separately and found that an age-dependent change in thoracic kyphosis mainly occurred in the lower level rather than in the upper level. These facts indicated that the lower thoracic spine has to withstand higher mechanical challenges than the upper level, which may be associated with the relatively higher fracture rate in the lower thoracic level during injury and trauma [74].

The influence of sex on thoracic kyphosis was inconclusive among the studies. Yukawa et al. [32] demonstrated that males in their 30s, 50s and 60s displayed a greater thoracic kyphosis than age-matched females. However, Fon et al. [26] demonstrated that females in their 50s, 60s and 70s exhibited a greater kyphosis than age-matched males. This heterogeneity might partly explain why studies with heterogeneous cohort sizes and different mean ages produced contradictory results. Therefore, the details of age and sex effects on thoracic kyphosis still merit discussion.

In each anatomical direction, thoracic mobility displayed a decreasing tendency with aging when determined non-radiologically [29]. However, it was impossible to quantify the age effect because of insufficient data. The effect of sex on thoracic mobility was also inconclusive [25], which might be due to the different thoracic profiles between males and females. Therefore, further long-term longitudinal study with large cohorts needs to be conducted to draw more consistent conclusions, because an age- and sex-specific evaluation and treatment for thoracic pathologies may be important for long-term patient satisfaction.

4.3. Lumbar spine (study 3)

Study 3 performed a systematic review and meta-analysis to investigate the effect of age and sex on lumbar lordosis and mobility in asymptomatic adults, as well as to compare the results determined by different measurement techniques.

Lumbar lordosis measured by radiological devices was normally greater than determined by non-radiological devices. This could be due to the different shapes between the dorsal skin surface (non-radiological) and the spinal curvature of the bony vertebrae (radiological). This difference is caused by the soft tissue as well by the difference between the curvature of the spinous process and vertebral bodies. Although investigators relied on radiological techniques for accurate measurements and direct anatomical exposure, non-radiological techniques were frequently used to determine lumbar lordosis because of the ease of performing repetitive trials. Furthermore, a high correlation was displayed between lumbar lordosis measured via back shape and determined radiologically in subjects with a body mass index <27.0 kg/m² [75, 76]. Therefore, both radiological and non-radiological techniques have their own advantages and the non-radiological results can reflect changes in radiological results.

In the meta-analysis, lumbar lordosis measured by X-ray at similar lumbar segments were pooled. The change of lumbar lordosis was non-monotonic with aging. From the

30s to 40s, both males and females displayed an increased lumbar lordosis. From the 40s to 50s, lumbar lordosis decreased in both sexes. An increase or decrease in lumbar lordosis may be dependent on the characteristic sagittal profiles and orientation of the pelvis, lumbosacral joint and sacrum [77, 78]. Therefore, the evolution of lumbar lordosis with aging could vary among different sagittal profiles for the sagittal balance and stability requirements. Regarding the effect of sex, females displayed a greater lumbar lordosis than males at each age range, which is because of a greater sacral slope than males [79]. Therefore, the evaluation of lumbar lordosis should be based on age and sex instead of a single value, because the age-specific spinal alignment targets for operation can reduce the incidence of postoperative complications, like proximal junction kyphosis [80].

With aging, the lumbar RoF tended to decrease when determined non-radiologically. However, the decreasing pattern was non-monotonic and differed between the sexes, with males displaying the greatest reduction from the 50s to 60s, while in females, this was from 30s to 40s. Regarding the lumbar RoE, a continuous reduction with aging was observed in both sexes. The RoLB also displayed a continuous decreasing pattern in both sexes and the age-dependent pattern was symmetric between the left and right sides. The reduction of lumbar mobility with aging is in agreement with the fact that the stiffness of the spinal segments increases in intervertebral discs [81]. The change of the RoAR with aging was not significant in both sexes, sometimes older subjects even displayed a greater RoAR (50s vs 60s in females during left RoAR). Here, it should be noted that only results from two studies were pooled [61, 65]; therefore, further studies are required to substantiate the effect of age on the lumbar RoAR.

For the effect of sex on lumbar mobility, males normally displayed a greater RoF than females, particularly in the 20s. Males and females displayed no significant difference in the RoE and the left and right RoLB. For the RoAR, females normally displayed a greater mobility than males, which was significant in the 40s during left RoAR and in the 50s during right RoAR. It is supposed that the possible basis for this apparent difference could be due to the differences in the sagittal profiles between males and females.

4.4. Limitations and further perspectives

For all three studies, the risk of an incomplete literature search and publication bias cannot be ruled out. Secondly, there was considerable variation in the devices used for non-radiological measurements, including their reliability and validity, such that the difference for a single device because of a limited number of studies could not be quantified, and the measuring techniques could only be assigned into two different categories (radiological and non-radiological). Furthermore, a major source of uncertainty was in the spinal levels that were determined in the different studies. For study 2, a meta-analysis could not be performed because of insufficient homogeneous data, which made the results less reliable. For studies 1 and 3, although meta-analyses were conducted, large heterogeneity existed among the analyzed studies. However, because of the limited number of studies, it was not possible to investigate the potential source of heterogeneity. We are also aware that most of the included studies were of a cross-sectional design with a moderate study design quality.

Despite these limitations, results from the current project indicated that a significant change of spinal shape and mobility, which frequently occurs in patients suffering from spinal pain, could also occur as a physiological age-related change in asymptomatic subjects. Therefore, it is not possible to compare the spinal shape and mobility between elder patients with spinal pain and young, healthy subjects, rather age- and sex-specific reference values are required. Future study should focus on establishing a consistent protocol (e.g., similar device, measuring levels, and posture) to measure spinal shape and mobility and thus make the results comparable. The most reliable results concerning the effect of age on spinal shape and mobility should be from a longitudinal study with a large homogenous cohort and a long-term follow-up. Future research should also focus on maintaining or enhancing spinal shape and mobility with aging through appropriate exercise or therapy, which is associated with an improved quality of life. Furthermore, the effect of age and sex on spinal shape and mobility in subjects with spinal pain should also be investigated, to ensure an extensive comparison between symptomatic and asymptomatic groups.

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Eidesstattliche Versicherung

„Ich, Fumin Pan, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *„The effect of age and sex on spinal shape and mobility in asymptomatic adults – systematic reviews and meta-analyses“* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Declaration of any eventual publications

1. **Pan F**, Arshad R, Zander T, Reitmaier S, Schroll A, Schmidt H. The effect of age and sex on the cervical range of motion - A systematic review and meta-analysis. Journal of biomechanics 2018; 75:13-27.

   Contribution in detail: Together with the corresponding author, Fumin Pan developed the idea for the study. He was responsible for the development of the study design. He also formed the searching strategy for the literature search. Together with the co-authors, he conducted the selection process to include relevant studies. He did the data extraction with Microsoft Excel. He conducted the statistical analysis with the Review Manager software. He designed the study's figures and tables, drafted and wrote the manuscript. Fumin Pan conducted the proofreading and discussed and edited the publication during the review process, supported by the co-authors.

2. **Pan F**, Firouzabadi A, Reitmaier S, Zander T, Schmidt H. The shape and mobility of the thoracic spine in asymptomatic adults - A systematic review of in vivo studies. Journal of biomechanics 2018; 78:21-35.

   Contribution in detail: Based on the results from the first study, Fumin Pan had the idea for the current study, and was primarily responsible for the planning and preparation of the study methodology. He developed the searching strategy and conducted the literature search. He conducted the selection process to include relevant studies with the support of the co-authors. He did the data extraction with the help of the second author. He designed the study's figures and tables, and drafted the manuscript. During the review process, Fumin Pan conducted the proofreading, discussed and edited the publication with the support of the co-authors.

3. Arshad R, **Pan F**, Reitmaier S, Schmidt H. Effect of age and sex on lumbar lordosis and the range of motion. A systematic review and meta-analysis. Journal of biomechanics 2019; 82:1-19.

   Contribution in detail: Fumin Pan supported the first author regarding the design and planning of the study. He also helped to conduct the literature search. He helped the first author in selection of relevant studies. He helped to design the study's figures and tables. He cooperated in drafting and revising the manuscript with the co-authors. He assisted the first author in the review and publication process of the manuscript.

Signature, date and stamp of the supervising University teacher:

Signature of the doctoral candidate:

Selected publications

Study 1: **Pan F**, Arshad R, Zander T, Reitmaier S, Schroll A, Schmidt H. The effect of age and sex on the cervical range of motion - A systematic review and meta-analysis. Journal of biomechanics. 2018;75:13-27.

Impact Factor: 2.431, *Eigenfactor*® Score: 0.02800

https://doi.org/10.1016/j.jbiomech.2018.04.047

Study 2: **Pan F**, Firouzabadi A, Reitmaier S, Zander T, Schmidt H. The shape and mobility of the thoracic spine in asymptomatic adults - A systematic review of in vivo studies. Journal of biomechanics. 2018;78:21-35.

Impact Factor: 2.431, *Eigenfactor*® Score: 0.02800

https://doi.org/10.1016/j.jbiomech.2018.07.041

Study 3: Arshad R, **Pan F**, Reitmaier S, Schmidt H. Effect of age and sex on lumbar lordosis and the range of motion. A systematic review and meta-analysis. Journal of biomechanics. 2019;82:1-19.

Impact Factor: 2.431, *Eigenfactor*® Score: 0.02800

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Source of Impact Factors: ISI Web of Science (February 2019)

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Complete list of publications

Publications (in English):

Pan F, Arshad R, Zander T, Reitmaier S, Schroll A, Schmidt H. The effect of age and sex on the cervical range of motion - A systematic review and meta-analysis. Journal of Biomechanics 2018; 75:13-27.

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Pan F, Shen B, Chy SK, Yong Z, Liu X, Ba Z, Liu Z, Zhu J, Wu D. Transforaminal endoscopic system technique for discogenic low back pain: A prospective Cohort study. International Journal of Surgery 2016; 35:134-138.

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Pan F, Wang S, Ma B, Zhao W, Wu D. MRI characteristics of lumbar disc degeneration in perimenopausal women. Journal of Spinal Surgery 2016; 14(5): 297-300. (ISSN：16722957)

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Huang Y, **Pan F**, Zhao W, Ba Z, Ma M, Wu D. A three-dimensional finite element analysis of effect of lumbar posterolateral fusion with pedicle screw on adjacent intervertebral discs. Journal of Spinal Surgery 2016; 14(6): 362-366. (ISSN：1672-2957)

Wang S, **Pan F**, Ma B, Zhao J, Pan Y, Zhao W, Wu D, Tan J. Clinical progress of cervical spondylosis with vertigo. Orthopedic Journal of China 2016; 24(17): 1587-1589. (ISSN：1005-8478)

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