Original Research

Association Between Self-Reported Spinal Morning Stiffness and Radiographic Evidence of **Lumbar Disk Degeneration in** Participants of the Cohort Hip and **Cohort Knee (CHECK) Study**

Roxanne van den Berg, Elisabeth M. Jongbloed, Natalia O. Kuchuk, Bart W. Koes, Edwin H.G. Oei, Sita M.A. Bierma-Zeinstra*, Pim A.J. Luijsterburg*

Background. Low back pain (LBP) is very common and is a main cause of limited activity and work absence. Patients with LBP may also report spinal morning stiffness; this symptom could be useful for identifying subgroups with signs and symptoms related to spinal osteoarthritis.

Objective. This study investigated whether an association exists between reported spinal morning stiffness and radiographic evidence of lumbar disk degeneration (LDD) in people with LBP and a history of pain of the hip and/or knee.

Design. This cross-sectional study used 8-year follow-up data from the Cohort Hip and Cohort Knee study.

Methods. The association between spinal morning stiffness and radiographic LDD features was assessed with multivariable logistic regression models.

Results. The presence of osteophytes was significantly associated with spinal morning stiffness (odds ratio [OR] = 2.1 [95% confidence interval [CI] = 1.3-3.2]) as was the presence of grade 2 or 3 disk space narrowing (OR = 2.0 [95% CI = 1.1-3.5]). There was also a significant association between morning stiffness persisting for > 30 minutes and grade 2 osteophytes (OR = 2.6 [95% CI = 1.1-6.2]) and grade 1 disk space narrowing (OR = 2.0[95% CI = 1.1-3.6]). Furthermore, there was a significant association between moderate spinal morning stiffness and the presence of osteophytes (OR = 2.0 [95% CI = 1.2-3.2]). Both the presence of osteophytes and disk space narrowing were significantly associated with severe spinal morning stiffness (for osteophytes: OR = 2.0 [95% CI = 1.2-3.7]; for narrowing at L1-S1: OR = 1.8 [95% CI = 1.1-3.1]).

Limitations. Only lumbar lateral radiographs were available for each participant, implying that the LDD features could have been underestimated. The quality of the radiographs was not consistent.

Conclusions. This study showed an association between self-reported spinal morning stiffness and symptomatic LDD. When morning stiffness lasted > 30 minutes, there was a significant association with the features of LDD. The association was stronger when the severity of spinal morning stiffness increased.

R. van den Berg, MD, Department of General Practice, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Address all correspondence to Dr van den Berg at: r.vandenberg.2@erasmusmc.nl.

E.M. Jongbloed, MD, Department of General Practice, Erasmus University Medical Center.

N.O. Kuchuk, MD, Department of Rheumatology and Clinical Immunology, University Medical Center, Utrecht, the Netherlands; and Department of Rheumatology, Tergooi Hospital, Hilversum, the Netherlands.

B.W. Koes, PhD, Department of General Practice, Erasmus University Medical Center.

E.H.G. Oei, MD, PhD, Department of Radiology & Nuclear Medicine, Erasmus University Medical Center.

S.M.A. Bierma-Zeinstra, PhD, Department of General Practice, and Department of Orthopedics, Erasmus University Medical Center.

P.A.I. Luiisterburg, PhD, Department of General Practice, Erasmus University Medical Center.

*S.M.A. Bierma-Zeinstra and P.A.J. Luijsterburg contributed equally to the

[van den Berg R, Jongbloed EM, Kuchuk NO, et al. Association between self-reported spinal morning stiffness and radiographic evidence of lumbar disk degeneration in participants of the Cohort Hip and Cohort Knee (CHECK) study. Phys Ther. 2020;100:255-267.]

© 2019 American Physical Therapy

Published Ahead of Print: November 19, 2019 Accepted: June 28, 2019 Submitted: December 12, 2017



ow back pain (LBP) is a common medical problem, and 70% to 80% of adults report experiencing an episode of LBP during their lifetime. Moreover, LBP is the most important musculoskeletal cause of activity limitation and work absence.² Nonspecific LBP is usually defined as pain, muscle tension, and stiffness, with or without leg pain (sciatica).3 A well-studied risk factor for LBP is lumbar disk degeneration (LDD),4-10 of which the most commonly used definition is radiographic evidence of osteophytes and disk space narrowing. 6,10,11 These features are considered to be part of spinal osteoarthritis and are frequent in the low back. However, because of the large and heterogeneous groups of adults with nonspecific LBP, Scheele et al¹² reported the importance of identifying subgroups regarding etiology, prognosis, acceptance, and participation with treatment in patients with nonspecific LBP. One of these subgroups could be patients with LBP with symptoms associated with LDD.

According to the American College of Rheumatology (ACR) criteria, besides pain, morning stiffness is an important clinical symptom of hip and knee osteoarthritis. 13,14 However, because LDD shows similar structural features to osteoarthritis8,11,15-17 and there are no official classification criteria for spinal osteoarthritis, spinal morning stiffness might be a clinical symptom of this degenerative disease. Overall, there is broad agreement on the key management of lower limb osteoarthritis recommended in guidelines by the various organizations, 18,19 including the large professional societies, research societies, and governmental organizations. In the guidelines, exercise therapy (consisting of strengthening exercise and general aerobic exercise) and education/self-management are widely recommended and seen as first-line treatment. For this reason, it could be useful for a physical therapist (and a general practitioner [GP]) to identify patients with symptomatic spinal osteoarthritis and see whether this subgroup will benefit by similar treatment.

Scheele et al12 also reported that an association between morning stiffness and LDD (adjusted odds ratio [OR] = 1.3[95% confidence interval [CI] = 1.1-1.6] for osteophytes and adjusted OR = 2.5 [95% CI = 1.4-3.4] for disk space narrowing). This association could imply that spinal morning stiffness is one of the symptoms that GPs and physical therapists could use to identify the subgroup of patients with LBP and symptoms due to spinal osteoarthritis. However, this association has only been shown once and was based on a single general population study only for persons aged 55 years and older. Therefore, the present study aimed to assess the association between spinal morning stiffness and radiographic features of LDD in people with LBP and with problems with the knee and/or hip, and examine the potential association between the duration and severity of spinal morning stiffness and LDD.

Methods

Study Design

For the present cross-sectional study, the 8-year follow-up data of the Cohort Hip and Cohort Knee (CHECK) study were used. CHECK is a multi-center cohort study with 1002 participants with pain of the hip and/or the knee, and the study initiated to investigate the progression of suspected early-stage osteoarthritis. The cohort was formed between October 2002 and September 2005 and currently has a follow-up of 10 years. A substantial part of the participants of the CHECK study also reported LBP. Details on the methodology of the CHECK study are published elsewhere. 20,21 In summary, GPs in the area of the 10 participating hospital departments of rheumatology in the Netherlands were invited to refer eligible people to these participating centers. Recruitment also took place via advertisements and articles in local newspapers and via the website of the Dutch Arthritis Association. People were eligible for inclusion if they had pain and/or stiffness of the knee and/or hip, were 45 to 65 years old, and had not yet visited a GP in the last 6 months for these symptoms. Exclusion criteria were other pathological conditions that could explain the existing problems (eg, recent trauma, tendinitis, bursitis, inflammatory arthritis) or comorbidity that did not allow physical evaluation and/or follow-up of at least 10 years, malignancy in the past 5 years, or inability to understand the Dutch language.20

After participants had provided informed consent, baseline measures, such as demographic characteristics and clinical variables (self-reported questionnaires, physical examination, radiographs of knee and hip), were collected. Participants with mild hip or knee symptoms visited the research center at baseline and at 2, 5, 8, and 10 years (follow-up). Participants with severe symptoms visited the research center each year. At the 8-year follow-up, a radiograph of the lumbar spine was obtained; this was the rationale to use these follow-up data to address the research question of this substudy. For inclusion in the present study, people needed to report LBP in the past 4 weeks and have received a lumbar radiograph.

Measurements

In addition to the standard questionnaires at the 8-year follow-up, participants also filled out a questionnaire that asked about LBP and the presence, severity, and duration of lumbar spinal morning stiffness. Furthermore, the severity of LBP, quality of life, neuropathic pain, and disability due to osteoarthritis were assessed. The questionnaires in the CHECK study included (among others) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the ACR criteria for hip and knee osteoarthritis.^{13–22} The following items for LBP and spinal morning stiffness were assessed when the participants had LBP in the past 4 weeks.

Spinal morning stiffness severity was measured on a 5-point numeric rating scale, with 0 representing no

morning stiffness and 5 representing very severe spinal morning stiffness. This was divided into 3 categories: none/mild (scores of 0 or 1), moderate (scores of 2 or 3), and severe (scores of 4 or 5). Spinal morning stiffness was defined as being present when scores were 2 or higher on the 5-point scale of spinal morning stiffness severity. The duration of morning stiffness was measured with 3 answer options: no spinal morning stiffness, spinal morning stiffness persisting for < 30 minutes, and spinal morning stiffness persisting for > 30 minutes.

The duration of LBP was measured in days and categorized as 3 months, 3 months to 1 year, and longer than 1 year. The severity of LBP was measured on an 11-point numeric rating scale, with 0 representing no pain and 10 representing the worst pain imaginable.^{23,24} Severe LBP was defined as being present when scores were 4 or higher on the 11-point numeric rating scale.

The presence of neuropathic pain²⁵ was assessed using 2 questions based on Douleur Neuropathique 4 questions²⁶: Does the pain have 1 or more of the following characteristics (burning, painful cold, electric shocks)? Is the pain associated with 1 or more of the following symptoms in the same area (tingling, pins and needles, numbness, itching)?

Disability due to back problems was measured with the short version of the Roland-Morris Disability Questionnaire.²⁷ The scores ranged from 0 to 11 (where 0 indicated no disability and 11 indicated maximum disability). The Roland-Morris Disability Questionnaire is recommended for evaluating disability in LBP, with 78% agreement.^{28,29}

The questionnaires used in the CHECK study were as follows.

Health-related quality of life was measured using the EuroQol Five Dimensions Questionnaire addressing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The utility score was determined using this information: 1 represents full health and -0.330 represents severe problems in all 5 dimensions.³⁰ The EuroQol Five Dimensions Questionnaire is a practical way of measuring the health of a population and detecting differences in subgroups of the population, such as patients with LBP.^{31,32}

Osteoarthritis symptoms were assessed with the WOMAC, which measures pain, stiffness, and physical impairment.^{33,34} The standardized score range is 0 to 100 (where 0 indicates the worst possible health status and 100 indicates the best health status). The WOMAC is an osteoarthritis-specific index with adequate reliability, validity, and responsiveness, and it is also used in patients with LBP.³⁵

The ACR clinical criteria were used to establish the clinical presence of osteoarthritis in the hip and knee. ^{13,14} These criteria were assessed with a questionnaire about hip and knee symptoms and with a physical examination of the hip and knee. The ACR criteria for the hip were hip pain and at least 2 of the following 3 features: erythrocyte sedimentation rate of < 22 mm/h, radiographic evidence of femoral or acetabular osteophytes, and radiographic evidence of joint space narrowing. The ACR criteria for the knee were knee pain and at least 3 of the following features: > 50 years of age, < 30 minutes of morning stiffness, crepitus on active motion, bony tenderness, bony enlargement, and no palpable warmth of the synovium.

Lumbar Radiographs

The recumbent lumbar radiographs were collected in all CHECK participants at the 8-year follow-up and independently scored by 2 observers for osteophytes and disk space narrowing (ie, 2 radiographic LDD features).³⁶ The presence of osteophytes and disk space narrowing was appraised with the 4 grades of the Lane atlas¹¹ (ie, grade 0 = none; grade 1 = mild; grade 2 = moderate; and grade 3 = severe).

The 2 independent observers were masked for the clinical characteristics of the participants and scored the vertebral levels from L1-L2 to L5-S1 for the presence of the different LDD features. Observers were trained by an experienced musculoskeletal radiologist.

Because of the low prevalence of some of the radiographic features, the interobserver reproducibility was established with the prevalence- and bias-adjusted kappa³⁷ rather than the usual kappa statistics. To assess interobserver reproducibility with the prevalence- and bias-adjusted kappa, the experienced musculoskeletal radiologist and the 2 observers independently scored a set of 40 lumbar radiographs. The scores of both observers were compared with those of the experienced radiologist. The results showed prevalence- and bias-adjusted kappa values of 0.5 and 0.7 for osteophytes and disk space narrowing, respectively; these data indicate moderate to substantial agreement.

Data Analysis

To report the characteristics of the participants, descriptive statistics were used. The chi-square test and independent t test were used to evaluate differences in the variables between participants with and without spinal morning stiffness. P < .05 was defined as statistically significant.

Multivariable logistic regression analyses were performed to determine the association between the presence of spinal morning stiffness and the presence of osteophytes and disk space narrowing. The association between the duration and severity of spinal morning stiffness and the

radiographic LDD features was also analyzed with multivariable logistic regression.

Because of the very low prevalence of grade 0 for the LDD feature osteophytes, the reference group was grade 0 and grade 1 osteophytes combined. For the LDD feature of disk space narrowing, grade 0 was used as a reference group. Because of the low prevalence of grade 3 (8%) disk space narrowing, grades 2 and grade 3 were combined for the analyses.

In the present study, we used the radiographic definitions of osteophytes (ie, an osteophyte of grade > 2 at 2 or more levels from L1-L2 to L5-S1) and disk space narrowing (ie, narrowing of grade ≥ 1 at 2 or more levels from L1-L2 to L5-S1).6

For analyzing the duration of spinal morning stiffness, we used 2 different reference groups: the first was no spinal morning stiffness, and the second was no spinal morning stiffness combined with morning stiffness persisting for < 30 minutes.

For the severity of spinal morning stiffness analysis, the reference group was the category none/mild (scores of 0 and 1). All analyses were adjusted for body mass index, age, and sex because these factors are associated with both spinal morning stiffness and the radiographic LDD features.^{6,38} For the associations regarding osteophytes, the analyses were also adjusted for the presence of bony bridging on 4 vertebral levels or more; this is a sign of diffuse idiopathic skeletal hyperostosis.39,40 Because of overlapping clinical symptoms, the presence of bony bridging could influence the association between radiographic evidence of LDD and spinal morning stiffness. For the association between spinal morning stiffness and radiographic evidence of LDD, ORs with 95% CIs are presented. P < .05 was defined as statistically significant. Statistical analyses were performed using SPSS (version 21; IBM SPSS, Chicago, IL, USA).

Role of the Funding Source

The institution was supported by grants from the Dutch Arthritis Foundation. No specific funding for this study was received, and no role was played by a funder.

Results

Participant Characteristics

The CHECK study started with 1002 participants at baseline. At 8-year follow-up measurement, 874 people (87%) participated. However, because 145 participants did not fill out the questionnaire and 30 participants had no lumbar radiograph, 699 people were eligible for the present study. Of these, 462 had LBP, of which 5 did not complete the required additional questionnaire. Thus,

finally, 457 participants (65%) were available for the present study (Fig. 1).

Table 1 shows the differences between participants with and without spinal morning stiffness. In brief, the mean age was 64 years, and there were more women than men; 65% of the participants with LBP reported spinal morning stiffness. The main differences between participants with spinal morning stiffness and those without were ability to work, scores on the 3 WOMAC subscales, prevalence of clinical hip and knee osteoarthritis, and the duration of LBP. Also, participants with spinal morning stiffness were more disabled based on the Roland-Morris Disability Ouestionnaire.

There was a high prevalence of the radiographic LDD feature osteophytes. Participants with spinal morning stiffness more often had radiographic features of LDD.

Presence of Spinal Morning Stiffness and LDD Features

Table 2 shows the association between the presence of spinal morning stiffness and the radiographic features of LDD. The presence of osteophytes was significantly associated with spinal morning stiffness as was the presence of grade 2 or 3 disk space narrowing.

Duration of Spinal Morning Stiffness and LDD Features

We examined whether the duration of spinal morning stiffness and the different LDD features were associated (Tab. 3). When no spinal morning stiffness was used as a reference group, there was a significant association between spinal morning stiffness persisting for ≥ 30 minutes and grade 2 osteophytes. Disk space narrowing was not significantly associated with spinal morning stiffness persisting for ≥ 30 minutes. There was no significant association between spinal morning stiffness persisting for ≤ 30 minutes and the LDD features.

When no spinal morning stiffness combined with spinal morning stiffness persisting for ≤ 30 minutes was used as a reference group, there was a significant association with grade 1 disk space narrowing.

Severity of Spinal Morning Stiffness and **LDD Features**

Table 4 presents the association between severity of spinal morning stiffness (none/mild vs moderate vs severe/very severe) and the LDD features.

There was a significant association between moderate spinal morning stiffness and the presence of osteophytes. Both LDD features (osteophytes and disk space narrowing) were significantly associated with severe spinal morning stiffness.

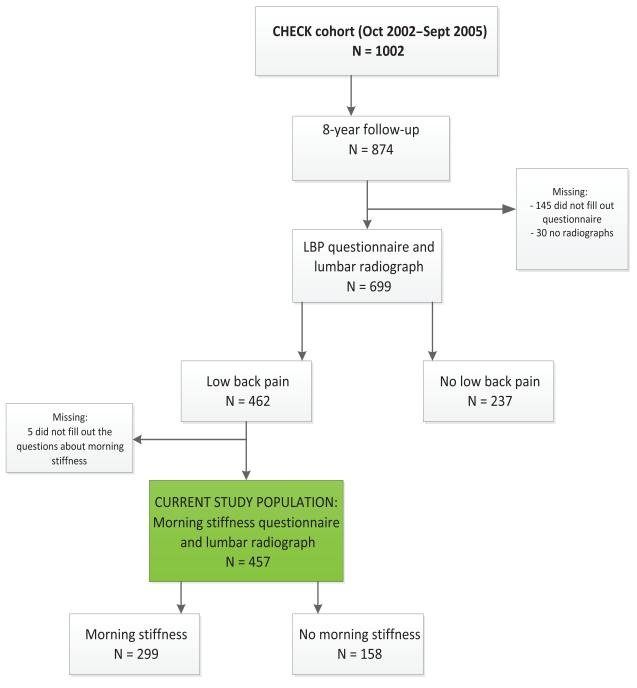


Figure 1. Flowchart of inclusion in the study.

Table 1. Characteristics of the Study Population^a

Characteristic	All (n = 457)	Spinal Morning Stiffness (n = 299)	No Spinal Morning Stiffness (n = 158)	P for Spinal Morning Stiffness vs No Spinal Morning Stiffness
General			ı	
Age, mean \pm SD, y	64.0 ± 5.2	63.9 ± 5.3	64.2 ± 5.0	.57
No. (%) of women	373 (82)	246 (82)	127 (80)	.62
Body mass index, mean \pm SD	$\textbf{26.4} \pm \textbf{4.2}$	26.7 ± 4.1	25.9 ± 4.5	.06
Educational level			1	
Primary school	10 (2)	7 (2)	3 (2)	.76
Secondary school	336 (74)	222 (74)	114 (72)	.64
Professional education	100 (22)	63 (21)	37 (23)	.56
Work description			I	
Employed (paid employment)	121 (26)	80 (27)	41 (26)	.35
Unemployed	6 (1)	5 (2)	1 (1)	.85
Disabled	36 (8)	31 (10)	5 (3)	<.01 ^b
Voluntarily unemployed	268 (59)	167 (56)	101 (64)	.09
EuroQoL utility score, c mean \pm SD	0.77 ± 0.17	0.74 ± 0.18	0.83 ± 0.12	<.01 ^b
WOMAC subscale score, d mean \pm SD		1		
Pain standardized	74.7 ± 19.0	69.9 ± 19.6	83.9 ± 13.9	<.01 ^b
Stiffness standardized	65.5 ± 23.8	57.6 ± 23.3	80.6 ± 16.2	<.01 ^b
Physical function standardized	73.0 ± 20.0	67.0 ± 20.2	84.6 ± 13.3	<.01 ^b
Total standardized	72.8 ± 19.2	66.8 ± 19.4	84.1 ± 12.7	<.01 ^b
Present hip osteoarthritis	104 (23)	80 (27)	24 (15)	<.01 ^b
Present knee osteoarthritis ^e	284 (62)	208 (70)	76 (48)	<.01 ^b
Radiologic evidence of hip osteoarthritis	84 (18)	53 (18)	31 (20)	.62
Radiologic evidence of knee osteoarthritis	278 (61)	177 (39)	101 (64)	.27
Chronic low back pain at 3 mo	411 (90)	273 (91)	138 (87)	.18
Chronic low back pain at 12 mo	353 (77)	245 (82)	108 (68)	<.01 ^b
Neuropathic pain	36 (8)	30 (10)	6 (4)	.02 ^b
Disability, g mean \pm SD	4.7 ± 3.1	5.8 ± 2.9	2.6 ± 2.39	<.01 ^b
Duration of morning stiffness				
< 30 min	293 (64)	191 (64)		
> 30 min	112 (25)	107 (36)		
Severity of morning stiffness		•		
Mild morning stiffness	129 (28)		129 (28)	
Moderate morning stiffness	191 (42)	191 (64)		
Severe/very severe morning stiffness	107 (23)	108 (36)		
Radiographic ^h				
Osteophytes at L1–S1				
Grade 0	5 (1)	4 (1)	1 (1)	.49
Grade 1	127 (28)	77 (26)	50 (32)	.49
Grade 2	209 (46)	137 (46)	72 (46)	.24

(Continued)

Table 1. Continued.

Characteristic	All (n = 457)	Spinal Morning Stiffness (n = 299)	No Spinal Morning Stiffness (n = 158)	P for Spinal Morning Stiffness vs No Spinal Morning Stiffness
Grade 3	116 (25)	81 (27)	35 (22)	.25
Definition ⁱ	220 (48)	158 (53)	62 (39)	<.01 ^b
Narrowing at L1–S1				
Grade 0	132 (29)	76 (25)	56 (35)	.03 ^b
Grade 1	196 (43)	133 (44)	63 (40)	<.01 ^b
Grade 2	92 (20)	67 (22)	25 (16)	.22
Grade 3	35 (8)	23 (8)	12 (8)	.66
Definition ^j	197 (43)	138 (46)	59 (37)	.07

^aData are reported as number (percentage) of participants unless otherwise indicated.

Discussion

This study demonstrated associations between the presence, duration, and severity of spinal morning stiffness and key radiographic features of LDD, namely, osteophytes and disk space narrowing, in participants with LBP.

CHECK is a multi-center cohort study including individuals with hip and/or knee pain initiated to study the progression of suspected early symptomatic osteoarthritis in knee and hip. People with osteoarthritis in the knee and hip often report morning stiffness in the affected joint.35,41 This selection in the CHECK population might imply that the prevalence of spinal morning stiffness was higher in our study population than in the general population of people who have LBP and visit a GP or physical therapist.

One of the most important consequences of LBP is disability.⁴² We showed that participants with spinal morning stiffness were more often unable to work, scored worse on all the WOMAC subscales, more often had chronic LBP, and scored worse on the Roland-Morris Disability Questionnaire (5.8 vs 2.6). The findings of the present study suggest that spinal morning stiffness is associated with LDD. This might indicate that people with spinal morning stiffness caused by LDD could be a clinically relevant subgroup that experiences more disability.

The degree of spinal morning stiffness might also reflect the degree of inflammation, and we should further explore whether antiinflammatory treatment should be tailored according to the degree of spinal morning stiffness.

The association between spinal morning stiffness and disk space narrowing was also explored with the exclusion of level L5-S1. Level L5-S1 is a difficult and potentially inaccurate level to assess on a lateral lumbar radiograph because of lumbosacral transitional vertebrae (prevalence 18.1%).43,44 However, results of the multivariable logistic regression analyses with the exclusion of level L5-S1 (disk space narrowing at L1-L5) were similar to the results analyzing disk space narrowing at levels L1 to S1. Scheele et al¹² excluded the L5-S1 level based on the findings of de Schepper et al,6 who concluded that the strength of the association between LBP and LDD increased by excluding level L5-S1. Because this is not the case in the current study, we included level L5-S1 in our analysis.

In our CHECK population, the high prevalence of osteophytes (99%) seen on radiographs was similar to that in other radiographic surveys. 45,46 This high prevalence was also found in the study of van den Berg et al,11 in which patients with nonspecific LBP and patients without nonspecific LBP were assessed (prevalence of osteophytes: 98%). There was a high prevalence of disk space narrowing (grade ≥ 1 disk space narrowing in 71% and definition of disk space narrowing in 43%). Vining et

^bSignificant at P < .05.

^cComputed with the EuroQoL Five Dimensions Questionnaire (-0.330 to 1).

^dWOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. The data were standardized to a range of values from 0 to 100, where 0 is the worst possible health status and 100 is the best health status.

epresent hip and knee osteoarthritis were classified using the American College of Radiology (ACR) criteria.

^fRadiologic hip or knee osteoarthritis was defined by a Kellgren-Lawrence grade of ≥ 2 .

⁹Determined with the Roland-Morris Disability Questionnaire, with scores ranging from 0 to 11 (0 = no disability, 11 = maximum disability).

^hFeatures of lumbar disk degeneration were scored using the highest grade of degeneration for all 5 levels of vertebrae per participant.

Definition of osteophytes = grade ≥ 2 osteophytes at 2 or more levels from L1-L2 to L5-S1.

Definition of narrowing at L1-S1 = grade ≥ 1 disk space narrowing at 2 or more levels from L1-L2 to L5-S1; definition of narrowing at L1-L5 = grade ≥ 1 disk space narrowing at 2 or more levels from L1-L2 to L4-L5.

Table 2. Association Between Presence of Spinal Morning Stiffness Reported in the Past Month and Radiographic LDD Features $(n = 457)^a$

- n	Spinal Morning Stiffness						
Radiographic LDD Feature ^b	No. (%) of Participants	OR (95% CI)	P				
Osteophytes at L1–S1							
Grade 0 or grade 1	132 (29)	1					
Grade 2	209 (46)	1.2 (0.8–2.0)	.43				
Grade 3	116 (25)	1.7 (0.7–3.3)	.13				
Not meeting definition	237 (52)	1					
Meeting definition	220 (48)	2.1 (1.3–3.2)	.00 ^c				
Narrowing at L1–S1							
Grade 0	132 (29)	1					
Grade 1	196 (43)	1.6 (1.0–2.5)	.06				
Grade 2 or grade 3	129 (28)	2.0 (1.1–3.5)	.03 ^c				
Not meeting definition	260 (57)	1					
Meeting definition	197 (43)	1.4 (0.9–2.1)	.11				

 $^{^{}o}$ Adjustments were made for age, body mass index, and sex. Missing values ranged up to 3%. CI = confidence interval; LDD = lumbar disk degeneration; OR = odds ratio.

al reported a 29% prevalence for single-level narrowing and 30% for multilevel narrowing⁴⁷ in patients with chronic LBP. However, this marked difference in prevalence might be explained by differences between the 2 study populations; for example, Vining et al explored the prevalence of radiographic findings in a much younger population (mean age of 44.8 years vs 64.0 years in the present study). Also, all of the patients in the Vining et al study had chronic LBP, defined as LBP lasting 12 weeks or longer, whereas in the present study, 90% of the participants had chronic LBP.

In the present study, severity of spinal morning stiffness was measured on a 5-point numeric rating scale, with 0 indicating no morning stiffness and 5 indicating very severe morning stiffness. To dichotomize the outcome spinal morning stiffness, we chose the arbitrary cutoff at 2 = mild spinal morning stiffness. We assumed that in a clinical setting, many people experience some mild spinal morning stiffness. There is no current literature to our knowledge regarding the optimal cutoff for the presence of spinal morning stiffness.

Scheele et al¹² also found an association between spinal morning stiffness and LDD features. The association between disk space narrowing and spinal morning stiffness was stronger than the association between osteophytes and morning stiffness (for disk space narrowing: OR = 1.8 [95% CI = 1.4–2.2]; for osteophytes:

OR = 1.2 [95% CI = 1.0-1.5]). In the present study, a stronger association was found between osteophytes and spinal morning stiffness compared with disk space narrowing (for osteophytes: OR = 2.1 [95% CI = 1.3-3.2]; for disk space narrowing: OR = 1.4 [95% CI = 0.9-2.1]). However, although the same scoring system was used, Scheele et al¹² conducted an open population-based study (all inhabitants of a district of the city of Rotterdam, the Netherlands, were invited to participate in this study) of participants aged a mean of 65.7 years (SD = 6.6), and the LDD definitions limited to levels L1 to L5 were used.12 In their research population, the prevalence of osteophytes and disk space narrowing was lower compared with our CHECK population (for osteophytes: 30% vs 48%; for disk space narrowing: 19% vs 43%), which can explain the difference in findings.

Scheele et al¹² excluded patients without LBP; this exclusion resulted in a smaller association between spinal morning stiffness and LDD. They discussed that the symptom spinal morning stiffness is possibly less discriminative in patients with LBP. However, the OR found in the present study was similar to that found by Scheele et al¹² for the presence of osteophytes and disk space narrowing in people with LBP, suggesting that spinal morning stiffness is also discriminative in detecting LDD in people with LBP.

We found a significant association between morning stiffness persisting for ≥ 30 minutes and the LDD features.

^bFeatures of LDD were scored using the highest grade of degeneration for all 5 levels of vertebrae per participant. Definition of osteophytes = grade \geq 2 osteophytes at 2 or more levels from L1–L2 to L5–S1. Definition of narrowing = grade \geq 1 disk space narrowing at 2 or more levels from L1–L2 to L5–S1. CSignificant at P < .05.

Table 3. Association Between Duration of Spinal Morning Stiffness Reported in the Past Month and Radiographic LDD Features $(n = 452)^{\circ}$

Radiographic LDD Feature ^b	No Spinal Morning Stiffness (n = 47)		Spinal Morning Stiffness Lasted ≤ 30 min (n = 293)		Spinal Morning Stiffness Lasted ≥ 30 min (n = 112)		No Spinal Morning Stiffness and Spinal Morning Stiffness Lasted ≤ 30 min (n = 340)		Spinal Morning Stiffness Lasted ≥ 30 min (n = 112)	
	OR(CI)	P	OR(CI)	P	OR(CI)	P	OR(CI)	P	OR(CI)	P
Osteophytes at L1–S1										
Grade 0 or grade 1	Reference		1		1		Reference		1	
Grade 2	Reference		1.7 (0.8–3.5)	.91	2.6 (1.1–6.2)	.03 ^c	Reference		1.7 (0.9–3.0)	.08
Grade 3	Reference		1.2 (0.5–3.4)	.70	2.7 (0.9–8.2)	.08	Reference		2.0 (1.0–4.2)	.08
Not meeting definition	Reference		1				Reference			
Meeting definition	Reference		1.3 (0.6–2.6)	.5	1.9 (0.9–4.1)	.12	Reference		1.5 (0.9–2.4)	.11
Narrowing at L1-S1										
Grade 0	Reference		1		1		Reference		1	
Grade 1	Reference		0.9 (0.4–2.0)	.88	1.6 (0.7–4.1)	.30	Reference		2.0 (1.1–3.6)	.02 ^c
Grade 2 or grade 3	Reference		0.7 (0.3–2.0)	.73	1.6 (0.6–4.5)	.38	Reference		1.9 (1.0–3.6)	.05
Not meeting definition	Reference		1		1		Reference		1	
Meeting definition	Reference		1.2 (0.6–2.4)	.55	1.4 (0.7–3.0)	.37	Reference		1.2 (0.8–1.9)	.45

 $^{^{}a}$ Adjustments were made for age, body mass index, and sex. LDD = lumbar disk degeneration; OR = odds ratio.

This corresponds to the outcomes of Scheele et al,¹² who reported a stronger association with the LDD feature disk space narrowing and spinal morning stiffness persisting for ≥ 30 minutes.

There was a trend of an increasing OR with increasing duration of spinal morning stiffness. Spinal morning stiffness lasting longer than 60 minutes may be a sign of an inflammatory condition such as ankylosing spondylitis.^{12,48} Based on knowledge from patients with rheumatoid arthritis, one assumes that in general it appears that longer duration of morning stiffness in a specific joint means more inflammation.^{49–52}

Patients with knee osteoarthritis experience intermittent flare-ups during which the pain worsens. 53,54 The main symptoms of a flare-up are inflammatory variables such as functional impairment, nocturnal awakening, swelling, warmth, and morning stiffness. 54 Also, when patients with knee synovitis received an intraarticular glucocorticoid injection, they showed better results in terms of variables associated with articular inflammation such as pain, edema, and morning stiffness persisting for ≥ 30 minutes than patients who received a systemic treatment. 55

In hip osteoarthritis, the duration of the morning stiffness is ≤ 60 minutes. The duration of morning stiffness is

reported to correlate with the degree of inflammation.⁵⁶ In patients with osteoarthritis, this morning stiffness is not always present and is mostly of short duration; however, there also are patients with longer morning stiffness. In the present study, participants with LBP more often have shorter duration of the spinal morning stiffness. Also, in patients with LBP, spinal morning stiffness might be a marker of the degree of inflammation, but more research on this topic is required.

A widely recommended and evidence-based treatment for both lower limb osteoarthritis and LBP is exercise therapy. 18,19,57 Also, the double-blind, randomized controlled trial of Burton et al58 concludes that carefully selected and presented information and advice about back pain can have a positive effect on patients' beliefs and clinical outcomes. However, in patients with LBP, it has not been extensively investigated which type and dose of exercise would be beneficial for patients with LDD-related symptoms. In a small randomized controlled trial, Krekoukias et al⁵⁹ assessed the efficacy of spinal mobilization in people with LBP due to spinal disk degeneration. They concluded that manual therapy (spinal mobilization, 5 sessions, lasting 10 minutes each) is preferable to conventional physical therapy (stretching exercises, transcutaneous electrical nerve stimulation, and

 $[^]b$ Features of LDD were scored using the highest grade of degeneration for all 5 levels of vertebrae per participant. Definition of osteophytes = grade \geq 2 osteophytes at 2 or more levels from L1–2 to L5–S1. Definition of narrowing = grade \geq 1 disk space narrowing at 2 or more levels from L1–L2 to L5–S1. c Significant at p < .05.

Table 4. Association Between Severity of Spinal Morning Stiffness and Radiographic LDD Features^a

Radiographic LDD Feature ^b	None/Mild (n = 156)		Moderate (n =	186)	Severe/Very Severe (n = 107)					
kadiographic LDD reature	OR	P	OR	P	OR	P				
Osteophytes at L1–S1	Osteophytes at L1–S1									
Grade 0 or grade 1	Reference		1		1					
Grade 2	Reference		1.3 (0.7–2.2)	.35	1.1 (0.6–2.1)	.77				
Grade 3	Reference		1.8 (0.9–3.7)	.11	1.4 (0.6–3.4)	.42				
Not meeting definition	Reference		1		1					
Meeting definition	Reference		2.0 (1.2–3.2)	.005 ^c	2.1 (1.2–3.7)	.01 ^c				
Narrowing at L1–S1										
Grade 0	Reference		1		1					
Grade 1	Reference		1.6 (0.9–2.7)	.08	1.6 (0.9–2.9)	.15				
Grade 2 or grade 3	Reference		1.8 (1.0–3.2)	.06	1.8 (0.9–3.6)	.11				
Not meeting definition	Reference		1		1					
Meeting definition	Reference		1.2 (0.8–1.9)	.38	1.8 (1.1–3.1)	.02 ^c				

 $^{^{}a}$ Adjustments were made for age, body mass index, and sex. Missing values represented < 3%. LDD = lumbar disk degeneration. ^bFeatures of LDD were scored using the highest grade of degeneration for all 5 levels of vertebrae per participant. Definition of osteophytes = grade \geq 2 osteophytes at 2 or more levels from L1-L2 to L5-S1. Definition of narrowing = grade \geq 1 disk space narrowing at 2 or more levels from L1-L2 to L5-S1. ^cSignificant at P < .05.

massage) to reduce pain intensity and disability in people with chronic LBP and associated with disk degeneration. This emphasizes the need to deliver specific interventions to patients with LBP caused by LDD. Future high-quality and large randomized controlled trials need to assess which therapy is most effective in the subgroup of patients with spinal osteoarthritis.

Because the current study is the second to find an association between spinal morning stiffness and LDD. spinal morning stiffness may be a symptom used by physical therapists to identify patients with signs of spinal osteoarthritis and to manage this subgroup of patients with specific information, education, and treatment. However, the present results are based on cross-sectional data, and therefore the relevance of defining such a subgroup in respect to prognosis and treatment needs to be assessed and conformed in future prospective observational and experimental research. Also, no studies have yet assessed if the presence of spinal morning stiffness is a moderator of treatment effect in patients with LBP due to spinal osteoarthritis. This should be investigated in large randomized controlled trials or with individual patient data meta-analysis.

In the future, we should investigate whether people with spinal morning stiffness, which could be an inflammatory symptom, derive more antiinflammatory effects from

treatment and exercise60,61 than people without spinal morning stiffness.

Our results confirm that there is an association between the presence of spinal morning stiffness and LDD features seen on a radiograph. Also, with increasing severity of spinal morning stiffness, the association between it and both LDD features was stronger.

This study had several strengths: it used standardized methods for assessing the radiographs and both observers were trained by an experienced musculoskeletal radiologist. Furthermore, validated questionnaires were used to measure patient-reported outcome measures. This study was performed within the CHECK study, which includes a large population of participants with suspected early knee and/or hip osteoarthritis and, therefore, possibly predisposed to develop lumbar degeneration. In addition, hip pain can be caused by LDD.62,63

This study also has several limitations. First, only lumbar lateral radiographs were available for each participant, implying that the grades of osteophytes and disk space narrowing could have been underestimated. Also, because only lateral radiographs were available, it was not possible to investigate the association between facet joint degeneration and spinal morning stiffness. The fact that facet joints are the only synovial joints in the spine might

have influenced the associations between spinal morning stiffness and LDD.

Second, the fact that the quality of the radiographs was not consistent (ie, there were different levels of radiographic quality among the 10 participating hospitals) and that the numbers of participants at the centers differed could have led to information bias. However, in our radiographic dataset, no structural poor quality was observed for any specific center. Moreover, no lumbar radiographs were excluded because of poor quality.

In conclusion, this study demonstrates an association between the presence of spinal morning stiffness and the LDD features disk space narrowing and osteophytes. When the severity of spinal morning stiffness increased, there was a stronger association with both LDD features. More studies are needed to validate these results in a similar population and to evaluate whether the clinical symptom spinal morning stiffness might play a role in identifying patients with spinal osteoarthritis, hopefully with respect to specific treatment or prognosis.

Author Contributions and Acknowledgments

Concept/idea/research design: R. van den Berg, B.W. Koes, S.M.A. Bierma-Zeinstra, P.A.J. Luijsterburg

Writing: R. van den Berg, E.M. Jongbloed, N.O. Kuchuk, S.M.A. Bierma-Zeinstra

Data collection: R. van den Berg, E.M. Jongbloed, N.O. Kuchuk, P.A.J. Luijsterburg

Data analysis: R. van den Berg, E.M. Jongbloed, S.M.A. Bierma-Zeinstra, P.A.J. Luijsterburg

Project management: P.A.J. Luijsterburg

Consultation (including review of manuscript before submitting): N.O. Kuchuk, B.W. Koes, E.H.G. Oei, P.A.J. Luijsterburg

The authors thank all the CHECK study participants for their valuable cooperation.

Ethics Approval

Ethics approval for the CHECK study was granted by the Medical Ethics Review Committee of UMC Utrecht.

Funding

The institution was supported by grants from the Dutch Arthritis Foundation. No specific funding for this study was received.

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

DOI: 10.1093/ptj/pzz170

References

1 Rubin DI. Epidemiology and risk factors for spine pain. *Neurol Clin.* 2007;25:353–371.

- 2 Murray CJL, Vos T, Lozano R, Naghavi M, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 2013;380:2197–2223.
- **3** Koes BW, Van MW, Thomas S. Diagnosis and treatment of low back pain. *BMJ*. 2006;7555:1430.
- 4 van MW, Assendelft WJJ, Koes BW, Bouter LM. Spinal radiographic findings and nonspecific low back pain: a systematic review of observational studies. *Spine*. 1997;22:427–434.
- **5** Pye SR, Reid DM, Lunt M, Adams JE, Silman AJ, O'Neill TW. Lumbar disc degeneration: association between osteophytes, end-plate sclerosis and disc space narrowing. *Ann Rheum Dis.* 2007;66:330–333.
- 6 de EIT, Damen J, van JBJ, et al. The association between lumbar disc degeneration and low back pain: the influence of age, gender, and individual radiographic features. *Spine*. 2010.35:531-536
- 7 Videman T, Battié MC, Gibbons LE, Maravilla K, Manninen H, Kaprio J. Associations between back pain history and lumbar MRI findings. *Spine*. 2003;28:582–588.
- 8 Kalichman L, Kim DH, Li L, Guermazi A, Hunter DJ. Computed tomography–evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. *Spine J.* 2010;10:200–208.
- 9 Steffens D, Hancock MJ, Maher CG, Williams C, Jensen TS, Latimer J. Does magnetic resonance imaging predict future low back pain? A systematic review. *Eur J Pain*. 2014;18: 755–765.
- 10 van den R, Jongbloed LM, Kuchuk NO, et al. The association between self-reported low back pain and radiographic lumbar disc degeneration of the Cohort Hip and Cohort Knee (CHECK) study. Spine (Phila Pa 1976). 2017;42:1464–1471.
- 11 Lane NE, Nevitt MC, Genant HK, Hochberg MC. Reliability of new indices of radiographic osteoarthritis of the hand and hip and lumbar disc degeneration. *J Rheumatol*. 1993;20:1911–1918.
- 12 Scheele J, De EIT, Van JBJ, et al. Association between spinal morning stiffness and lumbar disc degeneration: the Rotterdam study. *Osteoarthritis Cartilage*. 2012;20:982–987.
- 13 Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum*. 1991;34:505–514.
- 14 Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum*. 1986:29:1039–1049.
- 15 Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum*. 1986:29:1039–1049.
- **16** Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev.* 1988;10:1–28.
- 17 Raastad J, Reiman M, Coeytaux R, Ledbetter L, Goode AP. The association between lumbar spine radiographic features and low back pain: a systematic review and meta-analysis. Semin Arthritis Rheum. 2015;44:571–585.
- 18 Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Artbritis Rheum*. 2014;43:701–712.
- 19 Block JA. Osteoarthritis: OA guidelines—improving care or merely codifying practice? Nat Rev Rheumatol. 2014;10:324.
- 20 Wesseling J, Dekker J, Van den WB, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the osteoarthritis initiative. *Ann. Rheum Dis.* 2009;68: 1413–1419.

- 21 Wesseling J, Boers M, Viergever MA, et al. Cohort profile: Cohort Hip and Cohort Knee (CHECK) study. Int J Epidemiol.
- 22 Altman R. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. *Arthritis Rheum.* 1986;29:1039–1049.
- 23 Von M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. Spine. 2000;25:3140-3151.
- 24 Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth. 2008;101:17-24
- 25 Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630–1635.
- **26** Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114:29-36.
- 27 Stroud MW, McKnight PE, Jensen MP. Assessment of self-reported physical activity in patients with chronic pain: development of an abbreviated Roland-Morris disability scale. J Pain. 2004;5:257-263.
- 28 Chiarotto A, Deyo RA, Terwee CB, et al. Core outcome domains for clinical trials in non-specific low back pain. Eur Spine J. 2015;24:1127-1142.
- 29 Deyo RA, Battie M, Beurskens A, et al. Outcome measures for low back pain research: a proposal for standardized use. Spine. 1998;23:2003-2013.
- 30 Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff [in Dutch]. Ned Tijdschr Geneeskd. 2005;149:1574-1578.
- 31 Picavet HSJ, Hoeymans N. Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. *Ann Rheum Dis.* 2004;63:723–729
- 32 Suarez-Almazor ME, Kendall C, Johnson JA, Skeith K, Vincent D. Use of health status measures in patients with low back pain in clinical settings: comparison of specific, generic and preference-based instruments. Rheumatology. . 2000;39:783–790.
- 33 Bellamy N. Validation study of WOMAC: a health status instrument for measuring clinically-important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheumatol. 1988;1:95–108.
- 34 Roorda LD, Jones CA, Waltz M, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis. 2004;63:36–42.
- 35 Stupar M, Côté P, French MR, Hawker GA. The association between low back pain and osteoarthritis of the hip and knee: a population-based cohort study. J Manipulative Physiol Ther. 2010;33:349–354.
- 36 Varlotta GP, Lefkowitz TR, Schweitzer M, et al. The lumbar facet joint: a review of current knowledge. Part 1: anatomy, biomechanics, and grading. Skeletal Radiol. 2011;40:13-23.
- 37 Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol. 1993;46:423-429.
- 38 Pye SR, Reid DM, Adams JE, Silman AJ, O'Neill TW. Influence of weight, body mass index and lifestyle factors on radiographic features of lumbar disc degeneration. Ann Rheum Dis. 2007;66:426–427.
- 39 Resnick D, Shapiro RF, Wiesner KB, Niwayama G, Utsinger PD, Shaul SR. Diffuse idiopathic skeletal hyperostosis (DISH) [ankylosing hyperostosis of Forestier and rotes-Querol]. Semin Arthritis Rheum. 1978;7:153–187.
- 40 Weinfeld RM, Olson PN, Maki DD, Griffiths HJ. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. Skeletal Radiol. 1997;26:222-225.

- 41 van GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord. 2008;9. doi: 10.1186/1471-2474-9-95
- 42 Koes BW, Van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. BMJ. 2006;332:1430.
- 43 Nardo L, Alizai H, Virayavanich W, et al. Lumbosacral transitional vertebrae: association with low back pain. Radiology. 2012;265:497-503.
- 44 Tini PG, Wieser C, Zinn WM. The transitional vertebra of the lumbosacral spine: its radiological classification, incidence, prevalence, and clinical significance. Rheumatology. 1977;16:180–185
- 45 Pye SR, Reid DM, Smith R, et al. Radiographic features of lumbar disc degeneration and self-reported back pain. J Rheumatol. 2004;31:753-758.
- 46 Shao Z, Rompe G, Schiltenwolf M. Radiographic changes in the lumbar intervertebral discs and lumbar vertebrae with age. Spine. 2002:27:263-268.
- 47 Vining RD, Potocki E, McLean I, et al. Prevalence of radiographic findings in individuals with chronic low back pain screened for a randomized controlled trial: secondary analysis and clinical implications. J Manipulative Physiol Ther. 2014;37:678-687.
- 48 Goei The HS, Steven MM, Van Der Linden SM, Cats A Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis. Rheumatology. 1985:24:242-249
- **49** Yazici Y, Pincus T, Kautiainen H, Sokka T. Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with joint swelling and erythrocyte sedimentation rate. J Rheumatol. 2004;31:1723-1726.
- **50** Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet. 2008;371:205-214.
- 51 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-324.
- 52 Westhoff G, Buttgereit F, Gromnica-Ihle E, Zink A. Morning stiffness and its influence on early retirement in patients with recent onset rheumatoid arthritis. Rheumatology. 2008;47:980-984.
- 53 Conrozier T, Balblanc JC, Piperno M, Rinaudo M. Differences in the osteoarthritic synovial fluid composition and rheology between patients with or without flare-up: a pilot study. Osteoarthritis Cartilage. 2012;20:S244.
- 54 Marty M, Hilliquin P, Rozenberg S, et al. Validation of the KOFUS (knee osteoarthritis flare-ups score). Joint Bone Spine. 2009;76:268-272.
- 55 Konai MS, Furtado RNV, dos Santos MF, Natour J. Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: a randomized double-blind controlled study. Clin Exp Rheumatol. 2009;27:214.
- 56 Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheumatol. 1991;34:505-514.
- 57 Foster NE, Anema JR, Cherkin D, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet. 2018;391:2368-2383.
- 58 Burton AK, Waddell G, Tillotson KM, Summerton N. Information and advice to patients with back pain can have a positive effect: a randomized controlled trial of a novel educational booklet in primary care. Spine. 1999;24:2484.

- 59 Krekoukias G, Gelalis ID, Xenakis T, Gioftsos G, Dimitriadis Z, Sakellari V. Spinal mobilization vs conventional physiotherapy in the management of chronic low back pain due to spinal disk degeneration: a randomized controlled rial. *J Man Manip Ther*. 2017;25:66–73.
- 60 Runhaar J, Bierma-Zeinstra SMA. Should exercise therapy for chronic musculoskeletal conditions focus on the anti-inflammatory effects of exercise? *Br J Sports Med*. 2017;51:762–763.
- **61** Runhaar J, Deroisy R, van Middelkoop M, et al. The role of diet and exercise and of glucosamine sulfate in the prevention
- of knee osteoarthritis: further results from the Prevention of Knee Osteoarthritis in Overweight Females (PROOF) study. *Semin Arthritis Rheum.* 2016;45:S42–S48.
- **62** de Schepper EIT, Damen J, Bos PK, Hofman A, Koes BW, Bierma-Zeinstra SM. Disk degeneration of the upper lumbar disks is associated with hip pain. *Eur Spine J.* 2013;22: 721–726.
- **63** Dorleijn DMJ, Luijsterburg PAJ, Bierma-Zeinstra SMA, Bos PK. Is anesthetic hip joint injection useful in diagnosing hip osteoarthritis? A meta-analysis of case series. *J Arthroplasty*. 2014;29:1236, e1231–1242.