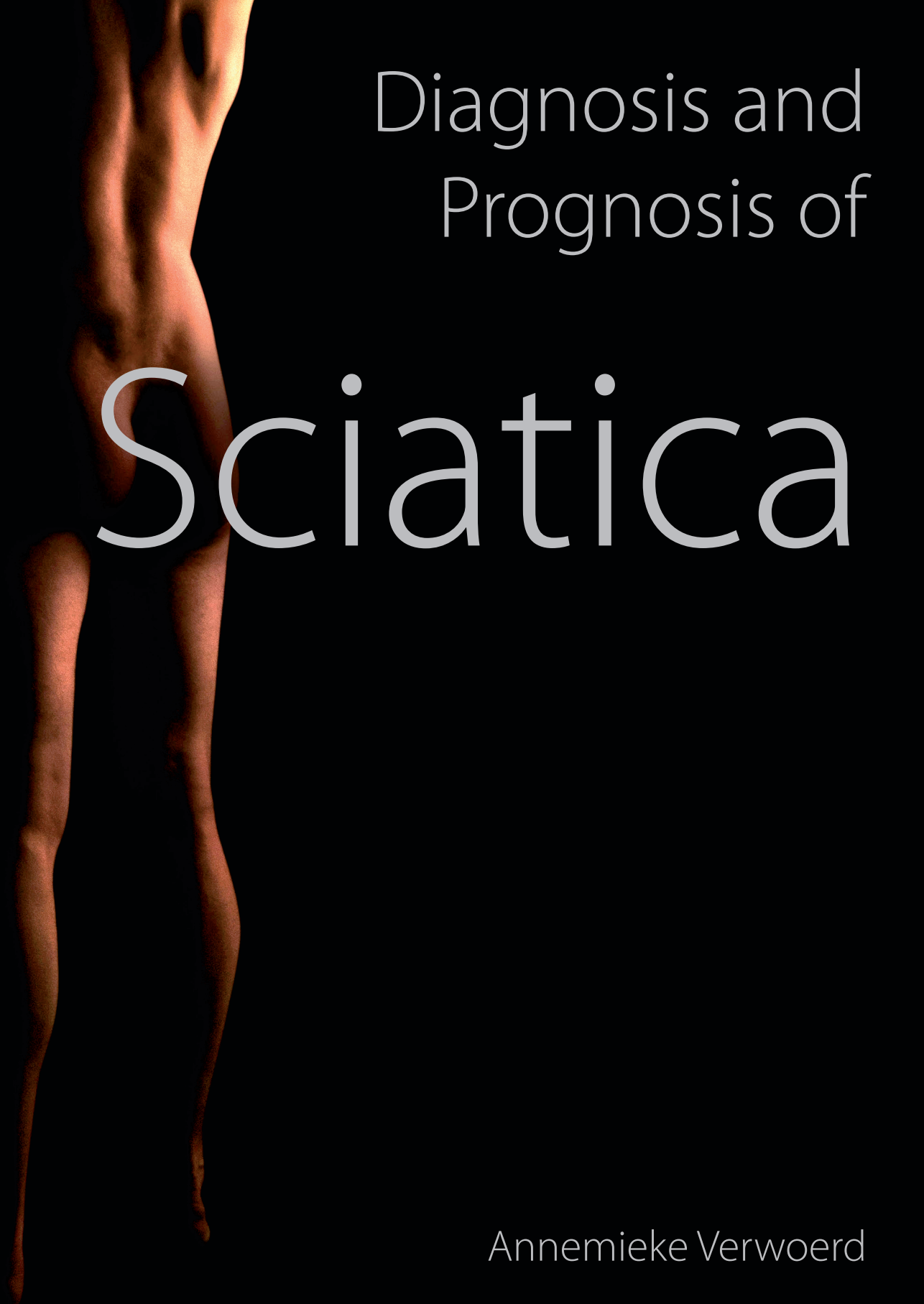

Diagnosis and Prognosis of Sciatica

Annemieke Verwoerd

Diagnosis and Prognosis of **Sciatica**

Annemieke (J.H.) Verwoerd

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Diagnose en prognose van het **lumbosacraal radiculair syndroom**

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1.
General introduction.

INTRODUCTION

Many different terms are used to describe radiating leg pain associated with back pain. Examples include sciatica, radiculopathy, sciatic neuralgia and lumbosacral radicular syndrome. Although the International Association for the Study of Pain (IASP) tried to accurately define all these terms,[1] it appears that many of them are used inconsistently and, sometimes, interchangeably. Therefore, more insight is needed into the terminology used to describe leg pain associated with back pain. The term 'sciatica' seems to be used most frequently and is often defined as intense leg pain in an area served by one or more spinal nerve roots and, occasionally, accompanied by neurological deficit.[2] Therefore, in this thesis we mainly use the term 'sciatica'. Sciatica is one of the most common lumbar spine disorders with a lifetime incidence of 12-40%[3] and associated with significant morbidity. Moreover, certainly in industrialized countries, back problems rank as one of the most costly and ubiquitous medical problems.[4]

ETIOLOGY AND PATHOGENESIS

The neurological syndrome of sciatica was already recognized in ancient times and many etiological explanations for sciatica have been proposed. However, it was not until 1934 that Mixter and Barr asserted that sciatica was caused by a herniated disc pressing against a nerve root.[5] Last decades, there is increasing evidence that mechanical pressure may not be the sole explanation of sciatica. Many patients with sciatica have no disc herniation on magnetic resonance imaging (MRI) and many patients with disc herniation on MRI do not have clinical symptoms.[6,7] Biochemical evidence for an inflammatory process has been observed in several studies.[8-11] Recent studies support the theory of a multifactorial etiologic origin in which spinal nerve irritation may result from compressive and non-compressive etiologies.[8]

DIAGNOSIS

The diagnosis of sciatica is mainly based on history taking and physical examination. A recent Cochrane review on physical examination for lumbar radiculopathy due to disc herniation showed poor diagnostic accuracy of most physical tests when used in isolation.[12] A more prominent role in diagnosing sciatica is ascribed to history taking.[13] However, few studies have examined the diagnostic accuracy of the various items of history taking.[13-15] One of these studies tried to develop a diagnostic model and subsequently determined the performance of this model by the area under the curve (AUC) of

the receiver operating characteristic analysis.[13] An AUC of 0.80 (indicating good discrimination) was found for the diagnostic model of history items ('age', 'duration of disease', 'paroxysmal pain', 'pain worse in leg than in back', 'typical dermatomal distribution', 'pain worse on coughing, sneezing or straining'), which only increased to 0.83 when items from physical examination ('finger-floor distance' and 'paresis') were added. However, validation (internal and external) of a model is necessary before any reliable clinical implications can made - and this model has not yet been validated.[16]

IMAGING

When severe symptoms persist after 6-8 weeks, patients may receive MRI. Imaging in patients with sciatica is essential when alarming symptoms (so-called 'red flags' such as an indication for infection, cancer or cauda equina syndrome) are present or when surgery is considered. The role of imaging in sciatica for other indications is controversial. For example, a high prevalence of lumbar disc herniations (range: 28-76%) has been demonstrated in persons without any symptoms.[7,17] Furthermore, one study showed that in patients treated for sciatica and lumbar disc herniation, MRI at 1-year follow-up could not distinguish between patients with a favorable and those with an unfavorable outcome.[18]

PROGNOSIS

The natural course in patients with sciatica is generally favorable, with improvement of symptoms in about 75% of patients within 3 months.[19,20] Although several studies tested the prognostic value of clinical symptoms in patients with sciatica, a clear and complete overview of the literature is still lacking.[21,22] In these studies, although some clinical symptoms (e.g. age; more pain on coughing, sneezing or straining) did predict clinical outcome, the results were not validated in other (subsequent) studies.[19,23,24] Very few studies have investigated whether MRI findings have prognostic value.[23-27] Thus, there is a need for a clear overview of prognostic factors in patients with sciatica.

TREATMENT

The vast majority of patients with sciatica are treated successfully in primary care with conservative treatment, such as giving information and advice about sciatica, and prescription of non-opioid medication. If no alarming symptoms are present, there is

broad consensus that treatment should be conservative for (at least) the first 6-8 weeks.[2] Several conservative treatments for sciatica are available and systematic reviews have evaluated the effect of most of these conservative treatments. In summary, these reviews concluded that the effect of pain medication is still unclear,[28] that there is some evidence for a lack of effect of supervised exercise programs,[29] and that epidural corticosteroid injections seem to offer only a small amount of short-term relief of leg pain and disability in patients with sciatica.[30] In addition, surgery gives a faster recovery compared to prolonged conservative care in patients with severe sciatica of 6-12 weeks duration, but without significant differences at 1-year follow-up.[31,32]

The best sequential management pathway of sciatica is not yet established. However, (although not fully evidence-based) from a clinical viewpoint it seems feasible to start the treatment of patients with sciatica by: i) informing them about the diagnosis and its favorable course, ii) advising them to stay active, and iii) to use non-opioids as the first-line pain medication. Patients whose pain is controlled in a manner acceptable to them, may be advised to postpone surgery beyond the period of 6-8 weeks as they have a good probability to recover without undergoing surgery. Nevertheless, because the best timing and order of treatment for patients with sciatica is based on limited evidence, shared decision-making between well-informed patients and their physicians should be the mainstay during the treatment.[33-35]

A shift from a 'one-size fits all' approach, where heterogeneous groups of patients receive broadly similar treatments, towards targeted treatments according to prognostic profiles or specific characteristics, may help to improve the treatment results.[36] Kinesiophobia (an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury[37]) might be such a specific characteristic: a study that included 466 patients with sciatica, showed that kinesiophobia was associated with non-success at 2-year follow-up.[38]

STUDY AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to reveal unknown elements related to the diagnosis and prognosis of sciatica. In the last decades new data on different clinical aspects of sciatica have emerged. **Chapter 2** summarizes this evidence in a narrative review. **Chapter 3** systematically reviews how radiating leg pain is defined in randomized controlled trials of conservative treatments in primary care: the rationale for this latter study is that many terms are used to describe radiating leg pain or symptoms associated with back pain and that these terms are used inconsistently and (sometimes) interchangeably.

Although the diagnosis of sciatica is based on history taking and physical examination, little is known about the diagnostic accuracy of the history items. **Chapter 4** reports on the diagnostic accuracy of history taking for the presence of lumbosacral nerve root compression or disc herniation on MRI in 395 patients with severe sciatica. **Chapter 5** presents a short report about whether differences in location of the worsening of pain (back and/or leg) on coughing, sneezing and straining, influences the diagnostic accuracy of this history item.

Although validated questionnaires are used on a regular basis in research and healthcare studies, their administration and completion is often time-consuming. **Chapter 6** investigates whether a single question can be used among patients with sciatica to predict outcome at 1-year as accurately as validated (but more extensive) questionnaires on kinesiophobia, disability, or health-related quality of life. Higher levels of kinesiophobia seem to be associated with poor recovery. **Chapter 7** describes the effect of physical therapy on the relationship between kinesiophobia at baseline and outcome in patients with sciatica in primary care.

Identification of prognostic factors in patients with sciatica is important to improve understanding of the clinical course, to inform patient and physician, to support decision-making, and to be able to predict the need for surgery in an early stage. **Chapter 8** systematically reviews prognostic factors predicting outcome in non-surgically treated patients with sciatica. MRI findings may have prognostic value in patients with intense sciatica and intuitively helps to identify subgroups of patients that might derive more benefit from either early surgery or a strategy of prolonged conservative care. **Chapter 9** reports on the prognostic value of MRI variables to predict outcome at follow-up in patients with severe sciatica and whether MRI facilitates the decision-making regarding early surgery versus prolonged conservative care.

Chapter 10 discusses the results of the studies present here and the implications for future research. Finally, **Chapter 11** presents a summary of this dissertation.

REFERENCES

1. Merskey, H., and N. Bogduk, *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* 1994: International Assocation for the Study of Pain / IASP Press.
2. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
3. Stafford, M.A., P. Peng, and D.A. Hill, *Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management.* Br J Anaesth, 2007. **99**(4): p. 461-73.
4. Dagenais, S., J. Caro, and S. Haldeman, *A systematic review of low back pain cost of illness studies in the United States and internationally.* Spine J, 2008. **8**(1): p. 8-20.
5. Mixter, W.J., and J.S. Barr, *Rupture of the Intervertebral Disc with Involvement of the Spinal Canal.* N Engl J Med 1934. **211**: p. 210-215.
6. El Barzouhi, A., et al., *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PLoS One, 2013. **8**(7): p. e68411.
7. Jensen, M.C., et al., *Magnetic resonance imaging of the lumbar spine in people without back pain.* N Engl J Med, 1994. **331**(2): p. 69-73.
8. Cuellar, J.M., et al., *Cytokine expression in the epidural space: a model of noncompressive disc herniation-induced inflammation.* Spine (Phila Pa 1976), 2013. **38**(1): p. 17-23.
9. de Souza Grava, A.L., L.F. Ferrari, and H.L. Defino, *Cytokine inhibition and time-related influence of inflammatory stimuli on the hyperalgesia induced by the nucleus pulposus.* Eur Spine J, 2012. **21**(3): p. 537-45.
10. Genevay, S., et al., *Elevated levels of tumor necrosis factor-alpha in periradicular fat tissue in patients with radiculopathy from herniated disc.* Spine (Phila Pa 1976), 2008. **33**(19): p. 2041-6.
11. Tufan, K., et al., *Comparison of E-selectin and the other inflammatory markers in lumbar disc herniation: a new promising therapeutical window for radicular pain.* J Spinal Disord Tech, 2012. **25**(8): p. 443-6.
12. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
13. Vroomen, P.C., et al., *Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression.* J Neurol Neurosurg Psychiatry, 2002. **72**(5): p. 630-4.
14. Coster, S., S.F. de Bruijn, and D.L. Tavy, *Diagnostic value of history, physical examination and needle electromyography in diagnosing lumbosacral radiculopathy.* J Neurol, 2010. **257**(3): p. 332-7.
15. Vucetic, N., et al., *Diagnosis and prognosis in lumbar disc herniation.* Clin Orthop Relat Res, 1999. **Apr**(361): p. 116-22.
16. Steyerberg, E.W., *Clinical prediction models: A practical approach to development, validation, and updating.* 2009: Springer-Verlag New York Inc.
17. Boos, N., et al., *1995 Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations.* Spine (Phila Pa 1976), 1995. **20**(24): p. 2613-25.
18. el Barzouhi, A., et al., *Magnetic resonance imaging in follow-up assessment of sciatica.* N Engl J Med, 2013. **368**(11): p. 999-1007.
19. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-23.
20. Weber, H., I. Holme, and E. Amlie, *The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam.* Spine (Phila Pa 1976), 1993. **18**(11): p. 1433-8.

21. Ashworth, J., K. Konstantinou, and K.M. Dunn, *Prognostic factors in non-surgically treated sciatica: a systematic review.* BMC Musculoskelet Disord, 2011. **12**: p. 208.
22. Pengel, L.H., et al., *Acute low back pain: systematic review of its prognosis.* BMJ, 2003. **327**(7410): p. 323.
23. Peul, W.C., et al., *Influence of gender and other prognostic factors on outcome of sciatica.* Pain, 2008. **138**(1): p. 180-91.
24. Vroomen, P.C., J.T. Wilmink, and M.C. de Krom, *Prognostic value of MRI findings in sciatica.* Neuroradiology, 2002. **44**(1): p. 59-63.
25. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
26. Peul, W.C., et al., *Improving prediction of "inevitable" surgery during non-surgical treatment of sciatica.* Pain, 2008. **138**(3): p. 571-6.
27. Valls, I., et al., *Factors predicting radical treatment after in-hospital conservative management of disk-related sciatica.* Joint Bone Spine, 2001. **68**(1): p. 50-8.
28. Pinto, R.Z., et al., *Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis.* BMJ, 2012. **344**: p. e497.
29. Lewis, R.A., et al., *Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses.* Spine J, 2013.
30. Pinto, R.Z., et al., *Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis.* Ann Intern Med, 2012. **157**(12): p. 865-77.
31. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
32. Jacobs, W.C., et al., *Surgery versus conservative management of sciatica due to a lumbar herniated disc: a systematic review.* Eur Spine J, 2011. **20**(4): p. 513-22.
33. Deyo, R.A., et al., *Involving patients in clinical decisions: impact of an interactive video program on use of back surgery.* Med Care, 2000. **38**(9): p. 959-69.
34. Phelan, E.A., et al., *Helping patients decide about back surgery: a randomized trial of an interactive video program.* Spine (Phila Pa 1976), 2001. **26**(2): p. 206-11;discussion 212.
35. Veroff, D., A. Marr, and D.E. Wennberg, *Enhanced support for shared decision making reduced costs of care for patients with preference-sensitive conditions.* Health Aff (Millwood), 2013. **32**(2): p. 285-93.
36. Konstantinou, K., et al., *Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol.* BMC Musculoskelet Disord, 2012. **13**: p. 4.
37. Kori, S.H., R.P. Miller, and D.D.Todd, *Kinesophobia: a new view of chronic pain behaviour.* Pain Manage, 1990. **Jan/Feb**: p. 35-43.
38. Haugen, A.J., et al., *Prognostic factors for non-success in patients with sciatica and disc herniation.* BMC Musculoskelet Disord, 2012. **13**: p. 183.

2.
Sciatica: a clinical review.

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(Submitted for publication)

ABSTRACT

Sciatica is a common neurological spine disease with significant disability. This clinical review discusses the literature on new developments. Recent studies support the theory of a multifactor etiologic origin in which spinal nerve irritation may result from compressive and non-compressive etiologies.

It is not known which combination of history items and physical examination tests most accurately predict the presence of a disc herniation on Magnetic Resonance Imaging (MRI). Discussion is ongoing regarding the role of MRI in sciatica. The role of MRI is essential for patients with alarming symptoms and for patients who are potential candidates for lumbar disc surgery, but seems to have limited value for other indications in sciatica.

About 75% of patients with sciatica improve within 3 months. In the absence of alarming symptoms, treatment should be conservative in at least the first 6-8 weeks. The best sequential management pathway of sciatica is insufficiently researched. The level of evidence of most conservative treatments is limited. Systematic reviews show short-term effects for some non-surgical treatment options (non-opioid medication, epidural injection), but most conservative treatments (bed rest, exercise therapy) do not show effectiveness. Early surgery fastens recovery as compared to prolonged conservative care with possible delayed surgery in patients who are surgical candidates, but without important differences in long-term outcome between these two approaches. More research is needed to identify subgroups of patients with different prognostic profiles, as treatment results are unsatisfactory in 15 up to even 40% of the patients. More research is also needed concerning new and potentially promising developments such as the potential effects of biological agents. For now, shared decision making between well-informed patients and their physicians should determine the individual treatment strategy.

Key summary points

- Recent studies support the theory of a multifactor etiologic origin of sciatica in which spinal nerve root irritation may result from compressive and non-compressive etiologies.
- No adequate set of history items and physical examination tests are known that can accurately predict the presence of a disc herniation on Magnetic Resonance Imaging (MRI).
- The role of MRI seems at present only essential for patients who are candidates for lumbar disc surgery, and for patients with alarming symptoms.
- The best sequential management pathway of sciatica is insufficiently researched.
- If there are no alarming symptoms present, there is consensus that treatment should be conservative in at least the first 6 to 8 weeks.
- Surgery fastens recovery as compared to conservative care, but without differences in long term outcome between these two approaches.
- Research is needed to identify subgroups of patients with different prognostic profiles to improve treatment results.

INTRODUCTION

Sciatica refers to back-related leg pain and is defined as intense leg pain in an area served by one or more spinal nerve roots and is occasionally accompanied by neurological deficit.[1] Sciatica is one of the most common lumbar spine disorders with a life time incidence of 12 to 40%.[2] It is associated with significant morbidity. Back problems rank, certainly in the industrialized countries, as one of the most costly and ubiquitous medical problems.[3] The neurological syndrome of sciatica has been recognized since ancient times and many etiological explanations for sciatica have been proposed. However, it was until 1934 that Mixter and Barr revolutionized the understanding of sciatica.[4,5] They asserted that sciatica was caused by a herniated disc pressing against a nerve root.[4] Their report greatly influenced medical thinking at the time, ushering in a greater interest in the (herniated) lumbar disc as a source of sciatica and in the surgical treatment of such a disorder.[6] In fact the report caused a change in clinical management of severe and persistent sciatica in which surgery took a more prominent role.[7,8]

Nowadays, many terms exist to describe radiating leg pain associated with back pain of which the non-specific term sciatica is mostly used.[9] However, no nomenclature on radiating leg pain associated with back pain has been widely recognized as authoritative or has been widely accepted in clinical practice. Especially the border between specific and nonspecific pain syndromes is rather vague. Many health care disciplines are involved in the treatment of sciatica and the number of proposed interventions is overwhelming. The vast majority of patients with sciatica are treated successfully in primary care with conservative treatment. Figure 1 shows a flow chart of the current medical route of patients with sciatica without alarming symptoms. During recent decades the literature is enriched with evidence discussing different clinical aspects of sciatica. This review aims to summarize this evidence.

ETIOLOGY AND PATHOGENESIS

A study published in 1989 among 9365 adult twin pairs stated an estimated heritability of 20.8% for self-reported sciatica (study participants were asked whether they had ever been told by a doctor that they had sciatica).[10] A larger hereditary role is ascribed to disc degeneration.[11] A recent systematic review evaluating genetic associations in lumbar disc degeneration on Magnetic Resonance Imaging (MRI) noted multiple polymorphisms in genes to be related with the development of lumbar disc degeneration, but mostly with a weak level of evidence.[12] The weak level of evidence was due to variation in study designs, sampling methods, populations and definitions of lumbar

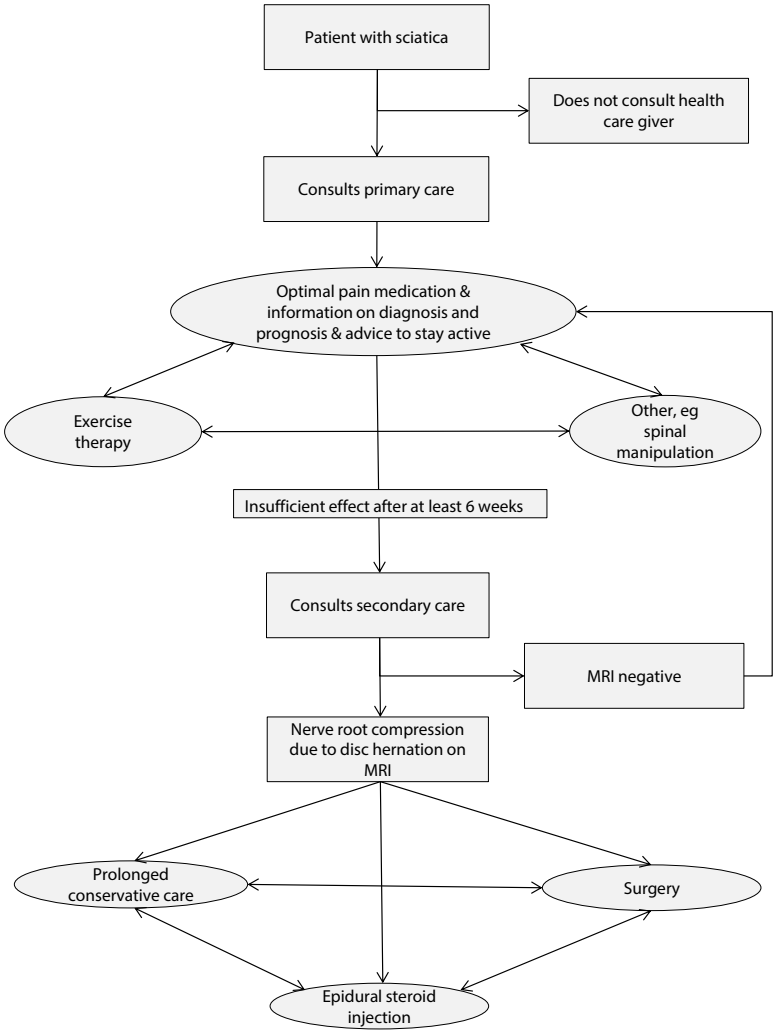


Figure 1. Flow chart of current medical route of patients with sciatica without alarming symptoms

disc degeneration phenotypes. Therefore, the authors recommended further evaluation in large population-based cohorts and clear definitions of lumbar disc degeneration phenotypes.

During recent decades, mechanical pressure of the disc material on the nerve root was widely accepted as the most important etiologic pathway of sciatica. However, evidence increasingly shows that mechanical pressure may not be the sole explanation of sciatica. In fact, soon after the landmark paper, Mixter and Ayers demonstrated in 1935 that

sciatica can occur without disc herniation, arising the question whether the mechanical compression is the only origin of pain in sciatica.[13] Later various studies showed that many patients with sciatica have no disc herniation on MRI and many patients have disc herniations on MRI without having any symptoms.[14,15] In the late 1940s and early 50s hypotheses were developed about other non-mechanical causes of sciatica and some hypothesized that inflammation may play an important role in the etiology of sciatica.[16,17] In the next decades, biochemical evidence for inflammation was observed in several studies.[18-22] Multiple cytokines have been described to be involved in the biochemical process, of which the TNF-α (Tumor Necrosis Factor α) is best known.[22] Recent studies support the theory of a multifactorial etiologic origin in which spinal nerve irritation may result from compressive and non-compressive etiologies.[23]

Recently, the theory on the causative influence of the bacteria propriones acnes on low back pain accompanying sciatica received much attention. Several studies have shown an association between this low virulent anaerobic bacteria and sciatica related low back pain.[6,24] In support is a recently conducted randomized controlled trial among 162 patients with chronic low back pain of greater than 6 months duration occurring after a previous disc herniation (47% of these patients had undergone surgery for disc herniation) and who also had bone edema demonstrated as Modic type 1 changes in the vertebrae adjacent to the previous herniation.[25] Patients were randomized to 100 days of antibiotic treatment (amoxicillin–clavulanate) or placebo. Patients who received the antibiotic treatment improved significantly more compared to those who received placebo with regard to both disability and low back pain. However, this study was performed in a small and specific subgroup of patients and results need to be replicated in other studies. Next to applause, the study also received criticism due to these limitations and a media launch based on this single study.[26]

DIAGNOSIS

The diagnosis of sciatica is mainly based on history taking and physical examination. Only a few well-designed studies have been performed on the diagnostic accuracy of history taking and physical examination for the diagnosis of sciatica. History items and physical examination items used in isolation generally show a poor diagnostic accuracy for detecting lumbar disc herniation and attempts to develop a clinically relevant and valid diagnostic model were unsuccessful up to now.[27,28] Although in daily clinical practice history items and physical examination tests are combined to diagnose sciatica, only a few studies tried to develop a diagnostic model consisting of these items.[29-31] Furthermore, with one exception, all studies on the diagnostic accuracy of history

items and physical examination test are performed in secondary care, where patients usually receive MRI. These studies are more prone to selection and verification bias (sciatica patients in secondary care are more likely to be surgical candidates). Studying the diagnostic accuracy of history items and physical examination tests is actually more interesting for primary care as decisions on the need for referral to secondary care and imaging are made in primary care. More good quality prospective research on diagnostic models in large primary care populations are needed to give more insight in the optimal diagnostic trajectory for patients with sciatica.

IMAGING

In recent decades techniques for spine imaging have improved considerably and are still improving.[32] Imaging in patients with sciatica is essential when alarming symptoms (so called 'red flags' like an indication for infection, cancer or cauda equina syndrome) are present and when surgery is considered. The role of imaging in sciatica for other indications is controversial. Despite MRI being regarded as the imaging procedure of choice for patients with sciatica who are surgical candidates because of a suspected lumbar disc herniation, a recent systematic review concluded that evidence for the diagnostic accuracy of MRI for detecting lumbar disc herniation compared to findings at surgery is not conclusive.[33] A scientific debate on the clinical relevance of MRI morphological variations is ongoing as several studies showed a high prevalence of lumbar disc abnormalities, ranging from 20 to 76%, in persons without any symptoms.[15,34] Besides, interpretation variation between observers may introduce bias.[14,35] A recent study, in contrast to earlier expert's opinions, also showed that MRI is not able to predict the subgroup of patients with future need of surgery in patients with sciatica who were, although surgical candidates, initially subjected to conservative care.[36] Therefore, the role of MRI seems at present limited to depict the anatomical features and the level of a herniated disc, necessary for the surgical technical approach, and seems not suitable as a prognostic tool in the shared decision-making discussion for surgery versus conservative care.

Physicians often order repeat MRI studies for patients with persistent or recurrent symptoms of sciatica.[37] However, a recently published article showed that MRI at 1-year follow-up could not distinguish patients with favorable from those with unfavorable outcome.[38,39] Other studies have reported similar results.[40,41] An interesting finding was also that in the majority of patients their disc herniations disappear or reduce in size over time without any surgery. Therefore, the role of repeated MRI in persistent sciatica seems limited to patients for whom surgery is considered months after the initial MRI (to

verify if a disc herniation with nerve root compression is still present) and when alarming symptoms appear.

Wanting diagnostic certainty is a frequent reason for repeated office visits of patients with chronic low back pain or sciatica.[42] Many patients believe that the more diagnostics tests performed the higher the quality of care.[43] The rates of spinal surgery have also increased dramatically over the past 20 years, which has for a significant part been linked to the increased availability of advanced imaging techniques.[44-47] Many physicians admit they succumb to their patients who are asking for spine imaging.[48] However, spine imaging may have an adverse effect as telling patients that they have an imaging abnormality could result in unintended harms related to disease labeling.[49,50] Multiple randomized controlled trials showed that patient's knowledge of imaging findings did not positively alter outcome and even may introduce iatrogenic effects.[51,52] Patient education about the limits of spine imaging may help to bring patient's expectations more in line with the evidence.

PROGNOSIS

The natural course in patients with sciatica is generally favorable with improvement of symptoms in about 75% of patients within 3 months.[53,54] Two recent systematic reviews found that evidence on prognostic factors predicting the outcome of non-surgically treated sciatica is sparse and heterogeneous.[55,56] Only high leg pain intensity seems to predict subsequent surgery.[56] Besides surgery, other outcomes reviewed were pain, disability and recovery. No association with recovery could be found for age, body mass index, smoking, increase on coughing/sneezing/straining, pain on sitting, slowly start of symptoms, leg pain intensity, sensory disturbance, Kemp's sign and finger-floor distance.[56] Other factors revealed limited, inconclusive or no evidence. Surprisingly, psychological factors, usually thought to predict outcome, are rarely investigated.[55,57]

TREATMENT

If there are no alarming symptoms present, there is broad consensus that treatment should be conservative in at least the first 6 to 8 weeks.[1] Several conservative treatments for sciatica exist, ranging from information on the favorable natural course, to analgesics and guided exercise. Recently, the clinical effectiveness of different treatment strategies for sciatica was compared in a systematic review and network meta-analysis.[58] Studies up to December 2009 were included. A network meta-analysis compares multiple treat-

ments using both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials that have only one intervention in common. The results of this comprehensive overview should therefore be interpreted with the knowledge of (potential) important bias due to violation of the key assumption that the relative treatment effect of one treatment versus another is the same across the entire set of studies.[59] Besides, the small number of relevant studies for some comparisons and the heterogeneity between studies give rise to interpret results with caution. The meta-analysis showed effectiveness of non-opioid medication, epidural injection and disc surgery as compared to inactive control or conventional care (like general practitioners' care).[58]

Exercise therapy

The previously mentioned network meta-analysis did not find support for the effectiveness of bed rest, opioid analgesia, traction or exercise therapy.[58] The recently published clinical guideline of the North American Spine Society also stated that insufficient evidence exists regarding the use of structured exercise programs as stand-alone treatments, but also mentions the option of a limited course of structured exercise for patients with mild to moderate symptoms.[60] The common message of other clinical guidelines for acute and subacute low back pain (of which some include the treatment of sciatica) is not to advice a supervised exercise therapy but to advice to stay as active as possible, to progressively increase activity levels and to return to work as soon as possible.[61,62] Although not fully evidence-based, the common advice to stay active and to return to work as soon as possible is broadly accepted.

Pain medication

Besides pain reduction as primary goal to improve wellbeing, pain reduction is also assumed to facilitate activity. A systematic review (inclusion up to 15 March 2010, with only partial overlap of included studies compared with the previously mentioned network meta-analysis) concluded that there is at best only low quality evidence to guide the prescription of drugs commonly prescribed for the management of sciatica.[63] Still, from a clinical and safety point of view it seems reasonable to start the initial treatment with non-opioids with a thorough monitoring of the patient's pain relief. From a cost-effectiveness point of view, it is also recommended to start with non-opioids.[64] An individual patient approach seems required, as pain mechanisms are complex (nociceptive and neuropatic pain) in patients with sciatica.

Biological agents

Attention to the potential effects of biological agents is rising, particularly for TNF-α inhibitors. Although non-significant in the network meta-analysis, the largest odds ratio

for global effect (treatment success versus failure) was found for biological agents.[58] TNF-α is an inflammatory factor involved in the pathophysiology of sciatica due to a herniated disc.[22] A systematic review on biological agents targeting TNF-α (search up to February 2012) concluded that there is insufficient evidence to recommend these agents as heterogeneity may have biased the results and statistically significant changes were only observed when non-randomized studies were included.[65] A recent update of this systematic review (4 additional studies, search up to July 2013) found that other than reducing the risk ratio for the need of discectomy or radicular block (combined endpoint) at medium-term follow-up, TNF- α inhibitors had only limited clinical value in the treatment of sciatica.[66] Results were limited because of the small sample sizes and inconsistent follow-up durations of the included studies. The observed adverse reactions were mild or not related to the use of TNF-α inhibitors (three serious adverse reactions were reported). A subsequent published well-conducted phase IIa clinical trial showed a trend for a higher reduction of mean daily worst leg pain for the epidural etanercept group as compared to the placebo group, but the differences were non-significant.[67] Larger phase III trials are needed to make more firm conclusions on the effectiveness of biological agents targeting TNF-α in patients with sciatica.

Epidural corticosteroid injections

The efficacy of epidural corticosteroid injections was also evaluated in another extensive meta-analysis (inclusion up to 27 April 2012, with only partial overlap of included studies compared with the previously mentioned network meta-analysis).[68] This meta-analysis concluded that epidural corticosteroid injections as compared with placebo offer only short-term relief of leg pain and disability for patients with sciatica. However, given the small size of treatment effect, the authors raised questions about the clinical utility of epidural corticosteroid injections.[68] Transforaminal epidural steroid injections to provide short-term (2-4 weeks) pain relief are recommended in the recently published clinical guideline for lumbar disc herniation with radiculopathy of the North American Spine Society.[60] The references of this recommendation concerns two studies that are also included in the previously mentioned meta-analysis on epidural corticosteroid injection.[68]

Surgery

Back surgery rates differ widely among countries and even within a country.[44,69] Contrary to what one might expect given the advancements in diagnostic imaging and surgical techniques, the results of lumbar disc surgery do not seem to have improved during recent decades. During longer follow-up, 15 up to even 40% of the patients do show recurring or persistent complaints after a first episode of sciatica regardless of having received surgical or nonsurgical treatment.[70-72] In 2006 and 2007, results of two major randomized controlled trials were published adding to our knowledge regarding the

role and the optimal timing of surgery for sciatica as compared to conservative care.[73,74] In the SPORT study (Spine Patient Outcomes Research Trial) 501 patients with imaging-confirmed lumbar disk herniation and persistent signs and symptoms of sciatica for at least 6 weeks were randomized to surgery or conservative treatment. The authors observed improvements in favor of surgery but differences were small and statistically non-significant. However, this study was limited by a substantial crossover resulting in a difference in surgery rates of only 14% at 6 weeks. Furthermore, only 59% of patients assigned to surgery actually underwent surgery during the first year of follow-up.[74] In the Sciatica Trial 283 patients with imaging-confirmed lumbar disk herniation and severe sciatica for 6 to 12 weeks were randomized to early surgery or to prolonged conservative treatment with surgery if needed. The trial showed faster recovery after early surgery as compared to a strategy of prolonged conservative care, but there were no significant differences in clinical outcomes after one, two and five years.[72,73,75] However, of those assigned to prolonged conservative care, 39% underwent surgery during the first year. Furthermore, surgery performed earlier than a symptom duration of 8-12 months is associated with a more favorable outcome compared to surgery after 8-12 months.[76-78]

RECOMMENDATIONS BASED ON RECENT LITERATURE

The role of MRI seems at present limited for patients with alarming symptoms and for patients who are candidates for surgery. Clinicians should be more cautious in requesting MRI for patients with persistent or recurrent symptoms of sciatica as it is difficult to relate anatomical abnormalities visible on MRI to persistent or recurrent symptoms of sciatica.[38] The mindset of patients and physicians that more imaging testing means better care should be abandoned in favor of a more evidence-based approach.[79] For example, adding epidemiologic information to lumbar spine MRI reports regarding findings in asymptomatic persons may assist in a better understanding of imaging results.[80] Patients asking for reimaging because of persistent or recurrent symptoms of sciatica should be informed about the difficulty in MRI interpretation.

The best sequential management pathway of sciatica is still insufficiently investigated. If there are no alarming symptoms present, there is consensus that treatment should be conservative in at least the first 6 to 8 weeks. There is some evidence of a lack of effect of supervised exercise programs, but it is broadly accepted to advice to stay active. Biological agents or antibiotics should not (yet) be prescribed in the treatment of sciatica as evidence for clinical usage of these agents is too limited. Based on the current evidence and clinical experience it seems reasonable to start the treatment of patients with sciatica by informing the patient on the diagnosis and its favorable course, to advice to

stay active and to use non-opioids as first-line pain medication with monitoring of pain relief and fast adjustments of pain regimens when necessary. Patients whose pain is controlled in a manner that is acceptable to them may be advised to postpone surgery beyond the period of 6-8 weeks as they have good chances to recover without undergoing surgery. As the best timing and order of treatments for patients with sciatica remain limited evidence-based, shared decision making between well-informed patients and their physicians should be the mainstay during the treatment.[81-83]

FUTURE RESEARCH

More research is needed on the role of inflammatory related pathways in the etiology and pathogenesis of sciatica. Subsequently, robust randomized controlled trials are needed to evaluate medical interventions targeting these pathways.

The optimal management of sciatica seems a difficult question to answer. More research is needed on the role of biological agents and pain medication. More research is also needed to identify subgroups of patients with different prognostic profiles, as treatment results are unsatisfactory in 15 up to even 40% of the patients.[70-72] Future studies should evaluate who benefits more from surgery and who from conservative care. A shift from a "one-size fits all" approach, where heterogeneous groups of patients receive broadly similar treatments, towards targeted treatments according to prognostic profiles or specific characteristics, may help to improve the treatment results.[84] Important considerations for the study design on the management of sciatica should be the recruitment of large study populations and the collection of clinically relevant outcomes.[63]

Finally, consensus on nomenclature on radiating leg pain associated with back pain is lacking. It is worthwhile to consider approaches how to reach more consensus and how to subsequently adhere to one nomenclature as this may prevent miscommunication and ease comparison between studies.

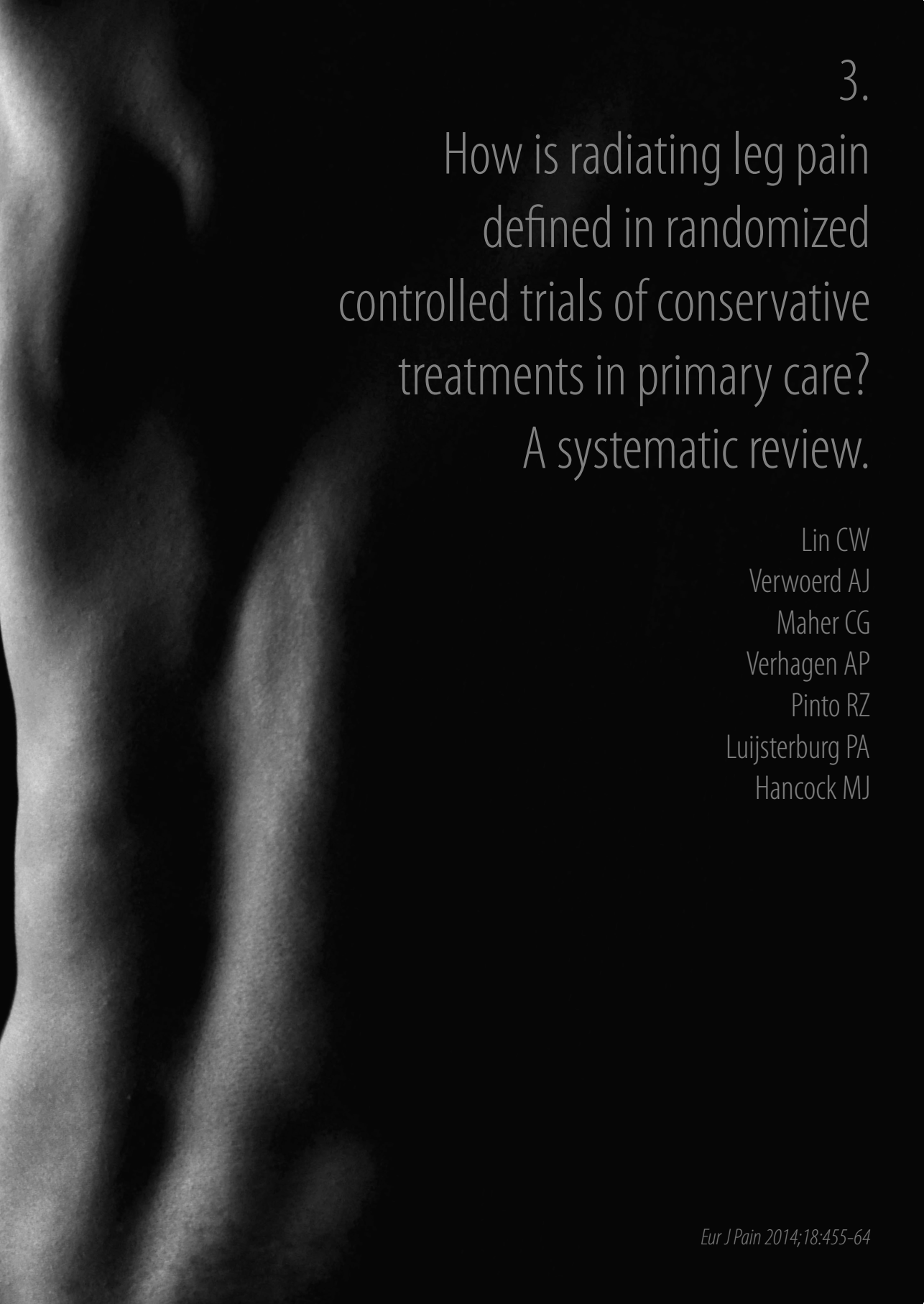
REFERENCES

1. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
2. Stafford, M.A., P. Peng, and D.A. Hill, *Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management.* Br J Anaesth, 2007. **99**(4): p. 461-73.
3. Dagenais, S., J. Caro, and S. Haldeman, *A systematic review of low back pain cost of illness studies in the United States and internationally.* Spine J, 2008. **8**(1): p. 8-20.
4. Mixter, W.J., and J.S. Barr, *Rupture of Intervertebral Disc with Involvement of Spinal Canal.* N Engl J Med 1934. **211**: p. 210-5
5. Robinson, J.S., *Sciatica and the lumbar disk syndrome: a historic perspective.* South Med J, 1983. **76**(2): p. 232-8.
6. Ropper, A.H., *Two centuries of neurology and psychiatry in the Journal.* N Engl J Med, 2012. **367**(1): p. 58-65.
7. Parisien, R.C. and P.A. Ball, *William Jason Mixter (1880-1958). Ushering in the "dynasty of the disc".* Spine (Phila Pa 1976), 1998. **23**(21): p. 2363-6.
8. Allan, D.B. and G. Waddell, *An historical perspective on low back pain and disability.* Acta Orthop Scand Suppl, 1989. **234**: p. 1-23.
9. Lin, C.W., et al., *How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review.* Eur J Pain, 2014. **18**(4): p. 455-64.
10. Heikkila, J.K., et al., *Genetic and environmental factors in sciatica. Evidence from a nationwide panel of 9365 adult twin pairs.* Ann Med, 1989. **21**(5): p. 393-8.
11. Battie, M.C., et al., *The Twin Spine Study: contributions to a changing view of disc degeneration.* Spine J, 2009. **9**(1): p. 47-59.
12. Eskola, P.J., et al., *Genetic association studies in lumbar disc degeneration: a systematic review.* PLoS One, 2012. **7**(11): p. e49995.
13. Mixter, W.J. and J.B. Ayers, *Herniation or rupture of the intervertebral disc into the spinal canal.* N Engl J Med, 1935. **213**: p. 385–395.
14. El Barzouhi, A., et al., *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PLoS One, 2013. **8**(7): p. e68411.
15. Jensen, M.C., et al., *Magnetic resonance imaging of the lumbar spine in people without back pain.* N Engl J Med, 1994. **331**(2): p. 69-73.
16. Lindahl, O. and B. Rexed, *Histologic changes in spinal nerve roots of operated cases of sciatica.* Acta Orthop Scand, 1951. **20**(3): p. 215-25.
17. Kelly, M., *Is pain due to pressure on nerves? Spinal tumors and the intervertebral disk.* Neurology, 1956. **6**(1): p. 32-6.
18. Genevay, S. and C. Gabay, *Is disk-related sciatica a TNFalpha-dependent inflammatory disease?* Joint Bone Spine, 2005. **72**(1): p. 4-6.
19. Valat, J.P., et al., *Sciatica.* Best Pract Res Clin Rheumatol, 2010. **24**(2): p. 241-52.
20. de Souza Grava, A.L., L.F. Ferrari, and H.L. Defino, *Cytokine inhibition and time-related influence of inflammatory stimuli on the hyperalgesia induced by the nucleus pulposus.* Eur Spine J, 2012. **21**(3): p. 537-45.
21. Tufan, K., et al., *Comparison of E-selectin and the other inflammatory markers in lumbar disc herniation: a new promising therapeutical window for radicular pain.* J Spinal Disord Tech, 2012. **25**(8): p. 443-6.
22. Di Martino, A., L. Merlini, and C. Faldini, *Autoimmunity in intervertebral disc herniation: from bench to bedside.* Expert Opin Ther Targets, 2013. **17**(12): p. 1461-70.

23. Cuellar, J.M., et al., *Cytokine expression in the epidural space: a model of noncompressive disc herniation-induced inflammation.* Spine (Phila Pa 1976), 2013. **38**(1): p. 17-23.
24. Stirling, A., et al., *Association between sciatica and Propionibacterium acnes.* Lancet, 2001. **357**(9273): p. 2024-5.
25. Albert, H.B., et al., *Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy.* Eur Spine J, 2013. **22**(4): p. 697-707.
26. McCartney, M., *Antibiotics for back pain: hope or hype?* BMJ, 2013. **346**: p. f3122.
27. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
28. Verwoerd, A.J., et al., *Diagnostic accuracy of history taking to assess lumbosacral nerve root compression.* Spine J, 2014. **14**(9): p. 2028-37.
29. Vroomen, P.C., et al., *Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression.* J Neurol Neurosurg Psychiatry, 2002. **72**(5): p. 630-4.
30. Vucetic, N., et al., *Diagnosis and prognosis in lumbar disc herniation.* Clin Orthop Relat Res, 1999. **Apr**(361): p. 116-22.
31. Coster, S., S.F. de Bruijn, and D.L. Tavy, *Diagnostic value of history, physical examination and needle electromyography in diagnosing lumbosacral radiculopathy.* J Neurol, 2010. **257**(3): p. 332-7.
32. Haughton, V., *Imaging intervertebral disc degeneration.* J Bone Joint Surg Am, 2006. **88 Suppl 2**: p. 15-20.
33. Wassenaar, M., et al., *Magnetic resonance imaging for diagnosing lumbar spinal pathology in adult patients with low back pain or sciatica: a diagnostic systematic review.* Eur Spine J, 2012. **21**(2): p. 220-7.
34. Boos, N., et al., *Natural history of individuals with asymptomatic disc abnormalities in magnetic resonance imaging: predictors of low back pain-related medical consultation and work incapacity.* Spine (Phila Pa 1976), 2000. **25**(12): p. 1484-92.
35. el Barzouhi, A., et al., *Reliability of gadolinium-enhanced magnetic resonance imaging findings and their correlation with clinical outcome in patients with sciatica.* Spine J, 2014. **14**(11): p. 2598-607.
36. el Barzouhi, A., et al., *Predictive value of MRI in decision making for disc surgery for sciatica.* J Neurosurg Spine, 2013. **19**(6): p. 678-87.
37. Lee, Y.S., E.S. Choi, and C.J. Song, *Symptomatic nerve root changes on contrast-enhanced MR imaging after surgery for lumbar disk herniation.* AJNR Am J Neuroradiol, 2009. **30**(5): p. 1062-7.
38. el Barzouhi, A., et al., *Magnetic resonance imaging in follow-up assessment of sciatica.* N Engl J Med, 2013. **368**(11): p. 999-1007.
39. Mushlin, A.I., *ACP Journal Club. In patients with sciatica, MRI at 1 year did not differentiate between a favorable or unfavorable outcome.* Ann Intern Med, 2013. **159**(4): p. JC12.
40. Barth, M., et al., *Two-year outcome after lumbar microdiscectomy versus microscopic sequestrectomy: part 2: radiographic evaluation and correlation with clinical outcome.* Spine (Phila Pa 1976), 2008. **33**(3): p. 273-9.
41. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
42. McPhillips-Tangum, C.A., et al., *Reasons for repeated medical visits among patients with chronic back pain.* J Gen Intern Med, 1998. **13**(5): p. 289-95.
43. Carman, K.L., et al., *Evidence that consumers are skeptical about evidence-based health care.* Health Aff (Millwood), 2010. **29**(7): p. 1400-6.

44. Lurie, J.D., N.J. Birkmeyer, and J.N. Weinstein, *Rates of advanced spinal imaging and spine surgery.* Spine (Phila Pa 1976), 2003. **28**(6): p. 616-20.
45. Jarvik, J.G., et al., *Rapid magnetic resonance imaging vs radiographs for patients with low back pain: a randomized controlled trial.* JAMA, 2003. **289**(21): p. 2810-8.
46. Webster, B.S. and M. Cifuentes, *Relationship of early magnetic resonance imaging for work-related acute low back pain with disability and medical utilization outcomes.* J Occup Environ Med, 2010. **52**(9): p. 900-7.
47. Verrilli, D. and H.G. Welch, *The impact of diagnostic testing on therapeutic interventions.* JAMA, 1996. **275**(15): p. 1189-91.
48. Campbell, E.G., et al., *Professionalism in medicine: results of a national survey of physicians.* Ann Intern Med, 2007. **147**(11): p. 795-802.
49. Fisher, E.S. and H.G. Welch, *Avoiding the unintended consequences of growth in medical care: how might more be worse?* JAMA, 1999. **281**(5): p. 446-53.
50. Webster, B.S., et al., *Iatrogenic consequences of early magnetic resonance imaging in acute, work-related, disabling low back pain.* Spine (Phila Pa 1976), 2013. **38**(22): p. 1939-46.
51. Chou, R., et al., *Imaging strategies for low-back pain: systematic review and meta-analysis.* Lancet, 2009. **373**(9662): p. 463-72.
52. Cohen, S.P., et al., *Effect of MRI on treatment results or decision making in patients with lumbosacral radiculopathy referred for epidural steroid injections: a multicenter, randomized controlled trial.* Arch Intern Med, 2012. **172**(2): p. 134-42.
53. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-23.
54. Weber, H., I. Holme, and E. Amlie, *The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam.* Spine (Phila Pa 1976), 1993. **18**(11): p. 1433-8.
55. Ashworth, J., K. Konstantinou, and K.M. Dunn, *Prognostic factors in non-surgically treated sciatica: a systematic review.* BMC Musculoskelet Disord, 2011. **12**: p. 208.
56. Verwoerd, A.J., et al., *Systematic review of prognostic factors predicting outcome in non-surgically treated patients with sciatica.* Eur J Pain, 2013. **17**(8): p. 1126-37.
57. Haugen, A.J., et al., *Prognostic factors for non-success in patients with sciatica and disc herniation.* BMC Musculoskelet Disord, 2012. **13**: p. 183.
58. Lewis, R.A., et al., *Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses.* Spine J, 2013.
59. Caldwell, D.M., A.E. Ades, and J.P. Higgins, *Simultaneous comparison of multiple treatments: combining direct and indirect evidence.* BMJ, 2005. **331**(7521): p. 897-900.
60. Kreiner, D.S., et al., *An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy.* Spine J, 2014. **14**(1): p. 180-91.
61. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
62. Vroomen, P.C., et al., *Lack of effectiveness of bed rest for sciatica.* N Engl J Med, 1999. **340**(6): p. 418-23.
63. Pinto, R.Z., et al., *Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis.* BMJ, 2012. **344**: p. e497.
64. Fitzsimmons, D., et al., *Cost-effectiveness of different strategies to manage patients with sciatica.* Pain, 2014. **155**(7): p. 1318-27.

65. Williams, N.H., et al., *A systematic review and meta-analysis of biological treatments targeting tumour necrosis factor alpha for sciatica.* Eur Spine J, 2013. **22**(9): p. 1921-35.
66. Wang, Y.F., et al., *Clinical Significance of Tumor Necrosis Factor-alpha Inhibitors in the Treatment of Sciatica: A Systematic Review and Meta-Analysis.* PLoS One, 2014. **9**(7): p. e103147.
67. Freeman, B.J., et al., *Randomized, double-blind, placebo-controlled, trial of transforaminal epidural etanercept for the treatment of symptomatic lumbar disc herniation.* Spine (Phila Pa 1976), 2013. **38**(23): p. 1986-94.
68. Pinto, R.Z., et al., *Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis.* Ann Intern Med, 2012. **157**(12): p. 865-77.
69. Cherkin, D.C., et al., *An international comparison of back surgery rates.* Spine (Phila Pa 1976), 1994. **19**(11): p. 1201-6.
70. Findlay, G.F., et al., *A 10-year follow-up of the outcome of lumbar microdiscectomy.* Spine (Phila Pa 1976), 1998. **23**(10): p. 1168-71.
71. Korres, D.S., G. Loupassis, and K. Stamos, *Results of lumbar discectomy: a study using 15 different evaluation methods.* Eur Spine J, 1992. **1**(1): p. 20-4.
72. Peul, W.C., et al., *Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: two year results of a randomised controlled trial.* BMJ, 2008. **336**(7657): p. 1355-8.
73. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
74. Weinstein, J.N., et al., *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort.* JAMA, 2006. **296**(20): p. 2451-9.
75. Lequin, M.B., et al., *Surgery versus prolonged conservative treatment for sciatica: 5-year results of a randomised controlled trial.* BMJ Open, 2013. **3**(5).
76. Nygaard, O.P., R. Kloster, and T. Solberg, *Duration of leg pain as a predictor of outcome after surgery for lumbar disc herniation: a prospective cohort study with 1-year follow up.* J Neurosurg, 2000. **92**(2 Suppl): p. 131-4.
77. Fisher, C., et al., *Outcome evaluation of the operative management of lumbar disc herniation causing sciatica.* J Neurosurg, 2004. **100**(4 Suppl Spine): p. 317-24.
78. Ng, L.C. and P. Sell, *Predictive value of the duration of sciatica for lumbar discectomy. A prospective cohort study.* J Bone Joint Surg Br, 2004. **86**(4): p. 546-9.
79. Chou, R., et al., *Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians.* Ann Intern Med, 2011. **154**(3): p. 181-9.
80. McCullough, B.J., et al., *Lumbar MR imaging and reporting epidemiology: do epidemiologic data in reports affect clinical management?* Radiology, 2012. **262**(3): p. 941-6.
81. Deyo, R.A., et al., *Involving patients in clinical decisions: impact of an interactive video program on use of back surgery.* Med Care, 2000. **38**(9): p. 959-69.
82. Phelan, E.A., et al., *Helping patients decide about back surgery: a randomized trial of an interactive video program.* Spine (Phila Pa 1976), 2001. **26**(2): p. 206-11;discussion 212.
83. Veroff, D., A. Marr, and D.E. Wennberg, *Enhanced support for shared decision making reduced costs of care for patients with preference-sensitive conditions.* Health Aff (Millwood), 2013. **32**(2): p. 285-93.
84. Konstantinou, K., et al., *Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol.* BMC Musculoskelet Disord, 2012. **13**: p. 4.



3.
How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review.

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ABSTRACT

Many terms exist to describe radiating leg pain or symptoms associated with back pain (e.g., sciatica or radiculopathy) and it appears that these terms are used inconsistently. We examined the terms used to describe, and the eligibility criteria used to define, radiating leg pain in randomized controlled trials of conservative treatments, and evaluated how the eligibility criteria compared to an international pain taxonomy. Eligible studies were identified from two systematic reviews and an updated search of their search strategy. Studies were included if they recruited adults with radiating leg pain associated with back pain. Two independent reviewers screened the studies and extracted data. Studies were grouped according to the terms used to describe radiating leg pain. Thirty-one of the seventy-seven included studies used multiple terms to describe radiating leg pain; the most commonly used terms were sciatica (60 studies) and disc herniation (19 studies). Most studies that used the term sciatica included pain distribution in the eligibility criteria, but studies were inconsistent in including signs (e.g., neurological deficits) and imaging findings. Similarly, studies that used other terms to describe radiating leg pain used inconsistent eligibility criteria between studies and to the pain taxonomy, except that positive imaging findings were required for almost all studies that used disc herniation to describe radiating leg pain. In view of the varying terms to describe, and eligibility criteria to define, radiating leg pain, consensus needs to be reached for each of communication and comparison between studies.

Database?

- Eligible studies were identified from the included studies of two recent systematic reviews.
- These systematic reviews searched Medline, EMBASE, CENTRAL, CINAHL, PsychINFO, PEDro, International Pharmaceutical Abstracts and LILACS, and performed citation tracking of the included studies and relevant reviews.
- In April 2013, we re-ran the searches of the two reviews to capture any new studies.

What does this review add?

- Over one-third of the 77 included studies used multiple terms to describe radiating leg pain; the most commonly used was sciatica.
- There were inconsistencies in the terms used to describe (e.g., sciatica), and eligibility criteria used to define, radiating leg pain and symptoms.
- Across the studies, there was a lack of consistent association between the terms used to describe and the eligibility criteria used to define radiating leg pain, and between the eligibility criteria used by studies and definition of terms provided in an international taxonomy of pain.
- There is a need to reach clear and consistent definitions to facilitate communication in clinical practice and research, e.g., when making treatment recommendations and for comparison between studies.

INTRODUCTION

Sciatica is a severe form of back pain characterized by radiating pain in the leg.[1] Other terms exist to describe radiating leg pain or symptoms associated with back pain, such as radiculopathy, radicular syndrome, nerve root pain and nerve root entrapment. Some of these terms imply a pain source (e.g., nerve root pain) or mechanism (e.g., nerve root entrapment) as the cause of the symptoms. However, it appears that many of these terms are used inconsistently and sometimes interchangeably despite potentially different meanings; e.g., radiating leg pain is referred to as nerve root or radicular pain in the European back pain guidelines[2,3] and sciatica or radiculopathy in the American guidelines.[4]

Attempts have been made to define and distinguish these terms (Table 1). The International Association for the Study of Pain (IASP) recommends that the term sciatica should be abandoned, as the description cannot differentiate different types of radiating leg pain or symptoms.[5] The IASP have defined lumbar *radicular pain* as lancinating leg pain caused by a spinal nerve or its roots, and lumbar *radiculopathy* as loss of sensory and/or motor function occurring in the distribution of a spinal nerve. In this context, *sciatica* may be considered a non-specific term, whereas *radicular pain* or *radiculopathy* relate to specific clinical presentations that may coexist or exist in isolation. Alternatively, some consider radiating leg pain to be a form of neuropathic pain[6], which has been defined by the IASP in its 2011 update as: 'pain caused by a lesion or disease of the somatosensory nervous system' (http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/ PainDefinitions/, accessed 1 March 2013).

Table 1. Descriptions of terms defining radiating leg pain or symptoms from the taxonomy of the International Society for the Study of Pain[5]

	Sciatica	Radicular pain	Radiculopathy
Related to symptoms	Pain that appears to travel along the sciatic nerve	Lancinating pain that travels along a narrow band	Subjective sensations of numbness and weakness, paraesthesia may be present
Related to signs	Nil	Nil	Sensory or motor changes confirmed by neurological examination or electrodiagnostic means
Pathology	Nerve root compression	Lesions that directly compromise the dorsal root ganglion mechanically or indirectly compromise the spinal nerve and its roots by ischemia or inflammation	Lesions that cause conduction block in axons of a spinal nerve or its roots directly by mechanical compression or indirectly by compromising their blood supply and nutrition

Despite attempts to standardize the use of terminology in this field, there are indications that confusion exists[7] and studies of radiating leg pain use varying criteria to define their study population. For example, a review reported that the prevalence of radiating leg pain ranged from 1% to 43%[9]; this wide range was in part due to the varying definitions of radiating leg pain used in individual studies. Genevay et al.[9] showed a wide variation in the eligibility criteria used in trials of two types of radiating leg pain or symptoms: radiculopathy due to disc herniation and neurogenic claudication due to spinal stenosis. However, this review was limited to two-arm trials published in the English language, a narrow population of radiating leg pain and a limited publication period (from 2006 to 2008).

The use of clear terms to describe and define a study population with radiating leg pain or symptoms and consistent eligibility criteria to select patients is essential to prevent miscommunication and to facilitate comparison across research trials. Reviewing the terms and eligibility criteria used in trials of radiating leg pain will provide insights into how consistently these terms and eligibility criteria are used in studies investigating people with radiating leg pain or symptoms. The aims of the current review are to (1) examine the terms used to describe, and eligibility criteria used to define, the population with radiating leg pain or symptoms associated with back pain in randomized controlled trials of conservative treatments conducted in primary care; (2) compare the eligibility criteria between studies using the same term to describe their study population; and (3) compare the eligibility criteria associated with specific terms to the descriptions provided by the IASP taxonomy for those terms.

METHODS

Search strategy

Eligible studies were identified from the included studies of two recent systematic reviews conducted by the authors.[10,11] Both systematic reviews used the search strategy recommended by the Cochrane Back Review Group to search for eligible studies in a number of electronic databases,[12] including MEDLINE, EMBASE and CENTRAL, as well as scanning the reference list of included studies. In addition, we re-ran the search strategies used by the reviews from the last date of search in each review [May 2004[10] and March 2010[11]] to April 2013. The first review investigated the effectiveness of conservative treatments in a primary care or occupational care settings.[10] Studies investigating patient groups described by the following search string (Medline) were eligible: [(lumbosacra* OR radicula*) AND syndrom*] OR sciatic* OR (herniat* AND disc) OR (prolaps* AND disc) OR 'hernia nuclei pulposi' OR (protrus* AND disc) OR (extrus* AND disc) OR

(sequestrat* AND disc). Excluded were studies of patients with radiating leg pain due to serious pathology. The second review investigated the effectiveness of pharmacological treatments in the primary care setting.[11] Studies investigating patient groups described by the following terms were eligible: sciatica, radiculopathy, nerve root compromise, nerve root compression, lumbosacral radicular syndrome, nerve root pain, nerve root entrapment and pain radiating down below the knee.

Inclusion/exclusion criteria

Studies including adults with radiating leg pain or symptoms associated with back pain were eligible for inclusion, including conditions described as sciatica, radiculopathy, radicular pain, radicular syndrome and/or lumbar disc herniation, but not cauda equina or any condition that would warrant immediate surgical intervention. We also excluded studies that specifically recruited patients with central canal stenosis, as this is widely considered a different clinical entity. Studies could compare a conservative intervention to another intervention (including surgery), placebo or no treatment.

Screening and data extraction

One reviewer retrieved the included studies from the two previous reviews and updated the search, and two independent reviewers screened the studies and extracted the following data: the term(s) used to describe the study population, description or definition of such terms (if provided), study details (treatment comparisons, sample size, symptom duration) and eligibility criteria related to radiating leg pain (i.e., the criteria used to define the study population). If studies included a mixed population (e.g., low back pain with or without radiating leg pain), only data related to the subgroup of people with radiating leg pain were extracted. Differences between the two reviewers were resolved by a third, independent reviewer.

Data analysis and presentation

We grouped studies according to the terms used to describe the study population. If multiple terms were used in a single study, then the study was included under each term used. For the eligibility criteria used to define radiating leg pain or symptoms, the criteria were divided into symptoms, signs, imaging and other. We compared the criteria with the descriptions provided in the IASP taxonomy (Table 1).[5] In studies where the term *sciatica* was used, we anticipated that there would be heterogeneity across studies on the eligibility criteria used to define the study population. In studies where specific terms such as *radicular pain* or *radiculopathy* were used, we anticipated that trial authors would focus on similar clinical features so there would be more consensus on the eligibility criteria used. Specifically, *radicular pain* relates to lancinating nerve root pain that is caused by nerve root irritation, and hence, we would expect to see a focus

on symptom-related eligibility criteria.[5] *Radiculopathy* relates to loss of sensory or motor function due to nerve root compromise, and hence, we would expect to see a focus on sign-related eligibility criteria.[5]

RESULTS

The search identified 2256 unique records and 93 full-text articles were screened for eligibility (Fig. 1). Of the studies that were included, two were each reported in two separate articles.[9,13,14,15] One article reported on five studies with varying eligibility criteria defining low back pain with or without radiating leg pain.[16] For the purpose of this review, the three studies including participants with radiating leg pain were considered as three separate studies with one citation[15] and the two studies that recruited participants with low back pain but no radiating leg pain or symptoms were excluded. Cuckler et al.[17] had separate eligibility criteria defining participants with radiating leg pain or central canal stenosis. We excluded the eligibility criteria concerning the participants with central canal stenosis. One publication reported on two separate studies with identical eligibility

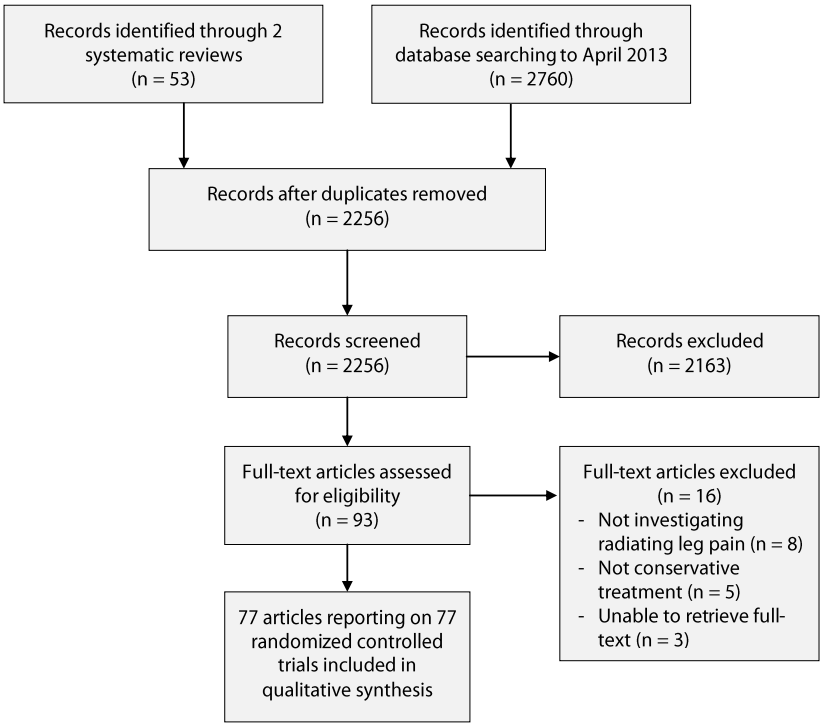

Figure 1. Study flow

criteria[18], so is considered as one study for the purpose of this review. In total, 77 articles reporting on 77 studies were included.

The characteristics of the included studies are described in Table 2. The sample size ranged from 15[19] to 1021[18], with a median of 60. The majority of the studies investigated the effectiveness of physical therapy, injection or medication compared with another conservative treatment or placebo. Six studies compared conservative treatment to an invasive treatment (surgery or chemonucleolysis). One-third of the studies recruited participants with a mixture of acute, sub-acute or chronic symptoms.

Table 2. Characteristics of the 77 included studies.

Characteristic	No. (%) of studies
Number of terms used for radiating leg pain or symptoms	
1/2/3/4	46/26/4/1
Term used	
Sciatica	60
Lumbar disc herniation or prolapse or discogenic	19
Radicular pain or syndrome	16
Radiculopathy	12
Lumbar nerve root compression	3
Lumbar nerve root pain	2
Other: lumbago-ischias/discal radiculalgia	1/1
Neuropathic pain	0
Main treatment comparison	
Physical therapy versus physical therapy, placebo or other conservative treatment	23 (29.9)
Injection versus injection or placebo	18 (23.4)
Medication versus medication or placebo	18 (23.4)
Injection versus medication or other conservative treatment	6 (7.8)
Conservative treatment versus surgery or chemonucleolysis	6 (7.8)
Other	6 (7.8)
Symptom duration	
Acute	17 (22.1)
Sub-acute	3 (3.9)
Chronic	11 (14.3)
Acute and sub-acute	9 (11.7)
Sub-acute and chronic	3 (3.9)
Acute, subacute and chronic	26 (33.8)
Not described	8 (10.4)

Acute = less than 6 weeks; sub-acute = 6 to 12 weeks; chronic = more than 12 weeks

Terms used to describe the study population with radiating leg pain or symptoms

The most commonly used term by far was sciatica (n= 60/77 studies). In 40% of the studies (n= 31/77), two or more terms were used. In addition to using a term and eligibility criteria to define the study population, 28 studies provided further description or definition on radiating leg pain or symptoms. There was consensus across these studies; 26 of 28 studies described disc herniation and/or nerve root compression as the underlying mechanism. Nine studies described radiating leg pain as pain below the knee that can be accompanied by nerve root tension or sensory, motor or reflex changes[14,15,20-22], pain radiating from the back into the leg following a dermatome[14,15,22,23], radicular pain[24] or radiating pain often associated with numbness or abnormal sensation along the sciatic nerve.[25-27] No study used the term neuropathic pain to define a study population with radiating leg pain or symptoms.

Eligibility criteria used to define the study population with radiating leg pain or symptoms (Table 3)

Sciatica (60 studies)

Just over half of the studies that used the term *sciatica* included pain distribution in the eligibility criteria (n= 34/60). This was most commonly expressed as pain below the knee (n= 11/60) or in the lumbar or sciatic dermatomal distribution (n= 9/60). The uni- or bilateral distribution of symptoms, whether back pain was present and the type of exacerbating factors were not important as few studies included these features in the eligibility criteria. Studies were inconsistent in including signs and imaging in the eligibility criteria. Approximately half of the studies required positive responses to neural mechanosensitivity tests (n= 31/60), while approximately one-third required positive neurological signs (n= 20/60) or imaging (n= 26/60). Three of sixty studies did not define any eligibility criteria related to radiating leg pain beyond using the term sciatica.[28-30] In 27 of 60 studies, at least one term other than sciatica was used to define the study population.

Disc herniation (19 studies)

Disc herniation is thought to be a common aetiology behind both *radicular pain* and *radiculopathy* (Table 1). For studies using the term *disc herniation*, just over half used pain distribution as an eligibility criterion (n= 10/19), but there was no consistency in sign-related eligibility criteria. Few studies (n= 5/19) required a positive neural mechanosensitivity test and studies differed in whether the presence or absence of positive neurological signs was required. The inconsistency may be off-set by a heavy reliance on

Table 3. Eligibility criteria used to define study participants with radiating leg pain. The first number indicates the number of included studies; the numbers in parenthesis denote the number of studies in which a criterion is optional.

	No. of studies					
Eligibility criteria	**Sciatica, n = 60**	**Disc herniation, n = 19**	**Radicular pain, n =16**	**Radiculopathy, n = 12**	**Nerve root compression, n = 3**	**Nerve root pain, n = 2**
Related to symptoms						
Pain distribution - anatomical						
Below the knee	11 (1)	0	5 (2)	3 (2)	0	(2)
Leg/below the gluteal fold, or from buttock/hip to leg/thigh or calf	7	5	2	1	1	0
At least to the buttock	1	0	0	0	0	0
Buttocks or leg	1	0	2	2	0	2
Posterior in the leg to the knee (sciatica) or anterior in the thigh or shin (cruralgia)	1	1	0	0	0	0
Pain distribution - neural						
L5 or S1/lumbar or sciatic dermatome	9	3	1 (1)	3	0	0
Sciatic nerve	3	0	2	0	0	0
Sciatic or femoral nerve	2	2	0	0	2	0
Nerve root pain/within the distribution of a nerve root	2	0	1	0	0	0
Uni- or bilateral						
Unilateral	13	2	4	3	1	0
Uni- or bilateral	5	0	2	3	0	2
Presence of low back pain	8 (8)	5 (1)	1 (2)	1 (2)	0	0
Exacerbating factors						
Coughing, straining/increased abdominal pressure	1 (3)	2	3 (1)	1	0	0
Paravertebral finger pressure	1	0	0	1	0	0
Other						
"Sciatica" or "sciatic symptoms"	11	5	0	0	0	0

Table 3. Eligibility criteria used to define study participants with radiating leg pain. The first number indicates the number of included studies; the numbers in parenthesis denote the number of studies in which a criterion is optional. (continued)

	No. of studies					
Eligibility criteria	**Sciatica, n = 60**	**Disc herniation, n = 19**	**Radicular pain, n =16**	**Radiculopathy, n = 12**	**Nerve root compression, n = 3**	**Nerve root pain, n = 2**
Radiating/radicular pain or symptoms	10 (1)	6	3 (1)	3	1	0
Leg pain at least comparable or worse than back pain	5	2	0	0	0	0
Lancinating, burning, stabbing or electrical sensation	1	1	0	0	0	0
Paraesthesia	1	0	0	0	0	0
Symptoms of single level disc protrusion	1	1	0	0	0	0
Symptoms of radiculopathy	1	0	0	0	0	0
Sudden onset during exertion or wrong movement, pain evolution with mechanical rhythm, no progressive aggravation, antalgic spine deviation or localized spinal stiffness, history of low back pain	(1)	0	0	0	0	0
Nocturnal pain relieved by standing	0	0	(1)	0	0	0
Related to signs						
Neural mechanosensitivity testing						
Positive straight leg raise test (degree of pain producing angle not specified)	12 (1)	1	4 (1)	2	0	0
Positive straight leg raise test (degree of pain producing angle, usually ≤60 degrees, specified)	10	1	6	4	1	2
Positive straight leg raise (degree of pain producing angle not specified)/positive sciatic nerve test or positive femoral nerve tests	9	2	0	0	1	0
Positive straight leg raise (degree of pain producing angle specified) or a positive femoral nerve test	0	1	1	0	0	0
Neurological testing						

Table 3. Eligibility criteria used to define study participants with radiating leg pain. The first number indicates the number of included studies; the numbers in parenthesis denote the number of studies in which a criterion is optional. (continued)

	No. of studies					
Eligibility criteria	**Sciatica, n = 60**	**Disc herniation, n = 19**	**Radicular pain, n =16**	**Radiculopathy, n = 12**	**Nerve root compression, n = 3**	**Nerve root pain, n = 2**
Neurological deficit/motor, sensory or reflex changes	20 (6)	6 (3)	10 (2)	5 (2)	3	2
No neurological deficit	1	2	0	0	0	0
Other signs						
No paresis/major or progressive motor/neurological impairment	18	4	7	2	1	0
Restricted back movement	6	1	0	1	0	0
Sciatic scoliosis	1	1	0	0	1	0
Symptoms consistent with L3-S1 radiculopathy	0	1	0	0	0	0
Side to side H-reflex latency	0	1	0	1	0	0
Imaging						
Positive imaging findings (a combination of radiographic, CT or MRI findings of disc herniation or nerve root involvement)	26 (2)	18	5 (1)	5 (1)	2	(1)
No sequestrated herniation	2	2	0	0	0	0
Negative myelogram findings	1	0	0	0	0	0
Other						
No cauda equina or loss of bladder or bowel control	8	7	7	1	1	0
No stenosis	10	6	3	1	0	0
No spondylolisthesis	0	1	0	0	0	0

CT = computed tomography; MRI = magnetic resonance imaging.

imaging. Consistent with the term disc herniation almost all studies (n= 18/19) required positive imaging findings in their study population.

Radicular pain (16 studies)

Most studies that used the term *radicular pain* (n= 12/16) used an eligibility criterion on pain distribution to define their study population. For almost one-third of the studies (n= 5/16), this was 'pain below the knee'. Whether the pain was uni- or bilateral, whether back pain was present and the type of exacerbating factors were not presented by at least half of the studies. In contrast to the IASP taxonomy on radicular pain (Table 1), two-thirds of studies (n=10/16) using the term *radicular pain* required motor, sensory or reflex changes for inclusion. Most studies (n= 11/16) also required a positive neural mechanosensitivity test, which, while consistent across studies, is not covered in the IASP taxonomy. Concordant with the IASP taxonomy, diagnosis for radicular pain was often made by clinical presentation as imaging findings were not a criterion in 11 of 16 studies. In addition to radicular pain, 9 of 16 studies also used the term *sciatica* to represent their participants with radiating leg pain, while 4 studies also used the term *radiculopathy*. Two studies that used both the terms *radicular pain* and *radiculopathy* included symptom-related (pain distribution) and sign-related (neurological deficits) eligibility criteria[31,32], concurring with the IASP taxonomy, while the other two only required symptom-related but not sign-related criteria.[33,34]

Radiculopathy (12 studies)

Most studies using the term *radiculopathy* used pain distribution to define their study population (n= 9). This is different from the IASP taxonomy of radiculopathy (Table 1), where the presence of pain is not included as a feature. This is likely to be because studies also used *sciatica* (n= 7/12), *radicular pain* (n= 4/12), disc herniation (n= 2/12) and/or *nerve root pain* (n= 2/6) as terms to define their populations. Neurological deficits are features of radiculopathy according to the IASP taxonomy, but were used as an eligibility criterion by only 5 of 12 studies by way of positive motor, sensory or reflex changes. Interestingly, the one study that used *radiculopathy* as the only term to define the study population did not have neurological deficits as an eligibility criterion.[35] Almost half of the studies (n= 5/12) required positive imaging findings in the eligibility criteria.

Nerve root compression (three studies)

The studies that used the term *nerve root compression* had eligibility criteria covering both symptom and sign-related criteria. These studies had the same eligibility criteria of pain in the sciatic or femoral nerve distribution or distal to the buttock, neurological deficits and positive imaging findings. Studies used at least one other term [sciatica[36,37], radiculopathy[37] or disc herniation[38]], to define their study populations.

Nerve root pain (two studies)
The two studies that used the term *nerve root pain* were conducted by the same study group[31,32] and had nearly identical eligibility criteria on symptoms, signs and imaging. These studies also used the terms *radicular pain* and *radiculopathy* to define the study population.

Lumbago-ischias (one study) or discal radiculalgia (one study)
Each term was used by only one study[39,40], which also used the term *sciatica* and has been included with the other studies that used the term *sciatica*. Due to the low number of studies, the differences and uniformity of the eligibility criteria were not separately assessed for these terms.

DISCUSSION AND CONCLUSIONS

Sciatica is by far the term most commonly used to describe the study population in studies evaluating conservative treatment of radiating leg pain or symptoms associated with back pain; however, over one-third of the studies used at least one other term. There was no consistency in the eligibility criteria used by studies that had used the term *sciatica* to describe their study population. Studies that adopted the IASP preferred terms *radicular pain* and *radiculopathy* had inconsistent eligibility criteria that did not typically concur with the IASP taxonomy. There was more consistency in the studies that used the term *disc herniation* as almost all studies required positive imaging findings as an eligibility criterion.

The key finding of our review is that the possible terms used to describe a population with radiating leg pain or symptoms are being used inconsistently and interchangeably despite better understanding of the mechanisms associated with some terms and attempts to publish consensus definitions. According to the IASP, 'radiculopathy' and 'radicular pain' are distinct entities yet we found that the terms are being used interchangeably with each other and with terms like sciatica. Our findings are similar to the results of a recent systematic review that included a smaller subset of studies (n= 12).[9] Our review methods are substantially different from this previous review, which focused on lumbar radiculopathy due to disc herniation, as we investigated the eligibility criteria of a broader range of conditions of radiating leg pain or symptoms associated with back pain. Furthermore, we add to existing literature by comparing the eligibility criteria studies used to an international taxonomy of pain. Our results are also similar to those of a review of eligibility criteria used to define cervical radiculopathy that found little consistency across studies.[41] This study found that, while the presence of pain was

included as an eligibility criterion in most studies of cervical radiculopathy, there was little consensus on the distribution of pain.[41]

The inconsistencies between the IASP taxonomy and how radiating leg pain or symptoms have been defined in clinical trials may highlight the need to re-examine the IASP taxonomy, which has not been updated since 1994.[5] For example, there is no guidance on how many positive neurological tests are required for a patient to meet the term radiculopathy, and the reliability of distinguishing radicular pain from somatic pain based on the quality (e.g., lancinating) or the distribution (e.g., narrow bands) has not been examined. Furthermore, little is known of the association between clinical features of radicular pain or radiculopathy and the pathology thought to cause these conditions. A recent Cochrane diagnostic review found that most tests used in physical examination (e.g., straight leg raise, motor, sensory or reflex testing) have poor diagnostic accuracy for lumbar radiculopathy due to disc herniation.[42]

An alternative way of defining a population with radiating leg pain could be to consider the definition for neuropathic pain. Because the features of radiating leg pain or symptoms are thought to be caused by compression or compromise to the spinal nerve or nerve root (Table 1), radiating leg pain may be considered a type of neuropathic pain.[6] The IASP defines neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system', where lesion is established by diagnostic investigations (e.g., imaging) or trauma and disease is used when the cause of the lesion is known (e.g., stroke) (http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/, accessed 1 March 2013). In our review, regardless of the term used to describe radiating leg pain, only a small proportion of studies used diagnostic investigations (i.e., imaging) as part of the eligibility criteria of their study population. The exceptions are studies using the term 'disc herniation' or 'nerve root compression', where almost all studies under each term required imaging. This is perhaps not surprising as these terms focus on the pathology compared with the other terms that focus on the clinical features of radiating leg pain or symptoms. Other than imaging, none of our included studies required other methods of diagnostic investigations as an eligibility criterion, e.g., neurophysiology or laboratory tests. The lack of requirement for diagnostic investigations could also be related to the type of treatments used. In our review, we included studies that investigated conservative treatments; these are treatments available in primary care so it makes sense that the studies relied more on clinical features than diagnostic investigations to define radiating leg pain. Our findings perhaps illustrate that the current definition of neuropathic pain has limited applicability in studies of conservative treatments for radiating leg pain associated with back pain. Nevertheless, most of studies in our review used eligibility criteria that would allow them to recruit a

population of people with a neuropathic pain component (e.g., neurological deficits, positive imaging findings of disc herniation or nerve root involvement), thus making the important distinction from somatic referred pain.[7]

Adding to the confusion on the terms and eligibility criteria used to define radiating leg pain is the situation where different professional bodies define radiating leg pain or symptoms differently. For example, in contrast to the IASP taxonomy, the American College of Physicians and the American Pain Society include pain in addition to neurological deficits in their definition of *radiculopathy*, and include *sciatica* (pain below the knee in the distribution of the sciatic nerve) as its most common symptom.[4] Clearly, it is essential that consensus on definitions be reached among professional bodies to facilitate effective communication in clinical practice and research, e.g., when triaging patients presenting with back pain or when making treatment recommendations based on existing evidence or understanding of pathology. A way forward is to achieve consensus among different professional groups via a Delphi process[43] or the establishment of a multidisciplinary taskforce, perhaps starting with reviewing and updating the IASP taxonomy devised in 1994. Similar actions have been taken in other areas of musculoskeletal conditions such as osteoarthritis and rheumatoid arthritis.[44,45] In addition, an important area of future research is to identify whether the presence or absence of different clinical features, such as pain distribution or quality, positive neural mechanosensitivity tests, neurological deficits and imaging findings, are associated with differences in recovery or response to specific interventions, and hence, how necessary it is to have different terms to delineate various clinical presentations. Recent systematic reviews of prognostic factors, including one conducted by our group, suggests conflicting but mainly negative results regarding the influence of pain, neurological deficit, neural mechanosensitivity and imaging findings on outcome.[46,47]

One limitation of our study is that we compared the eligibility criteria used in studies to the IASP taxonomy for the same terms, but over one-third of the included studies (n= 31/77) were published before the publication of the IASP taxonomy. However, even without the comparison to the IASP taxonomy, we found few consistencies in the eligibility criteria between studies using the same term to define the study population, and few distinctions in the eligibility criteria between studies using different terms.

In conclusion, our review found inconsistencies in the terms used to describe, and eligibility criteria used to define, the population in studies investigating conservative treatments for radiating leg pain and symptoms, and no consistent association between the term used and the eligibility criteria was reported. This suggests that these terms are being used interchangeably and not according to specific definitions such as the IASP

taxonomy. The findings also highlight the need to examine how necessary it is to have different terms of radiating pain to delineate various clinical presentations, as currently we have limited information on the influence of different clinical features in relation to recovery time or treatment response. Because clear and consistent definitions are required for ease of communication, comparison between studies and when making treatment recommendations, professional bodies need to reach consensus on the classifications and definitions of radiating leg pain or symptoms associated with back pain.

REFERENCES

1. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
2. Airaksinen, O., et al., *Chapter 4. European guidelines for the management of chronic nonspecific low back pain.* Eur Spine J, 2006. **15 Suppl 2**: p. S192–300.
3. van Tulder, M., et al., *Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care.* Eur Spine J, 2006. **15 Suppl 2**: p. S169–91.
4. Chou, R., et al. *Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and The American Pain Society.* Ann Intern Med, 2007. **147**(7): p. 478–91.
5. Merskey, H. and N. Bogduk, *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* 1994 (Seattle: IASP Press).
6. Dworkin, R.H., et al. *Pharmacologic management of neuropathic pain: evidence-based recommendations.* Pain, 2007. **132**(3): p. 237–51.
7. Bogduk, N. *On the definitions and physiology of back pain, referred pain, and radicular pain.* Pain, 2009. **147**(1-3): p. 17–9.
8. Konstantinou, K. and K.M. Dunn, *Sciatica: Review of epidemiological studies and prevalence estimates.* Spine (Phila Pa 1976), 2008. **33**(22): p. 2464–72.
9. Genevay, S., S.J. Atlas, and J.N. Katz, *Variation in eligibility criteria from studies of radiculopathy due to a herniated disc and of neurogenic claudication due to lumbar spinal stenosis: A structured literature review.* Spine (Phila Pa 1976), 2010. **35**(7): p. 803–11.
10. Luijsterburg, P.A., et al., *Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review.* Eur Spine J, 2007. **16**(7): p. 881–99.
11. Pinto, R.Z., et al., *Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis.* BMJ, 2012. **344**: p. e497.
12. van Tulder, M., et al., *Updated method guidelines for systematic reviews in the cochrane collaboration back review group.* Spine (Phila Pa 1976), 2003. **28**(12): p. 1290-9.
13. Genevay, S., et al., *Adalimumab in acute sciatica reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial.* Ann Rheum Dis, 2012. **71**(4): p. 560-2.
14. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
15. Peul, W.C., et al., *Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: two year results of a randomised controlled trial.* BMJ, 2008. **336**(7657): p. 1355-8.
16. Mathews, J.A., et al., *Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections.* Br J Rheumatol, 1987. **26**(6): p. 416-23.
17. Cuckler, J.M., et al., *The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study.* J Bone Joint Surg Am, 1985. **67**(1): p. 63-6.
18. Dreiser, R.L., et al., *Oral meloxicam is effective in acute sciatica: two randomised, double-blind trials versus placebo or diclofenac.* Inflamm Res, 2001. **50 Suppl 1**: p. S17-23.
19. Atkinson, J.H., et al., *A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain.* Pain, 1998. **76**(3): p. 287-96.

20. Luijsterburg, P.A., et al., *Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up.* Eur Spine J, 2008. **17**(4): p. 509-17.
21. Memeo, A. and M. Loiero, *Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study.* Clin Drug Investig, 2008. **28**(8): p. 495-500.
22. Baron, R., et al., *The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy.* Pain, 2010. **150**(3): p. 420-7.
23. Genevay, S., et al., *Adalimumab in severe and acute sciatica: a multicenter, randomized, double-blind, placebo-controlled trial.* Arthritis Rheum, 2010. **62**(8): p. 2339-46.
24. Finckh, A., et al., *Short-term efficacy of intravenous pulse glucocorticoids in acute discogenic sciatica. A randomized controlled trial.* Spine (Phila Pa 1976), 2006. **31**(4): p. 377-81.
25. Herrmann, W.A. and M.S. Geertsen, *Efficacy and safety of lornoxicam compared with placebo and diclofenac in acute sciatica/lumbo-sciatica: an analysis from a randomised, double-blind, multicentre, parallel-group study.* Int J Clin Pract, 2009. **63**(11): p. 1613-21.
26. Laiq, N., et al., *Comparison of Epidural Steroid Injections with conservative management in patients with lumbar radiculopathy.* J Coll Physicians Surg Pak, 2009. **19**(9): p. 539-43.
27. Prasad, K.S., et al., *Inversion therapy in patients with pure single level lumbar discogenic disease: a pilot randomized trial.* Disabil Rehabil, 2012. **34**(17): p. 1473-80.
28. Braun, H. and R. Huberty, *[Therapy of lumbar sciatica. A comparative clinical study of a corticoid-free monosubstance and a corticoid-containing combination drug].* Med Welt, 1982. **33**(13): p. 490-1.
29. Schuermans, Y. and A. Rauis, *Comparative clinical trial of two injectable NSAIDs, tiaprofenic acid and alclofenac, in acute sciatica.* Drugs, 1988. **35 Suppl 1**: p. 83-5.
30. Huber, J., et al., *The effect of early isometric exercises on clinical and neurophysiological parameters in patients with sciatica: An interventional randomized single-blinded study.* Isokinet Exerc Sci, 2011. **19**(3): p. 207–214.
31. Khoromi, S., et al., *Topiramate in chronic lumbar radicular pain.* J Pain, 2005. **6**(12): p. 829-36.
32. Khoromi, S., et al., *Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain.* Pain, 2007. **130**(1-2): p. 66-75.
33. Keynan, O., et al., *Safety and Efficacy of Dietary Agmatine Sulfate in Lumbar Disc-associated Radiculopathy. An Open-label, Dose-escalating Study Followed by a Randomized, Double-blind, Placebo-controlled Trial.* Pain Med, 2010. **11**(3): p. 356-68.
34. Omar, A.S., M.A. Awadalla, and M.A. El-Latif, *Evaluation of pulsed electromagnetic field therapy in the management of patients with discogenic lumbar radiculopathy.* Int J Rheum Dis, 2012. **15**(5): p. e101-8.
35. Yildirim, K., et al., *The effectiveness of gabapentin in patients with chronic radiculopathy.* Pain Clin, 2003. **15**(3), p. 213–218.
36. Dilke, T.F., H.C. Burry, and R. Grahame, *Extradural corticosteroid injection in management of lumbar nerve root compression.* Br Med J, 1973. **2**(5867): p. 635-7.
37. Fritz, J.M., et al., *Is there a subgroup of patients with low back pain likely to benefit from mechanical traction? Results of a randomized clinical trial and subgrouping analysis.* Spine (Phila Pa 1976), 2007. **32**(26): p. E793-800.
38. Snoek, W., H. Weber, and B. Jorgensen, *Double blind evaluation of extradural methyl prednisolone for herniated lumbar discs.* Acta Orthop Scand, 1977. **48**(6): p. 635-41.
39. Grevsten, S. and H. Johansson, *Phenylbutazone in treatment of acute lumbago-sciatica.* Z Rheumatol, 1975. **34**(11-12): p. 444-7.

40. Thomas, E., et al., *Efficacy of transforaminal versus interspinous corticosteroid injectionin discal radiculalgia - a prospective, randomised, double-blind study.* Clin Rheumatol, 2003. **22**(4-5): p. 299-304.
41. Thoomes, E.J., et al., *Lack of uniform diagnostic criteria for cervical radiculopathy in conservative intervention studies: a systematic review.* Eur Spine J, 2012. **21**(8): p. 1459-70.
42. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
43. Stanton, T.R., et al., *A modified Delphi approach to standardize low back pain recurrence terminology.* Eur Spine J, 2011. **20**(5): p. 744-52.
44. Altman, R., et al., *Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.* Arthritis Rheum, 1986. **29**(8): p. 1039-49.
45. Singh, J.A., et al., *Development of classification and response criteria for rheumatic diseases.* Arthritis Rheum, 2006. **55**(3): p. 348-52.
46. Ashworth, J., K. Konstantinou, and K.M. Dunn, *Prognostic factors in non-surgically treated sciatica: a systematic review.* BMC Musculoskelet Disord, 2011. **12**: p. 208.
47. Verwoerd, A.J., et al., *Systematic review of prognostic factors predicting outcome in non-surgically treated patients with sciatica.* Eur J Pain, 2013. **17**(8): p. 1126-37.

4.
Diagnostic accuracy of history taking to assess lumbosacral nerve root compression.

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ABSTRACT

Background context: The diagnosis of sciatica is primarily based on history and physical examination. Most physical tests used in isolation show poor diagnostic accuracy. Little is known about the diagnostic accuracy of history items.

Purpose: To assess the diagnostic accuracy of history taking for the presence of lumbosacral nerve root compression or disc herniation on magnetic resonance imaging in patients with sciatica.

Study design: Cross-sectional diagnostic study.

Patient sample: A total of 395 adult patients with severe disabling radicular leg pain of 6 to 12 weeks duration were included.

Outcome measures: Lumbosacral nerve root compression and disc herniation on magnetic resonance imaging were independently assessed by two neuroradiologists and one neurosurgeon blinded to any clinical information.

Methods: Data were prospectively collected in nine hospitals. History was taken according to a standardized protocol. There were no study-specific conflicts of interest.

Results: Exploring the diagnostic odds ratio of 20 history items revealed a significant contribution in diagnosing nerve root compression for "male sex," "pain worse in leg than in back," and "a non-sudden onset." A significant contribution to the diagnosis of a herniated disc was found for "body mass index <30", "a non-sudden onset," and "sensory loss." Multivariate logistic regression analysis of six history items pre-selected from the literature (age, gender, pain worse in leg than in back, sensory loss, muscle weakness, and more pain on coughing/sneezing/straining) revealed an area under the receiver operating characteristic curve of 0.65 (95% confidence interval, 0.58–0.71) for the model diagnosing nerve root compression and an area under the receiver operating characteristic curve of 0.66 (95% confidence interval, 0.58–0.74) for the model diagnosing disc herniation.

Conclusions: A few history items used in isolation had significant diagnostic value and the diagnostic accuracy of a model with six pre-selected items was poor.

INTRODUCTION

Sciatica (also called lumbosacral radicular syndrome) is a clinical diagnosis characterized by radiating pain in the leg and related impairments. The most common cause of sciatica is a herniated disc.[1] The annual prevalence of disc-related sciatica in the general population is estimated at 2.2%.[2] Other causes of sciatica are non-compressive irritation of the nerve root, such as infection, lumbar stenosis, or (rarely) a tumor. Despite the presence of symptoms of sciatica, nerve root compression is not always found on magnetic resonance imaging (MRI).

The diagnosis of sciatica in clinical practice is usually based on history and physical examination. Diagnostic imaging is only necessary in certain patients, mainly when assessing the need for invasive treatment. A recent Cochrane review on physical examination for lumbar radiculopathy due to disc herniation showed poor diagnostic performance of most physical tests when used in isolation.[3] In the diagnosis of sciatica, the main component is probably history taking.[4] Although few studies have examined the value of history taking, it seems that no single history item or physical examination test has both high sensitivity and specificity in patients suspected of sciatica due to disc herniation.[5] Better performance might be obtained when history items are combined. However, because it remains unknown which combination offers the best diagnostic importance, improved understanding of the diagnostic accuracy of history taking regarding sciatica is necessary.[6]

The presence of lumbar disc herniation is frequently used as outcome measure in studies on sciatica. Nerve root compression can also occur without a herniated disc, and disc herniation can exist without nerve root compression.[7] Adding that the anatomical basis of sciatic symptoms lies in compression or irritation of a lumbar or sacral nerve root (or the sciatic nerve), one may state from an anatomical viewpoint that nerve root compression might be a better outcome measure than disc herniation in studies on sciatica. The aim of the present study was to determine the diagnostic accuracy of history taking for the presence of lumbosacral nerve root compression and disc herniation on MRI in patients with sciatica.

METHODS

Design

This is a cross-sectional diagnostic study using two datasets: the baseline data of a randomized controlled trial (RCT) comparing early surgery and prolonged conservative

treatment for sciatica and of a cohort alongside that trial that includes those patients who were excluded from this RCT after they had undergone MRI.[8,9] All data were prospectively collected in nine hospitals in a large region in the western part of the Netherlands. The medical ethics committees at the nine participating hospitals approved the protocol. Written informed consent was obtained from all patients. There were no study-specific conflicts of interest. Details on the methods are described in the original publications.[8,9]

Study population

Patients with severe sciatica visiting their family physician or referred to a neurologist were assessed for eligibility. Eligible patients were aged 18 to 65 years and had received a diagnosis of an incapacitating lumbosacral radicular syndrome that had lasted for 6 to 12 weeks from a neurologist. Patients were excluded if they presented with cauda equina syndrome, insufficient strength to move against gravity, another episode of symptoms similar to those of the current episode during the past 12 months, previous spine surgery, pregnancy, or severe coexisting disease.

Baseline measures

Six research nurses were trained in taking history according to a standardized protocol. In the first visit to the research nurses, a total of 42 history items were assessed for each patient; patient characteristics such as age and sex were also classified as history items. Of these 42 items, 15 were patient characteristics and 27 were symptom-related items (eg, duration of symptoms and questions on provocation of pain). Most questions had a 2, 3, or 4-point answer option; however, for the purpose of the present study, response options were dichotomized. Questionnaires were not classified as history items.

Reference tests

The reference test was an MRI scan performed according to a standardized protocol tailored to a 1.5 Tesla scanner (including Gadolinium series). Both lumbosacral nerve root compression and the presence of a herniated disc as assessed on MRI were defined as reference tests (gold standard). Two radiologists and one neurosurgeon independently assessed the MRI scans according to a standardized protocol.[10] To prevent information bias, they were blinded for any clinical information and thus unaware of history and physical examination findings. None of the readers had been involved in either the selection or care of the included patients. Observer experience in reading spine MRIs was 7 and 6 years post-residency for the neuroradiologists and 4 years post-residency for the neurosurgeon. A 4-point scale was used for both the presence of nerve root compression and the presence of a herniated disc on MRI. This scale corresponds to the highest grade (ie, "compression") of the rating scheme of Pfirrmann et al., with the difference that the readers could express their uncertainties.[11] Our 4-point scale consisted

of "definite about the presence," "probable about the presence" if there was some doubt but probability >50%, "possible about the presence" if there was reason to consider but probability <50%, and "definite about the absence".[10,12] The first two categories were combined and labeled as having nerve root compression or a herniated disc. The last two categories were combined and labeled as not having the abnormalities present. The majority opinion of the three readers regarding the MRI characteristics (answers independently given by a minimum of two readers) was used in the statistical analysis. Interobserver agreement was calculated in a previous study and resulted in a multirater kappa statistic of 0.66 for the presence of nerve root compression and a kappa of 0.71 for the presence of disc herniation, meaning substantial agreement.[10] Herniation was defined as a localized displacement of disc material beyond the normal margins of the intervertebral disc space (based on the Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology).[10,13] Each subsequent appearance of the term "disc herniation" in this manuscript refers precisely to this definition.

Statistical analysis

Descriptive statistics were used to present baseline characteristics of the patients, time between the index and reference test, and results of MRI. Based on the literature, clinical practice guidelines and clinical practice, we selected 20 history items as most likely having diagnostic value. We exploratively screened the diagnostic accuracy of these items by calculating diagnostic odds ratios (DORs) and the corresponding 95% confidence intervals (CIs). Diagnostic odds ratio calculates the ratio of the odds of a positive result in diseased patients and the odds of a positive test in non-diseased patients. Additionally, sensitivity, specificity, and corresponding 95% CIs were calculated.

Multivariate logistic regression analyses were performed to determine which history items significantly contributed to the discrimination of patients with nerve root compression and of patients with disc herniation on MRI. Because of the rule of at least 10 cases per variable of interest, we could include eight variables in the multivariate regression analysis to create a diagnostic model with nerve root compression as outcome measure and six variables for the diagnostic model of disc herniation.[14] Based on the literature and on the history items most often used[6] a priori, we selected the following variables for both models before any statistical analysis was done: age[15], gender[15], pain worse in leg than in back[15,16], subjective sensory loss in the leg[15,17], subjective muscle weakness in the leg[17], and leg and/or back pain worse on coughing/sneezing/straining.[15,17]

Receiver operating characteristic (ROC) curve analysis was used to determine the performance of both models to classify patients as positive or negative over the whole

range of possible cut-off points.[18] The area under the ROC curve (AUC) can be interpreted as the probability that a patient with the outcome of interest is given a higher probability of that outcome by the model than a randomly chosen patient without the outcome. An AUC of 0.5 indicates no discrimination and an AUC of 1.0 indicates perfect discrimination. If the continuous measure AUC is classified into categories for more ease of interpretation, the following classification can be made: AUC 0.9 to 1.0 excellent, AUC 0.8 to 0.9 good, AUC 0.7 to 0.8 fair, AUC 0.6 to 0.7 poor, and AUC <0.6 fail.[19]

The bootstrap resampling technique was used to correct for overfitting and quantify optimism in model performance. Random bootstrap samples were drawn with replacement (1,000 replications) from the dataset. Three variables were excluded from the bootstrap analysis because they were only applicable for patients with paid employment (ie, "health-related absenteeism," "having an intellectually heavy job," and "having a physically heavy job"). It is unlikely that these variables have a significant influence on the results due to the non-significant univariate results of these variables.

Sensitivity analysis was done using ROC curve analysis to determine the AUC of both models if only "definite about the presence" or "definite about the absence" of nerve root compression or disc herniation was taken as outcome measure, instead of "definite about the presence" and "probable about the presence" versus "possible about the presence" and "definite about the absence." Besides, as literature on the diagnostic accuracy of history items is sparse and we exploratively screened the diagnostic value of 20 (some not previously examined) history items, we added the history items that revealed a significant ($p<0.05$) DOR to the diagnostic model of the six pre-selected variables thereby creating extra diagnostic models.

We finished our search for an accurate diagnostic model by validation of the diagnostic model reported by Vroomen et al.[15] Because evidence for diagnostic accuracy of history taking is limited, making the pre-selection of variables for our diagnostic model somewhat weak, we decided to validate the multivariate diagnostic models reported in the literature in our dataset. As far as we know, three multivariate diagnostic models on the diagnosis of sciatica have been published.[15,17,20] However, only the diagnostic model of Vroomen et al. reported an AUC.[15] This latter model (with nerve root compression on MRI as outcome) was developed in a primary care population and showed an AUC of 0.80 (that increased to 0.83 when physical examination items were added). The model of history items reported by Vroomen et al. comprised the following items: "age" (categorized in 16–40, 41–50, or 51–81 years), "duration of disease" (<15, 15–30, >30 days), "paroxysmal pain," "pain worse in leg than in back," "typical dermatomal distribution," and "pain worse on coughing, sneezing, or straining." This model was adjusted to our

dataset by removing "typical dermatomal distribution" as this was not measured in our population and by changing the cut-off point of duration of disease to 9 weeks as only patients with a 6 to 12 week duration of complaints were included in the present study.

RESULTS

Between November 2002 and February 2005, 599 patients were assessed for eligibility and 395 patients were included in this study (Fig. 1). Of the included patients, 25 already had undergone MRI before history taking and therefore blinding for the results of MRI was not warranted for these patients. Table 1 shows the most important patient characteristics, mean time between history taking and MRI, and the results of MRI. In total, 310 MRIs (80%) were scored positive on nerve root compression and 331 MRIs (85%) on disc herniation. Only two patients had nerve root compression not caused by disc herniation on MRI. Therefore, the reference test of having nerve root compression

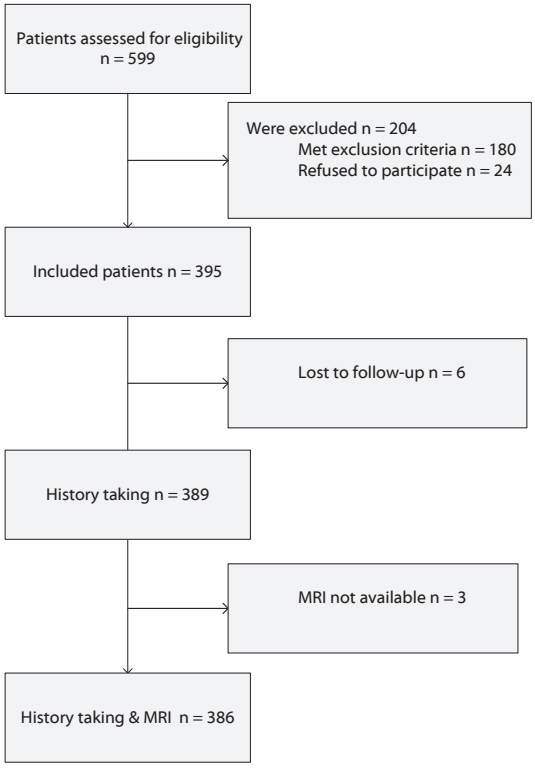

Figure 1. Flow chart of the eligible patients
MRI = magnetic resonance imaging

on MRI is an approximate of having nerve root compression and disc herniation on MRI. Of the 25 patients for whom blinding was not warranted, 22 patients (88%) had nerve root compression and all (100%) had a herniated disc on MRI. For each variable, <5% of values were missing, except for body mass index (BMI) (5.3% missing). Therefore, missing values were not imputed in the analyse.

Table 1. Characteristics of the included patients.

Age in years	42.8±10.0
Male sex, no. (%)	248 (63)
Duration of leg pain in weeks	7.0±2.3
Roland Disability Questionnaire Score[1]	16.0±4.3
Score on the visual-analogue scale of pain in the leg[2]	63.0±22.1
Days between history taking and MRI	7.2±9.0
MRI (n=389): nerve root compression[3]	
'Definite about the presence', no. (%)	225 (58)
'Probable about the presence (chance >50%)', no. (%)	85 (22)
'Possible about the presence (chance <50%)', no. (%)	41 (11)
'Definite about the absence', no. (%)	38 (10)
MRI: disc herniation[3]	
'Definite about the presence', no. (%)	295 (76)
'Probable about the presence (chance >50%)', no. (%)	36 (9)
'Possible about the presence (chance <50%)', no. (%)	8 (2)
'Definite about the absence', no. (%)	50 (13)
MRI: with both nerve root compression and disc herniation, no. (%)	308 (79)
MRI: with nerve root compression, but no disc herniation, no. (%)	2 (1)
MRI: with disc herniation, but no nerve root compression, no. (%)	23 (6)

MRI = magnetic resonance imaging.

[1] The Roland Disability Questionnaire for sciatica is a disease-specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0-23, with higher scores indicating worse functional status.

[2] The intensity of pain was measured by a horizontal 100-mm visual analog scale, with 0 representing no pain and 100 the worst pain ever experienced.

[3] When all three medical spine experts scored different categories, the intermediate category was taken as consensus scoring.

Nerve root compression (univariate anaysis)

Table 2 shows the results of univariate analysis (sensitivity, specificity, and DORs) of the 20 a priori selected items from history taking on the diagnosis of lumbosacral nerve root compression and disc herniation. Male sex, the presence of more pain in the leg than in the back, and a non-sudden onset showed a significant positive contribution to the diagnosis of nerve root compression on MRI.

Table 2. Diagnostic value of the patient characteristics and history items regarding the presence of lumbosacral nerve root compression and/or disc herniation on MRI in patients with sciatica.

Characteristics	Nerve root compression						Herniated disc				
	Number (total MRI) %	MRI+ = TP (total MRI+)	MRI- = FP (total MRI-)	Sensitivity (95%CI)	Specificity (95%CI)	OR (95% CI)	MRI+ = TP (total MRI+)	MRI- = FP (total MRI-)	Sensitivity (95%CI)	Specificity (95%CI)	OR (95% CI)
Age > 40 years / Age continuous (per year)	224 (383); 58	176 (307)	48 (76)	0.57 (0.52-0.63)	0.37 (0.26-0.49)	0.78 (0.47-1.32)	189 (328)	35 (55)	0.58 (0.52-0.63)	0.36 (0.24-0.50)	0.78 (0.43-1.40)
						0.99 (0.97-1.02)					0.98 (0.96-1.01)
Male sex	245 (387); 63	203 (308)	42 (79)	0.66 (0.60-0.71)	0.47 (0.36-0.58)	**1.70 (1.03-2.81)**	213 (329)	32 (58)	0.65 (0.59-0.70)	0.45 (0.32-0.58)	1.49 (0.85-2.62)
BMI ≥ 30 / BMI continuous (per kg/m^2)	54 (369); 15	38 (269)	16 (73)	0.13 (0.09-0.17)	0.78 (0.67-0.87)	0.53 (0.27-1.01)	39 (316)	15 (53)	0.12 (0.09-0.17)	0.72 (0.57-0.83)	**0.36 (0.18-0.71)**
						0.95 (0.89-1.01)					**0.90 (0.84-0.97)**
Health-related absenteeism[1] (n=319)	245 (307); 80	193 (242)	52 (65)	0.80 (0.74-0.85)	0.20 (0.11-0.32)	0.99 (0.50-1.95)	207 (257)	38 (50)	0.81 (0.75-0.85)	0.24 (0.14-0.38)	1.31 (0.64-2.68)
Having an intellectually heavy job[1] (n=319)	212 (317); 67	172 (248)	40 (69)	0.69 (0.63-0.75)	0.42 (0.30-0.55)	1.64 (0.95-2.84)	181 (264)	31 (53)	0.69 (0.63-0.74)	0.42 (0.28-0.56)	1.55 (0.85-2.83)
Having a physically heavy job[1] (n=319)	124 (317); 39	94 (248)	30 (69)	0.38 (0.32-0.44)	0.57 (0.44-0.68)	0.79 (0.46-1.36)	103 (264)	21 (53)	0.39 (0.33-0.45)	0.60 (0.46-0.73)	0.98 (0.53-1.78)
Smoking	151 (385); 39	118 (306)	33 (79)	0.39 (0.33-0.44)	0.58 (0.47-0.69)	0.88 (0.53-1.45)	127 (327)	24 (58)	0.39 (0.34-0.44)	0.59 (0.45-0.71)	0.90 (0.51-1.59)
Duration of pain in the leg ≥ 9 weeks / Duration of pain in leg continuous (per week)	100 (384); 26	79 (305)	21 (79)	0.26 (0.21-0.31)	0.73 (0.62-0.82)	0.97 (0.55-1.69)	83 (326)	17 (58)	0.25 (0.21-0.31)	0.71 (0.57-0.82)	0.82 (0.44-1.53)
						0.99 (0.88-1.10)					1.01 (0.90-1.15)
Pain worse in leg than in back	195 (384); 51	163 (305)	32 (79)	0.53 (0.48-0.59)	0.59 (0.48-0.70)	**1.69 (1.02-2.79)**	171 (326)	24 (58)	0.52 (0.47-0.58)	0.59 (0.45-0.71)	1.56 (0.89-2.75)
Having pain in the back for > 12 weeks	138 (383); 36	105 (305)	33 (78)	0.34 (0.29-0.40)	0.58 (0.46-0.69)	0.72 (0.43-1.19)	116 (326)	22 (57)	0.36 (0.30-0.41)	0.61 (0.48-0.74)	0.88 (0.49-1.57)
Sudden onset	238 (384); 62	178 (305)	60 (79)	0.58 (0.53-0.64)	0.24 (0.15-0.35)	**0.44 (0.25-0.78)**	194 (326)	44 (58)	0.60 (0.54-0.65)	0.24 (0.14-0.37)	**0.47 (0.25-0.89)**
Paroxysmal pain	148 (384); 39	116 (306)	32 (78)	0.38 (0.32-0.44)	0.59 (0.47-0.70)	0.88 (0.53-1.46)	126 (327)	22 (57)	0.39 (0.33-0.44)	0.61 (0.48-0.74)	1.00 (0.56-1.78)

Table 2. Diagnostic value of the patient characteristics and history items regarding the presence of lumbosacral nerve root compression and/or disc herniation on MRI in patients with sciatica. (continued)

Characteristics	Nerve root compression						Herniated disc				
	Number (total MRI) (%)	MRI+ = TP (total MRI+)	MRI- = FP (total MRI-)	Sensitivity (95%CI)	Specificity (95%CI)	OR (95% CI)	MRI+ = TP (total MRI+)	MRI- = FP (total MRI-)	Sensitivity (95%CI)	Specificity (95%CI)	OR (95% CI)
Having had pain in the same leg previously	45 (384); 12	37 (305)	8 (79)	0.12 (0.09-0.16)	0.90 (0.81-0.95)	1.23 (0.55-2.75)	40 (326)	5 (58)	0.12 (0.09-0.16)	0.91 (0.80-0.97)	1.48 (0.56-3.93)
Subjective sensory loss	333 (381); 87	269 (303)	64 (78)	0.89 (0.85-0.92)	0.18 (0.11-0.29)	1.73 (0.88-3.41)	290 (324)	43 (57)	0.90 (0.86-0.93)	0.25 (0.15-0.38)	**2.78 (1.38-5.59)**
Subjective muscle weakness	260 (385); 68	202 (306)	58 (79)	0.66 (0.60-0.71)	0.27 (0.18-0.38)	0.70 (0.41-1.22)	220 (327)	40 (58)	0.67 (0.62-0.72)	0.31 (0.20-0.45)	0.93 (0.51-1.69)
Positive family history	158 (385); 41	128 (306)	30 (79)	0.42 (0.36-0.48)	0.62 (0.50-0.73)	1.18 (0.71-1.95)	139 (327)	19 (58)	0.43 (0.37-0.48)	0.67 (0.54-0.79)	1.52 (0.84-2.74)
Pain worse on coughing/ sneezing/ straining	272 (385); 71	218 (306)	54 (79)	0.71 (0.66-0.76)	0.32 (0.22-0.43)	1.15 (0.67-1.96)	232 (327)	40 (58)	0.71 (0.66-0.76)	0.31 (0.20-0.45)	1.10 (0.60-2.01)
Worsening on sitting	285 (385); 74	223 (306)	62 (79)	0.73 (0.67-0.78)	0.22 (0.13-0.32)	0.74 (0.41-1.33)	240 (327)	45 (58)	0.73 (0.68-0.78)	0.22 (0.13-0.36)	0.80 (0.41-1.55)
Sports participation	209 (383); 55	173 (305)	36 (78)	0.57 (0.51-0.62)	0.54 (0.42-0.65)	1.53 (0.93-2.52)	180 (325)	29 (58)	0.55 (0.50-0.61)	0.50 (0.37-0.63)	1.24 (0.71-2.17)
Having a preference for surgery	137 (382); 36	111 (305)	26 (77)	0.36 (0.31-0.42)	0.66 (0.54-0.76)	1.12 (0.66-1.90)	121 (326)	16 (56)	0.37 (0.32-0.43)	0.71 (0.58-0.82)	1.48 (0.79-2.75)

MRI = magnetic resonance imaging; TP = true positive; FP = false positive; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index
OR and 95% CI are bold if the 95% CI does not overlap the value of 1
[1] In patients with paid employment (n=319)

Sensitivity analysis was performed to compare the overall results obtained with the results obtained when patients who already had undergone MRI (n=25) were excluded from the analyses. This sensitivity analysis revealed comparable DORs; however, due to minimally non-significant and significant results, three items crossed the border of significance. When the 25 unblinded cases were excluded, in diagnosing nerve root compression the item "male sex" changed from minimally significant to minimally non-significant (DOR=1.70, 95% CI 1.03–2.81 to DOR=1.66, 95% CI 0.99–2.76), the item "more pain in the leg than in the back" also changed from minimally significant to minimally non-significant (DOR=1.69, 95% CI 1.02–2.79 to DOR=1.63, 95% CI 0.98–2.72), and the item "BMI≥30" changed from minimally non-significant contribution to minimally significant (DOR=0.53, 95% CI 0.27–1.01 to DOR=0.51, 95% CI 0.26–0.98).

Disc herniation (univariate analysis)

A BMI <30, a non-sudden onset, and having subjective sensory loss showed a significant positive value in diagnosing disc herniation on MRI in univariate analysis. The sensitivity analysis to compare the overall results obtained with the results obtained when patients who already had undergone MRI (n=25) were excluded from the analyses, showed comparable DORs .

Nerve root compression (diagnostic model)

Multivariate logistic regression analysis of the six pre-selected history items from the literature revealed an AUC of 0.65 (95% CI 0.58–0.71) of the model diagnosing nerve root compression on MRI (Table 3). This result can be labeled as poor. Bootstrapping of this diagnostic model resulted in an AUC of 0.62 (Fig. 2). Sensitivity analysis of the model of the six pre-selected history items on the outcome "definite about the presence" (instead

Table 3. Multivariate logistic regression analysis of the six pre-selected history items in patients with sciatica (n=377).

Characteristics	Nerve root compression	Disc herniation
	OR (95%CI)	OR (95%CI)
Age (yr)	1.00 (0.97-1.03)	0.99 (0.96-1.02)
Male sex	1.77 (1.05-3.00)	1.51 (0.83-2.76)
Pain worse in leg than in back	1.67 (0.99-2.81)	1.45 (0.80-2.63)
Sensory loss	2.31 (1.10-4.85)	3.54 (1.64-7.64)
Muscle weakness	0.57 (0.31-1.05)	0.69 (0.35-1.36)
Pain worse on coughing/ sneezing/ straining	1.20 (0.68-2.11)	1.10 (0.58-2.10)
AUC of the model	0.65 (0.58-0.71)	0.66 (0.58-0.74)

OR = odds ratio; CI = confidence interval; AUC = area under the receiver operating characteristic curve

of "definite" and "probable") of nerve root compression resulted in an AUC of 0.57 (95% CI 0.51–0.63). Sensitivity analysis of the same model on the outcome "definite about the absence" of nerve root compression resulted in an AUC of 0.73 (95% CI 0.65–0.81). Adding "sudden onset" (the only not already included item with a significant ($p<.05$) DOR) to the original diagnostic model resulted in an AUC of 0.67 (95% CI 0.61–0.74). Bootstrapping of this model resulted in an AUC of 0.62.

Disc herniation (diagnostic model)

Multivariate logistic regression analysis of the six pre-selected history items from the literature revealed an AUC of 0.66 (95% CI 0.58–0.74) of the model diagnosing disc herniation. This result can also be labelled as poor. Bootstrapping of this model resulted in an AUC of 0.63 (Fig. 2). Sensitivity analysis of the model of the six pre-selected history items on the outcome "definite about the presence" (instead of "definite" and "probable") of disc herniation resulted in an AUC of 0.66 (95% CI 0.60–0.72). Sensitivity analysis of the same model on the outcome "definite about the absence" resulted in an AUC of 0.68 (95% CI 0.60–0.75).

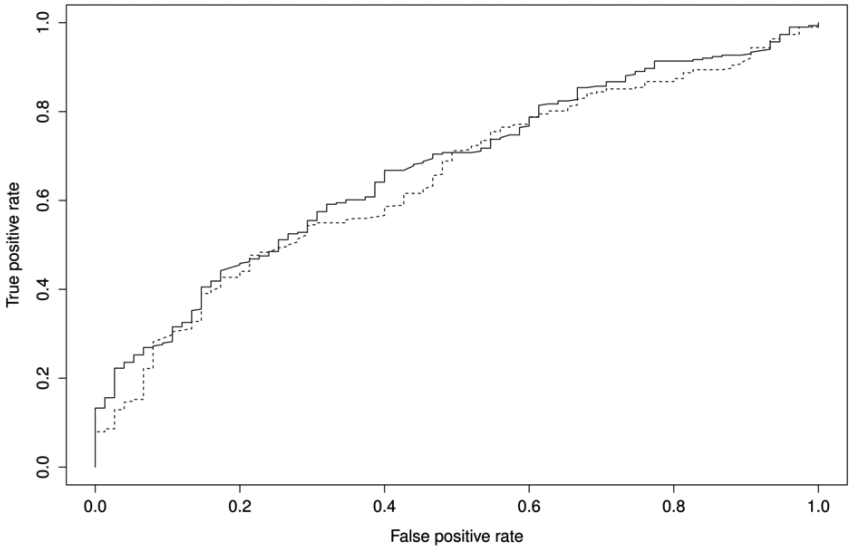

Figure 2. Receiver operating characteristic curves of the models with outcome measure nerve root compression.
Dotted line: model of the 6 pre-selected history items
Solid line: model of the 6 pre-selected history items after adding 'sudden onset' (significant [$p<0.05$] in univariate analysis)

Subsequently, the items with a significant (p<.05) DOR were added to the original diagnostic model. After adding "BMI" as a continuous measure and "sudden onset," the AUC of the diagnostic model of disc herniation increased substantially to 0.72 (95% CI 0.65–0.79). Bootstrapping of this model resulted in an AUC of 0.65 (Fig. 3).

Validation of the adjusted diagnostic model reported by Vroomen et al. in our dataset resulted in an AUC of 0.58 (0.51–0.65).

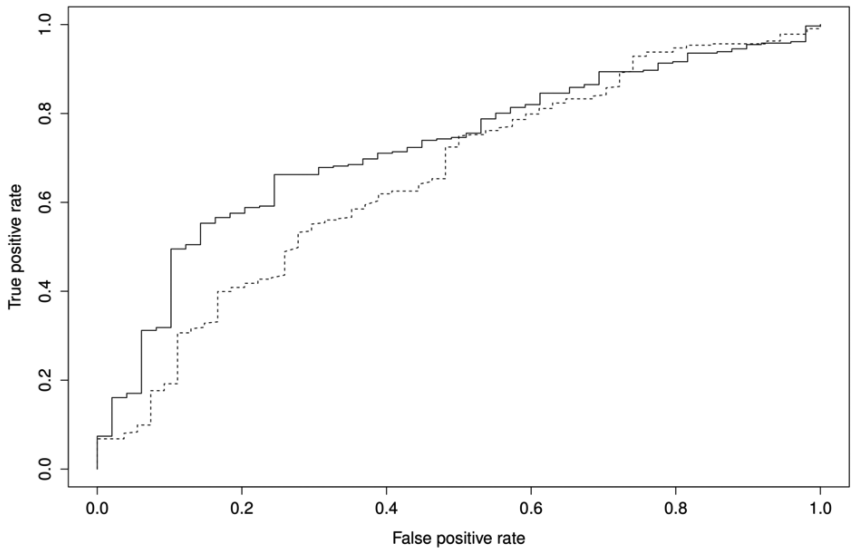

Figure 3. Receiver operating characteristic curves of the models with outcome disc herniation.
Dotted line: model of the 6 pre-selected history items
Solid line: model of the 6 pre-selected history items after adding 'body mass index' and 'sudden onset' (significant [p<0.05] in univariate analysis).

DISCUSSION

This cross-sectional diagnostic study in patients with severe sciatica shows that of 20 history items, "male sex," "pain worse in the leg than in the back," and a "non-sudden onset" have a significant positive value in diagnosing lumbosacral nerve root compression on MRI in univariate analysis. A "BMI <30," a "non-sudden onset," and having "sensory loss" made a significant positive contribution in diagnosing disc herniation on MRI. The accuracy of the diagnostic models with six history items pre-selected from the literature was poor.

The accuracy of the diagnostic models was lower than expected. This may partly be explained by our selection of variables for the models. To prevent overfitting of our models, we choose to include variables based on the literature and supported by clinical experience. Because literature on the diagnostic accuracy of history items is sparse, the selection of variables to create the diagnostic models was based on four studies. This may have resulted in the selection of variables with low/no diagnostic value due to an insufficient evidence-based selection. In daily clinical practice, information from history taking and physical examination is more extensive and combined with the physician's experience. If necessary, the diagnostic pattern is repeated at different time points. It is not possible to combine all this information in a useful diagnostic model. Despite that more information is available in clinical practice, our study shows that although some history items yield useful diagnostic information, the diagnostic accuracy of history taking in assessing lumbosacral nerve root compression and disc herniation might be more limited than previously assumed. The evidence on which to base an optimal diagnostic trajectory of history taking and physical examination in patients with sciatica remains limited and warrants further study.

Area under the ROC curve of the model of the six pre-selected history items on the outcome nerve root compression differed substantially between the three possible cut-off points of the 4-point outcome scale used. The model using the outcome "definite about the absence" showed a fair discrimination of patients with and without definite absence of nerve root compression on the basis of the six pre-selected history items. The differences in AUCs between the models using different cut-off points may be biased by the multi-testing bias and may partly be explained by our 4-point outcome measure that takes uncertainties into account. However, AUC of the model with outcome "definite about the presence" of nerve root compression can even be interpreted as "fail," and AUCs of the same models on the presence of disc herniation did not differ between the different cut-off points. Our finding of a fair discrimination may well indicate that diagnosing the absence of nerve root compression may best be possible on the basis of history items. Further research is necessary before any conclusion can be made.

This is the first diagnostic study in patients with sciatica that used both nerve root compression and disc herniation on MRI as outcomes. Comparison of DORs and AUCs between the outcome measure nerve root compression and the outcome measure disc herniation revealed no clear differences. This shows that we did not find evidence that nerve root compression and disc herniation are very distinct diagnostic constructs in our selected study population.

Although the diagnosis of sciatica is primarily based on history taking and physical examination, only few studies investigated the value of history.[5] Nevertheless, three reviews published between 1999 and 2010 on the diagnostic accuracy of history taking and/or physical examination show generally poor diagnostic accuracy.[3,5,21] Only the study of Vroomen et al. calculated an AUC of their multivariate diagnostic model.[15] Their diagnostic model of history items revealed an AUC of 0.80 (increasing to only 0.83 when adding physical examination items).[15] Validation of this model in the data of our cohort resulted in a much lower AUC of 0.58. This may (for a small part) be caused by our omitting one variable of the original model. However, it is more likely that this considerable difference is largely explained by the setting and the selection of variables. As we selected a secondary care population of patients who are potential candidates for lumbar disc surgery instead of a primary care population, patients with less severe symptoms and symptoms of shorter duration were probably underrepresented, resulting in less contrast in symptomatology. Also, our model was based on items selected from the literature and not from "data-driven" step-wise logistic regression analysis that may be severely overoptimistic.[22] This finding may confirm the instability of the explored diagnostic models for sciatica.

History taking is the basis of many diagnoses in psychiatry, physical examination is the basis of many dermatological diseases, laboratory tests are the basis for many hematological diseases, and imaging is the basis for many conditions potentially needing surgery. The diagnostic accuracy of history items depends on the components and limitations of the reference standard of a disease. There is discussion on the reference standard of nerve root compression and disc herniation.[23] A recent meta-analysis of five studies on the diagnostic accuracy of MRI for identifying disc herniation showed a sensitivity of 75% and a specificity of 77% compared with findings at surgery.[23] A recent study of our research group shows that MRIs performed at 1-year follow-up in patients who had been treated for sciatica and lumbar disc herniation did not distinguish between those with a favorable outcome and those with an unfavorable outcome.[12] One might conclude to lessen focus on MRI findings and pay more attention to clinical outcome measures or operative findings. However, imaging is frequently indicated in patients with severe sciatica who fail to respond to conservative treatment for 6 to 8 weeks as surgery might be considered as treatment option. Imaging is therefore still an important link in our study population. Operative findings probably approach the gold standard better than imaging; however, operative findings are prone to verification bias. As MRI was the reference test in our study, this may have influenced the revealed diagnostic accuracy. However, assessment of MRIs by three spine experts may have lessened this bias.

One limitation of our study is the highly selected population of patients (sequential ordering bias). Therefore, generalizability to less selected populations (as in primary care) is limited. Secondly, inclusion of physical examination in the diagnostic models was not possible. Soon after initiation of the original RCT, history taking and physical examination as described in the protocol proved to be too time-consuming for the attending neurologists. Therefore, history taking was moved to the patient's first visit to the research nurse. However, physical tests were only carried out at the time of randomization during the original RCT after the results of MRI were discussed with the patients. This means that the requirement of blinding to the results of MRI was violated. Another limitation is the risk of multi-testing bias, as we tested 20 history items on two outcomes and created four diagnostic models for each of both outcomes.

CONCLUSION

In conclusion, the present study shows that a few history items used in isolation have significant diagnostic value, but the diagnostic accuracy of a model with six pre-selected items was poor. For now, the diagnostic accuracy of history taking in assessing lumbosacral nerve root compression and disc herniation on MRI seems to be more limited than previously assumed. This may cause difficulty in distinguishing between specific symptoms and non-specific symptoms. Thus, the evidence on which to base an optimal diagnostic trajectory of history taking and physical examination in patients with sciatica remains limited and warrants further study.

REFERENCES

1. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
2. Younes, M., et al., *Prevalence and risk factors of disk-related sciatica in an urban population in Tunisia.* Joint Bone Spine, 2006. **73**(5): p. 538-42.
3. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
4. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-123.
5. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Diagnostic value of history and physical examination in patients suspected of sciatica due to disc herniation: a systematic review.* J Neurol, 1999. **246**(10): p. 899-906.
6. Haswell, K., J. Gilmour, and B. Moore, *Clinical decision rules for identification of low back pain patients with neurologic involvement in primary care.* Spine (Phila Pa 1976), 2008. **33**(1): p. 68-73.
7. Jensen, M.C., et al., *Magnetic resonance imaging of the lumbar spine in people without back pain.* N Engl J Med, 1994. **331**(2): p. 69-73.
8. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
9. Peul, W.C., et al., *Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial [ISRCT 26872154].* BMC Musculoskelet Disord, 2005. **6**: p. 8.
10. el Barzouhi, A., et al., *Magnetic Resonance Imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PLoS ONE, 2013. **8**(7): p. e68411.
11. Pfirrmann, C.W., et al., *MR image-based grading of lumbar nerve root compromise due to disk herniation: reliability study with surgical correlation.* Radiology, 2004. **230**(2): p. 583-8.
12. el Barzouhi, A., et al., *Magnetic resonance imaging in follow-up assessment of sciatica.* N Engl J Med, 2013. **368**(11): p. 999-1007.
13. Fardon, D.F. and P.C. Milette, *Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology.* Spine (Phila Pa 1976), 2001. **26**(5): p. E93-E113.
14. Peduzzi, P., et al., *A simulation study of the number of events per variable in logistic regression analysis.* J Clin Epidemiol, 1996. **49**(12): p. 1373-9.
15. Vroomen, P.C., et al., *Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression.* J Neurol Neurosurg Psychiatry, 2002. **72**(5): p. 630-4.
16. Pople, I.K. and H.B. Griffith, *Prediction of an extruded fragment in lumbar disc patients from clinical presentations.* Spine (Phila Pa 1976), 1994. **19**(2): p. 156-8.
17. Coster, S., S.F. de Bruijn, and D.L. Tavy, *Diagnostic value of history, physical examination and needle electromyography in diagnosing lumbosacral radiculopathy.* J Neurol, 2010. **257**(3): p. 332-7.
18. Hanley, J.A. and B.J. McNeil, *The meaning and use of the area under a receiver operating characteristic (ROC) curve.* Radiology, 1982. **143**(1): p. 29-36.
19. Roelen, C.A., et al., *The development and validation of two prediction models to identify employees at risk of high sickness absence.* Eur J Public Health, 2012. **23**(1): p. 128-33.
20. Vucetic, N., et al., *Diagnosis and prognosis in lumbar disc herniation.* Clin Orthop Relat Res, 1999(361): p. 116-22.

21. van den Hoogen, H.M., et al., *On the accuracy of history, physical examination, and erythrocyte sedimentation rate in diagnosing low back pain in general practice. A criteria-based review of the literature.* Spine (Phila Pa 1976), 1995. **20**(3): p. 318-27.
22. Steyerberg, E.W., et al., *Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets.* Stat Med, 2000. **19**(8): p. 1059-79.
23. Wassenaar, M., et al., *Magnetic resonance imaging for diagnosing lumbar spinal pathology in adult patients with low back pain or sciatica: a diagnostic systematic review.* Eur Spine J, 2012. **21**(2): p. 220-7.

5.
Does localization of worsening of pain during coughing, sneezing and straining matter in the assessment of lumbosacral nerve root compression? A short report.

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(Under review)

ABSTRACT

Background context: Recently we investigated the diagnostic accuracy of history items to assess disc herniation and nerve root compression on magnetic resonance imaging (MRI). One of the questions asked to patients was the influence of coughing, sneezing and straining on the intensity of pain. This question could be answered on a 4 point scale: no worsening of pain, worsening of back pain, worsening of leg pain, worsening of back and leg pain. In our initial analyses we dichotomized these answer categories into "worsening of leg and/or back pain" versus "no worsening of pain". Post hoc we wondered if we used the best dichotomization option in our analysis.

Purpose: To test whether variations in dichotomizing answer options (related to the localization of pain) influences the diagnostic accuracy of the question if pain worsens during coughing, sneezing or straining to assess the presence of lumbosacral nerve root compression and disc herniation on MRI.

Study design: Post hoc analysis of a cross-sectional diagnostic study.

Patient sample: A total of 395 adult patients with severe sciatica of 6 to 12 weeks duration.

Outcome measures: Lumbosacral nerve root compression and disc herniation on MRI were independently assessed by three spine experts blinded to any clinical information.

Methods: Data were prospectively collected in 9 hospitals. History was taken according to a standardized protocol. Diagnostic odds ratio's (DORs) were calculated for the various dichotomization options. There were no study-specific conflicts of interests.

Results: The DOR changed into significant values when the answer option was more narrowed to worsening of leg pain. The highest DOR was observed for the answer option 'worsening of leg pain' with a DOR of 2.28 (95% CI 1.28-4.04) for the presence of nerve root compression and a DOR of 2.50 (95% CI 1.27-4.90) for the presence of a herniated disc on MRI.

Conclusions: Worsening of leg pain during coughing, sneezing or straining has a significant diagnostic value for the presence of nerve root compression and disc herniation on MRI in patients with sciatica. This study highlights the importance of the formulation of answer options in history taking.

INTRODUCTION

The diagnosis of sciatica is based on history taking and physical examination. A recent Cochrane review showed poor diagnostic performance of most physical tests when used in isolation to identify lumbar disc herniation.[1] Recently we investigated the diagnostic accuracy of history items to assess the presence of disc herniation and nerve root compression on magnetic resonance imaging (MRI) in 395 patients with severe sciatica.[2] We observed 'male sex', 'pain worse in the leg than in back' and 'a non-sudden-onset' to be significantly associated with the presence of nerve root compression on MRI and we observed a 'body mass index <30', 'a non-sudden onset', and 'sensory loss' to significantly contribute to the diagnosis of a herniated disc on MRI.[2] The history item 'more pain on coughing, sneezing and straining' did not show a significant contribution. Although just a few trials investigated the diagnostic accuracy of history items, two previous studies did report a significant diagnostic value for this history item.[3,4]

In our study, some history items did not have a yes/no answer option, but a 3- or 4-point answer option which was dichotomized in the analysis. The question on worsening of pain on coughing, sneezing or straining had a 4-point answer option: no worsening of pain, worsening of back pain, worsening of leg pain, worsening of back and leg pain. We initially dichotomized this answer option into 'no worsening of pain' versus 'worsening of pain' regardless of the location of pain (back or leg). Post hoc we wondered if we used the best dichotomization option. In theory, coughing, sneezing or straining increases pressure which results in more irritation or mechanical compression of the nerve root giving more radiating pain in the leg but not in the back. The aim of the present study therefore was to assess whether the diagnostic accuracy of this history item depends on the dichotomization choice of the answer options.

METHODS

Design

This study is a post-hoc analysis of a recently published cross-sectional diagnostic study on the diagnostic accuracy of history items in patients with sciatica.[2] This cross-sectional study consisted of the patients screened for eligibility, including an MRI, for a randomized controlled trial comparing early surgery and prolonged conservative care for severe sciatica.[5] Details on the methods are described in the publications of the randomized controlled trial and the cross-sectional diagnostic study.[2,5,6] There were no study-specific conflicts of interest.

Study population

Eligible patients were 18 to 65 years of age and were diagnosed with severe sciatica that had lasted for 6 to 12 weeks.

Baseline measures

History was taken according to a standardized protocol by six trained research nurses. Worsening of pain on coughing, sneezing or straining could be answered with

A) 'no worsening of pain'
B) 'worsening of back pain'
C) 'worsening of leg pain'
D) 'worsening of back and leg pain'

In the original diagnostic study we dichotomized this answer option into "B, C, D (Worsening of leg and/or back pain)" versus "A (no worsening of pain)". For the present study we also dichotomized this 4-point answer option into "C and D (Worsening of leg pain (with or without back pain))" versus "A and B", and "C (sole worsening of leg pain)" versus "A,B, D".

Reference tests

The presence of lumbosacral nerve root compression and the presence of a herniated disc on MRI were independently assessed by two radiologists and one neurosurgeon blinded to any clinical information. The majority opinion was used in the statistical analysis.[7]

Statistical analysis

Diagnostic odds ratio's (DORs) were calculated for the various dichotomization options. Additionally, sensitivity, specificity, and corresponding 95% confidence intervals (CIs) were calculated.[2]

RESULTS

In total 395 patients were included between November 2002 and February 2005. Table 1 shows the baseline characteristics and outcome measures. Variations in the answer options of the history item on coughing, sneezing and straining did change the perceived diagnostic value (Table 2). The DOR changed into significant values when the answer option was more narrowed to worsening of leg pain. As expected, the sensitivity decreased and the specificity increased. The highest DOR was observed for the answer option 'sole worsening of leg pain', with a DOR of 2.28 (95% Confidence Interval [CI] 1.28-4.04) for the presence of nerve root compression and a DOR of 2.50 (95% CI 1.27-4.90) for the presence of a herniated disc on MRI.

Table 1. Characteristics of the baseline and outcome measures (total n=395)

Age in years	42.8 ± 10.0
Male sex	248 (63)
Duration of leg pain in weeks	7.0 ± 2.3
Score on the visual-analogue scale of pain in the leg[1]	63.0 ± 22.1
Days between history taking and MRI	7.2 ± 9.0
Coughing, sneezing or straining: 'no worsening of pain'	115 (30)
Coughing, sneezing or straining: 'worsening of back pain'	72 (19)
Coughing, sneezing or straining: 'worsening of leg pain'	141 (36)
Coughing, sneezing or straining: 'worsening of back and leg pain'	60 (16)
Assessed as having nerve root compression on MRI	310 (80)
Assessed as having disc herniation on MRI	331 (85)

Values are n (%) or means ± SD.
MRI = magnetic resonance imaging.
[1] The intensity of pain was measured by a horizontal 100-mm visual analog scale, with 0 representing no pain and 100 the worst pain ever experienced.

DISCUSSION

The current post-hoc analysis shows that variations in dichotomizing answer options to the question on coughing, sneezing and straining importantly influenced its sensitivity, specificity and diagnostic accuracy. This result highlights the importance of the formulation of answer options in history taking. Worsening of leg pain on coughing, sneezing or straining appeared to have a significant diagnostic value for the presence of nerve root compression and disc herniation on MRI in patients with severe sciatica.

In both previous diagnostic studies in which a significant diagnostic accuracy of the present history item was found, no location specification of the pain was mentioned.[3,4] One study mentioned 'pain worse on coughing/sneezing/straining' and the other study 'more pain on coughing, sneezing or straining'. No other studies on the diagnostic accuracy of worsening on coughing, sneezing or straining in patients with sciatica were found.

Post-hoc analysis should always be interpreted with caution; we have to bear in mind that there is the risk of multi-testing bias, giving an increased risk that a statistically significant result will arise by chance. Therefore we limited our post-hoc analysis only to the history item on coughing, sneezing and straining. Another limitation is the highly selected population of secondary care patients, which may limit the generalizability.

Table 2. Diagnostic value of the history item on coughing, sneezing or straining for the presence of lumbosacral nerve root compression and/or disc herniation on MRI in patients with sciatica.

	Nerve root compression						Herniated disc				
Characteristics	**Number (total MRI) (%)**	**MRI+ = TP (total MRI+)**	**MRI- = FP (total MRI-)**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**OR (95% CI)**	**MRI+ = TP (total MRI+)**	**MRI- = FP (total MRI-)**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**OR (95% CI)**
Worsening of leg and/or back pain	272 (385) 71%	218 (306)	54 (79)	0.71 (0.66-0.76)	0.32 (0.22-0.43)	1.15 (0.67-1.96)	232 (327)	40 (58)	0.71 (0.66-0.76)	0.31 (0.20-0.45)	1.10 (0.60-2.01)
Worsening of leg pain (with or without back pain)	201 (385) 52%	170 (306)	31 (79)	0.56 (0.50-0.61)	0.61 (0.49-0.72)	**1.94 (1.17-3.21)**	177 (327)	24 (58)	0.54 (0.49-0.60)	0.59 (0.45-0.71)	1.67 (0.95-2.94)
Sole worsening of leg pain	141 (385) 37%	123 (306)	18 (79)	0.40 (0.35-0.46)	0.77 (0.66-0.86)	**2.28 (1.28-4.04)**	129 (327)	12 (58)	0.39 (0.34-0.45)	0.79 (0.67-0.89)	**2.50 (1.27-4.90)**

MRI = magnetic resonance imaging; TP = true positive; FP = false positive; OR = odds ratio; 95% CI = 95% confidence interval

In summary, in this study of patients with severe sciatica the choice of answer option to the question whether pain worsens on coughing, sneezing or straining importantly influenced the diagnostic accuracy of this history item in patients with sciatica. Worsening of leg pain on coughing, sneezing or straining showed a significant diagnostic value for the presence of nerve root compression and disc herniation on MRI in patients with sciatica.

REFERENCES

1. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
2. Verwoerd, A.J., et al., *Diagnostic accuracy of history taking to assess lumbosacral nerve root compression.* Spine J, 2014. **14**(9): p. 2028-37.
3. Coster, S., S.F. de Bruijn, and D.L. Tavy, *Diagnostic value of history, physical examination and needle electromyography in diagnosing lumbosacral radiculopathy.* J Neurol, 2010. **257**(3): p. 332-7.
4. Vroomen, P.C., et al., *Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression.* J Neurol Neurosurg Psychiatry, 2002. **72**(5): p. 630-4.
5. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
6. Peul, W.C., et al., *Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial [ISRCT 26872154].* BMC Musculoskelet Disord, 2005. **6**: p. 8.
7. El Barzouhi, A., et al., *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PLoS One, 2013. **8**(7): p. e68411.

6.
A single question was as predictive of outcome as the Tampa Scale for Kinesiophobia in people with sciatica: an observational study.

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ABSTRACT

Question: In people with sciatica in primary care, can a single question be used to predict outcome at 1 year follow-up as accurately as validated questionnaires on kinesiophobia, disability, and health-related quality of life?

Design: Observational study within a randomised cohort.

Participants: 135 people with sciatica in primary care.

Outcome measures: Kinesiophobia was measured with the Tampa Scale for Kinesiophobia (TSK), disability with the Roland Morris Disability Questionnaire (RDQ), and health-related quality of life with the EQ-5D and the 36-item Short Form (SF-36) Physical Component Summary. Participants also answered a newly devised substitute question for each questionnaire on an 11-point numerical rating scale. Global perceived effect and severity of leg pain were recorded at 1 year follow-up.

Results: The correlation coefficient between the TSK and its substitute question was $r = 0.46$ ($p < 0.001$). The substitute question was better at predicting pain severity in the leg at 1 year follow-up than the TSK (addition of explained variation of 11% versus 4% in a logistic regression analysis). The TSK and its substitute question did not significantly differ in their prediction of global perceived effect at 1 year follow-up. The other substitute questions and both the RDQ and EQ-5D did not contribute significantly to one or both of their prediction models.

Conclusion: It may be feasible to replace the TSK by a single substitute question for predicting outcome in people with sciatica in primary care. The other substitute questions did not consistently predict outcome at 1 year follow-up.

INTRODUCTION

Sciatica, also called lumbosacral radicular syndrome, is characterised by radiating pain in the leg that extends to below the knee in one or more lumbar or sacral dermatomes. A herniated disc is the most common cause of sciatica. The estimated incidence of sciatica in the Netherlands is 9 per 1000 inhabitants per year.[1] Although the natural course is generally favourable, social and economic effects are large.

Validated questionnaires are used on a regular basis in health care and research. Four questionnaires are part of a recommended set of patient-based outcome measures in spinal disorders and are frequently used in people with sciatica.[2,3] The four questionnaires are the Tampa Scale for Kinesiophobia[4], the Roland Morris Disability Questionnaire[5], the EQ-5D[6], and the 36-item Short Form (SF-36).[7] The Tampa Scale for Kinesiophobia measures fear of movement, the Roland Morris Disability Questionnaire measures disability, and the EQ-5D and the SF-36 measure health-related quality of life. The term kinesiophobia was introduced by Kori et al[4] as *an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury*. Assessing kinesiophobia, disability and health-related quality of life in people presenting with sciatica provides important information and may support decision-making in daily clinical practice.

Although these questionnaires may be valuable, they are time consuming to administer. Therefore, modifications and abbreviations of the Tampa Scale for Kinesiophobia, Roland Morris Disability Questionnaire, and SF-36 have been developed and validated to make them easier to use. The 18-item version of the Roland Morris Disability Questionnaire and the 12-item version of the SF-36 are well-known examples.[8,9] In clinical practice it would be more efficient if just one question could assess kinesiophobia, disability, or health-related quality of life validly in people with sciatica. Such questions would be likely to increase assessment by clinicians of these important parameters during consultations. All four questionnaires have multiple purposes, including assessment of the severity of symptoms and their change over time, as well as the provision of prognostic information. To our knowledge, individual questions have not been tested for their ability to replace the Tampa Scale for Kinesiophobia, the Roland Morris Disability Questionnaire, the EQ-5D, or the SF-36 in people with sciatica for any of these purposes. Therefore, the research question of our study was: In people with sciatica in primary care, can a single question be used to predict outcome at 1 year follow-up as accurately as validated questionnaires on kinesiophobia, disability, or health-related quality of life?

METHOD

Design

This was an observational study using the data of 135 people with sciatica who participated in a randomised controlled trial that assessed the cost-effectiveness of physical therapy plus general practitioner care versus general practitioner care alone.[10] Of 170 people screened, 11% were ineligible and 9% refused to participate. Measures were taken at baseline, at 3, 6 and 12 weeks, and at 1 year.

Participants

General practitioners in Rotterdam and the surrounding area invited people with acute sciatica to participate. Participants were required to be aged 18 to 65 years, to be able to speak and read Dutch, and to have radiating pain in the leg extending to below the knee with a duration of <6 weeks and a severity of pain scored above 3 on an 11-point numerical rating scale (NRS) where 0 = no pain and 10 = maximum pain.[11] Another inclusion criterion was the presence of one of the following symptoms: more pain on coughing, sneezing or straining, decreased muscle strength in the leg, sensory deficits in the leg, decreased reflex activity in the leg or a positive straight leg raise test.

Candidate predictors

The Tampa Scale for Kinesiophobia, Roland Morris Disability Questionnaire, EQ-5D and SF-36 were completed at baseline. In a consensus meeting of the investigators of the trial, newly devised questions that were thought to be able to cover and therefore substitute for the entire questionnaire (ie, substitute questions) were discussed and chosen on the basis of consensus. Each substitute question was answered on an 11-point numerical rating scale, as described below. The substitute questions were devised and used in Dutch but have been translated by a native speaker for publication in English. The substitute questions were completed at the same time as the questionnaires.

Kinesiophobia: The Tampa Scale for Kinesiophobia is a validated questionnaire to measure fear of movement.[4,12] The Tampa Scale for Kinesiophobia consists of 17 questions that can be answered on a 4-point Likert scale (strongly disagree, disagree, agree, and strongly agree). The substitute question for the Tampa Scale for Kinesiophobia was introduced with the sentence, *You visited your general practitioner because of complaints in your back or leg*, followed by the question *How much 'fear' do you have that these complaints would be increased by physical activity?* (scores range from 0 = no fear, to 10 = very much fear).

Disability: The Roland Morris Disability Questionnaire for sciatica is a validated measurement for disability.[5,13] It contains 24 questions that can be answered with 'yes' or 'no'. The

substitute question for the Roland Morris Disability Questionnaire was, *In your normal daily activities, how much trouble do you have from your back or leg complaints?* (scores range from 0 = no trouble, to 10 = maximal trouble).

Health-related quality of life: The EQ-5D is a validated measurement of health outcome.[6,14] The EQ-5D was developed by the EuroQol group and consists of 5 questions on mobility, self care, usual activities, pain/discomfort, and anxiety/depression, with 3 answer categories. A weighted sum results in a score in the range –0.3 to 1, with higher scores indicating better health status. The SF-36 is a validated questionnaire to survey health status.[7,15] It contains 36 questions, each with 2 to 5 response options. The SF-36 has no overall score, but two summary scores can be calculated: a physical component summary and a mental component summary. Because of a large overlap, we created one substitute question for both the EQ-5D and the SF-36 physical component summary. This substitute question was, *How would you rate your general health?* (scores range from 0 = excellent, to 10 = very poor).

Outcome measures

Outcome measures were global perceived effect and pain severity in the leg at 1 year follow-up. Assessment of the outcome measures was done using a mailed questionnaire to be filled out by each participant. Global perceived effect was measured on a 7-point scale ranging from 1 = completely recovered, to 7 = vastly worsened. Global perceived effect is regarded as a clinically relevant, reliable, and responsive outcome measure.[2,16] We dichotomised the ratings into 'recovered' ('completely recovered' and 'much improved') and 'not recovered' ('slightly improved' to 'worse than ever').[17] Pain severity in the leg was scored on an 11-point numerical rating scale ranging from 0 = no pain, to 10 = unbearable pain.[11] A numerical rating scale is regarded as a clinically relevant, reliable, valid, and responsive pain scale.[16]

Data analysis

Missing values in the original trial database were imputed by assigning the last available score. Our research question was answered by calculating correlations and applying logistic regression models. First, descriptive statistics of scores on the questionnaires and substitute questions were calculated. Next, Pearson correlation coefficients were calculated between the baseline scores of the Tampa Scale for Kinesiophobia, Roland Morris Disability Questionnaire, EQ-5D, the SF-36 physical component summary, and the substitute question for each questionnaire. A correlation coefficient of 0.10 was classified as small, 0.30 as medium, and 0.50 as a large correlation.[18] For every Pearson correlation the corresponding assumptions were tested and variables were transformed if the assumptions of normal distribution were violated.

Finally, multivariate logistic regression analyses were performed to predict recovery (global perceived effect) at 1 year follow-up. We respected the rule of 10 cases per eligible variable and adjusted the analyses for three covariates.[19] The participants in the original trial were randomised between physical therapy plus general practitioner care versus general practitioner care alone. As physical therapy did influence global perceived effect at 1 year follow-up, the analyses were adjusted for treatment.[17] We also adjusted for gender[20-23] and duration of symptoms at baseline[24-28] because of their reported influence on outcome in patients with sciatica. To avoid problems due to multicollinearity we decided to perform three distinct regression analyses. The independent variables that were entered in the analysis differed between these models: A) treatment, gender, and duration of symptoms; B) same as A + the unique substitute question; and C) same as A + the score of the questionnaire. Differences in the predictive power between these models were analysed using the Nagelkerke R^2.[29] R^2 represents the proportion of variation explained by variables in regression models. If a model could perfectly predict outcome at 1 year follow-up, the explained variation would be close to 100%. We considered the same, or an even higher, explained variation of model B compared to model C as an indication that it might be feasible to replace the questionnaire by its substitute question in predicting outcome at 1 year follow-up. The same multivariate analyses were carried out with severity of pain in the leg as the dependent variable. The residuals of a linear regression model with outcome pain showed a non-normal distribution and thus corresponding assumptions for linear regression analysis were violated. Therefore, we decided to do a binary logistic regression analysis with the outcome 'pain severity in the leg' in our population dichotomised as ≤ 1 = no pain and > 1 = pain. We also checked for consistency in results when changing the threshold from 1 to 2 or 3. In every model we tested for interaction between treatment and the substitute question, or treatment and score of the questionnaire, and reported if the interaction made a significant contribution to the model. We tested this interaction because the effect on prognosis of the severity of disease at baseline, expressed in the scores of the questionnaires and substitute questions, may depend on the treatment received.

For the substitute questions that were at least as good as their questionnaires in predicting outcome, the test-retest reliability was assessed by using the Pearson correlation coefficient. It is suggested that a reliability coefficient of 0.7 or higher is acceptable.[30] As the natural course of sciatica is favourable, we chose the measures at 3 and 6 weeks follow-up for calculation of the test-retest correlations as these were assumed to be the least influenced by the favourable natural course of sciatica. Also, the participants were already used to the trial setting, the treatment determined by randomisation and to answering the substitute questions and questionnaires.

RESULTS

Table 1 shows the baseline characteristics of the 135 participants and the outcomes at 1 year follow-up; 18 participants were lost to follow-up or had incomplete data at 1 year, necessitating carry forward of the last available score.

Table 1. Baseline characteristics of participants and outcomes at 1 year follow-up.

	Baseline (n=135)	1-year follow-up (n=135)
Age *(yr)*, mean (SD)	43 (11)	
Gender, n male (%)	70 (52)	
Duration of sciatica *(days)*, mean (SD)	13 (10)	
More pain on coughing, sneezing or straining, n (%)	77 (57)	
Positive straight leg raise test, n (%)	72 (53)	
Decreased muscle strength, n (%)	92 (68)	
Sensory deficits, n (%)	107 (79)	
TSK score *(17 to 68)*[1], mean (SD)	40 (7)	
Substitute question TSK *(0 to 10)*[2], mean (SD)	4.0 (2.7)	
RDQ score *(0 to 24)*[3], mean (SD)	16 (4)	
Substitute question RDQ *(0 to 10)*[2], mean (SD)	7.1 (2.1)	
EQ-5D score *(-0.3 to 1)*[4], mean (SD)	0.5 (0.3)	
SF-36 PCS *(0 to 100)*[5], mean (SD)	34 (8)	
Substitute question EQ-5D and SF-36 PCS *(0 to 10)*[2], mean (SD)	4.5 (2.4)	
Leg pain on NRS *(0 to 10)*[6], mean (SD)	6.3 (2.2)	2.4 (2.5)
Not recovered, n (%)		44 (33)
Leg pain >1 on NRS[6], n (%)		69 (51)

[1] TSK = Tampa Scale for Kinesiophobia; higher scores indicate more kinesiophobia.
[2] Higher scores indicate more complaints.
[3] RDQ = Roland Morris Disability Questionnaire; higher scores indicate more disability.
[4] Higher scores indicate better health status.
[5] SF-36 PCS = 36-item Short Form Physical Component Summary; higher scores indicate better health status. US norm population: 50 ± 10.
[6] NRS = Numerical Rating Scale; higher scores indicate more pain.

Kinesiophobia

Testing the correlation between the Tampa Scale for Kinesiophobia and its unique substitute question at baseline resulted in a correlation coefficient of 0.46 (Table 2). Table 3 shows the explained variation of the three separate models on global perceived effect and severity of leg pain at 1 year follow-up, as well as the p values of the contribution of the substitute question and the original questionnaire to their models. Both the Tampa Scale for Kinesiophobia and its substitute question had prognostic properties to predict

global perceived effect and pain at 1 year follow-up. The substitute question explained more of the variation in pain severity in the leg than did the Tampa Scale for Kinesiophobia. The interaction term between treatment and the score of the substitute question contributed significantly to the pain model.

The mean score of the substitute question at 3 weeks follow-up was 3.7 (SD 2.8) and at 6 weeks follow-up was 3.6 (SD 2.9). The Pearson correlation coefficient between these scores of the substitute questions was 0.65, indicating acceptable test-retest reliability, taking into account that the reliability coefficient is directly dependent on the number of items. In classical test theory, a test with a limited number of items has a lower reliability, which limits the obtainable reliability for a single question.[31]

Table 2. Pearson correlation coefficients between the four analysed questionnaires and their substitute questions at baseline.

Questionnaire	Correlation with substitute question (Pearson correlation coefficient)	*p* value
Tampa Scale for Kinesiophobia	0.464	<0.001
Roland Morris Disability Questionnaire	0.319	<0.001
EQ-5D	0.131	0.128
36-item Short Form Physical Component Summary	0.134	0.122

Table 3. Explained variations of the three logistic regression models related to the Tampa Scale for Kinesiophobia with the outcomes global perceived effect and pain and the corresponding *p* values of the contribution of the substitute question or the TSK to the models.

Model	Independent Variables	Global perceived effect		Pain	
		R^2	*p* value	R^2	*p* value
A	Treatment, gender, duration of complaint	0.127		0.047	
B	Model A + substitute question of TSK[1]	0.174	0.027	0.253 (0.156)[2]	0.876 (0.001)[2]
C	Model A + TSK score	0.178	0.022	0.088	0.040

TSK = Tampa Scale for Kinesiophobia; R^2 = Nagelkerke's R^2.

[1] The contribution of the substitute question to the Pain model was dependent on the presence of the interaction term *treatment*substitute question*.

[2] Without interaction term.

Disability

The correlation coefficient between the Roland Morris Disability Questionnaire and its unique substitute question was 0.32 (Table 2). Table 4 shows the explained variation of the models predicting global perceived effect and pain. The substitute question did not have a prognostic ability to predict global perceived effect and pain severity in the

leg at 1 year follow-up. The Roland Morris Disability Questionnaire made a significant contribution to the model in predicting pain severity at 1 year follow-up.

Health-related quality of life

The correlation between the EQ-5D and its substitute question was 0.13 (Table 2). Table 4 shows the explained variation of the three separate models on global perceived effect and pain at 1 year follow-up, and the contribution of the EQ-5D and the substitute question to their models. The EQ-5D did not have a significant contribution in its prediction models. The substitute question only contributed significantly to the model predicting pain severity in the leg.

Table 4. Explained variations of the three logistic regression models related to the Roland Morris Disability Questionnaire, the EQ-5D and the 36-item Short Form Physical Component Summary with the outcomes global perceived effect and pain at 1 year follow-up, and the corresponding *p* values of the contribution of the substitute question or the questionnaires to the models.

Questionnaire	Independent Variables	Global perceived effect		Pain	
Model		R^2	*p* value	R^2	*p* value
RDQ					
A	Treatment, gender, duration of complaint	0.127		0.047	
B	Model A + substitute question of RDQ	0.139	0.268	0.056	0.325
C	Model A + RDQ score	0.130	0.567	0.100	0.020
EQ-5D					
A	Treatment, gender, duration of complaint	0.127		0.047	
B	Model A + substitute question of EQ-5D	0.144	0.177	0.120	0.006
C	Model A + EQ-5D score	0.143	0.183	0.058	0.286
SF-36 PCS					
A	Treatment, gender, duration of complaint	0.127		0.047	
B	Model A + substitute question of SF-36 PCS	0.144	0.177	0.120	0.006
C	Model A + SF-36 PCS score	0.168	0.040	0.086	0.043

RDQ = Roland Morris Disability Questionnaire; SF-36 PCS = 36-item Short Form Physical Component Summary; R^2 = Nagelkerke's R^2

The correlation coefficient between the SF-36 Physical Component Summary and its substitute question was 0.13 (Table 2). Table 4 shows the explained variation of the three separate prediction models on global perceived effect and pain at 1 year follow-up, and the contribution of the SF-36 Physical Component Summary and its substitute question to their models. The SF-36 Physical Component Summary had prognostic properties to predict both global perceived effect and pain. The substitute question only made a significant contribution to the model in predicting pain severity in the leg.

Changing the cut-off point for dichotomisation of the outcome measure pain to 2 or 3 resulted in a relatively stable decrease in the explained variation in all the models.

DISCUSSION

The present study shows that it may be feasible to replace the Tampa Scale for Kinesiophobia by its unique substitute question when predicting outcome at 1 year follow-up in people with sciatica. These results are promising and suggest that it is worth testing the validity of the substitute question in additional studies. The substitute questions for the Roland Morris Disability Questionnaire, the EQ-5D, and the SF-36 Physical Component Summary did not contribute significantly to one or both of their models and therefore were not able, or were not consistently able, to predict outcome at 1 year follow-up in people with sciatica.

Some correlations between the different questionnaires and their substitute questions were small, while others were close to large, providing strong evidence of convergent validity.[18] The weak correlation between both the EQ-5D and SF-36 Physical Component Summary and their substitute question can be explained by the multidimensionality of both questionnaires and their solid psychometric basis. Therefore, it is not very likely that the EQ-5D and SF-36 Physical Component Summary can be replaced by one question. Although both single questions and multi-item measures have their strengths and weaknesses, the classic measurement theory holds that multi-item measures result in more reliable and precise scores. This is because more items produce replies that are more consistent and less prone to distortion from sociopsychological biases. This enables the random error of the measure to be cancelled out. In this respect, the substitute question for the Tampa Scale for Kinesiophobia showed acceptable convergent validity and test-retest reliability.

The correlation between the Tampa Scale for Kinesiophobia and its substitute question ($r = 0.46$) approximated the value nominated as large ($r = 0.50$) by Cohen.[18] The substitute question showed the same prognostic properties as the Tampa Scale for Kinesiophobia in predicting recovery at 1 year follow-up, and even better prognostic properties in predicting severity of leg pain at 1 year follow-up. Although the explained variations of the models decreased when the cut-off point of the outcome pain severity in the leg was set at 2 or 3 instead of 1, the decrease was relatively stable in the models and did not change the conclusions derived from our data. These consistent findings show that it might be feasible to replace the Tampa Scale for Kinesiophobia by its unique substitute question in predicting outcome at 1 year follow-up in people with sciatica

in primary care. Nevertheless, these results need to be further evaluated and validated in additional studies. Extensive psychometric testing of the substitute question for the Tampa Scale for Kinesiophobia was not done in this present study as this was not our aim, but will be necessary in future studies. Especially, further testing of the reliability, validity, and responsiveness of the substitute question is needed to establish the usefulness of this question in daily clinical practice. Item Response Theory can be applied to determine whether the scales are uni-dimensional and measure the same underlying construct as the substitute questions.

No study was found that reported on the prognostic properties of the Tampa Scale for Kinesiophobia and EQ-5D in people with sciatica. On the other hand, the Roland Morris Disability Questionnaire[32,33,34] and the SF-36 Physical Component Summary[32,35] are prognostic in people with sciatica. In the present exploratory analyses, both the Tampa Scale for Kinesiophobia and the SF-36 Physical Component Summary were consistently prognostic.

Although this study presents novel results, its exploratory design brings inevitable limitations. First, we do not know if the substitute questions exactly cover the scope and content of the questionnaires for which they were developed. It is possible that the substitute question explains a different part of the model and that comparing the explained variations between the models may not be fully valid. Second, firm conclusions on the replacement of the Tampa Scale for Kinesiophobia by its substitute question cannot be made as further extensive psychometric testing is needed. Third, the relatively small sample size may have limited the power of the analyses. Finally, because we tested the feasibility of replacing a questionnaire by one unique substitute question in a prediction model only in people with sciatica in primary care, the generalisability of these results to other groups is limited. Nevertheless, the single question was as predictive of outcome as the Tampa Scale for Kinesiophobia in this population, so it may represent a more time-efficient means for clinicians to ascertain the likely outcome of people with sciatica.

REFERENCES

1. Mens, J.M., et al., *NHG-Standaard Lumbosacraal radiculair syndroom.* Huisarts Wet, 2005. **48**(4): p. 171-8.
2. Bombardier, C., *Outcome assessments in the evaluation of treatment of spinal disorders: summary and general recommendations.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3100-3.
3. Deyo, R.A., et al., *Outcome measures for low back pain research. A proposal for standardized use.* Spine (Phila Pa 1976), 1998. **23**(18): p. 2003-13.
4. Kori, S.H., R.P. Miller, and D.D. Todd, *Kinesophobia: a new view of chronic pain behaviour.* Pain Manage, 1990. **Jan/Feb**: p. 35-43.
5. Roland, M. and R. Morris, *A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain.* Spine (Phila Pa 1976), 1983. **8**(2): p. 141-4.
6. The EuroQol Group, *EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group.* Health Policy, 1990. **16**(3): p. 199-208.
7. Ware, J., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
8. Stratford, P.W. and J.M. Binkley, *Measurement properties of the RM-18. A modified version of the Roland-Morris Disability Scale.* Spine (Phila Pa 1976), 1997. **22**(20): p. 2416-21.
9. Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.
10. Luijsterburg, P.A., et al., *Cost-effectiveness of physical therapy and general practitioner care for sciatica.* Spine (Phila Pa 1976), 2007. **32**(18): p. 1942-8.
11. Von Korff, M., M.P. Jensen, and P. Karoly, *Assessing global pain severity by self-report in clinical and health services research.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3140-51.
12. Haugen, A.J., et al., *Cross-cultural adaptation and validation of the Norwegian version of the Tampa scale for kinesiophobia.* Spine (Phila Pa 1976), 2008. **33**(17): p. E595-601.
13. Patrick, D.L., et al., *Assessing health-related quality of life in patients with sciatica.* Spine (Phila Pa 1976), 1995. **20**(17): p. 1899-908; discussion 1909.
14. Lamers, L.M., et al., *The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies.* Health Econ, 2006. **15**(10): p. 1121-32.
15. Aaronson, N.K., et al., *Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations.* J Clin Epidemiol, 1998. **51**(11): p. 1055-68.
16. Dworkin, R.H., et al., *Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.* Pain, 2005. **113**(1-2): p. 9-19.
17. Luijsterburg, P.A., et al., *Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up.* Eur Spine J, 2008. **17**(4): p. 509-17.
18. Cohen, J., *A power primer.* Psychol Bull, 1992. **112**(1): p. 155-9.
19. Peduzzi, P., et al., *A simulation study of the number of events per variable in logistic regression analysis.* J Clin Epidemiol, 1996. **49**(12): p. 1373-9.
20. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
21. Peul, W.C., et al., *Influence of gender and other prognostic factors on outcome of sciatica. Pain*, 2008. **138**(1): p. 180-91.

22. Skouen, J.S., et al., *Cerebrospinal fluid protein concentrations in patients with sciatica caused by lumbar disc herniation: an investigation of biochemical, neurologic, and radiologic predictors of long-term outcome.* J Spinal Disord, 1997. **10**(6): p. 505-11.
23. Weber, H., Lumbar disc herniation. *A prospective study of prognostic factors including a controlled trial. Part II.* J Oslo City Hosp, 1978. **28**(7-8): p. 89-113.
24. Carragee, E.J. and D.H. Kim, *A prospective analysis of magnetic resonance imaging findings in patients with sciatica and lumbar disc herniation. Correlation of outcomes with disc fragment and canal morphology.* Spine (Phila Pa 1976), 1997. **22**(14): p. 1650-60.
25. Tubach, F., J. Beaute, and A. Leclerc, *Natural history and prognostic indicators of sciatica.* J Clin Epidemiol, 2004. **57**(2): p. 174-9.
26. Valls, I., et al., *Factors predicting radical treatment after in-hospital conservative management of disk-related sciatica.* Joint Bone Spine, 2001. **68**(1): p. 50-8.
27. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-23.
28. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *When does the patient with a disc herniation undergo lumbosacral discectomy?* J Neurol Neurosurg Psychiatry, 2000. **68**(1): p. 75-9.
29. Nagelkerke, N.J., *A Note on a General Definition of the Coefficient of Determination.* Biometrika, 1991. **78**(3): p. 691-692.
30. Cicchetti, D.V., *Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology.* Psychological Assessment, 1994. **6**(4): p. 284-290.
31. Cronbach, L.J., *Essentials of psychological testing.* 5th ed1990, New York: Harper Collins.
32. Edwards, R.R., et al., *Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes.* Pain, 2007. **130**(1-2): p. 47-55.
33. Jensen, O.K., C.V. Nielsen, and K. Stengaard-Pedersen, *One-year prognosis in sick-listed low back pain patients with and without radiculopathy. Prognostic factors influencing pain and disability.* Spine J, 2010. **10**(8): p. 659-75.
34. Peul, W.C., et al., *Improving prediction of "inevitable" surgery during non-surgical treatment of sciatica.* Pain, 2008. **138**(3): p. 571-6.
35. Atlas, S.J., et al., *The impact of disability compensation on long-term treatment outcomes of patients with sciatica due to a lumbar disc herniation.* Spine (Phila Pa 1976), 2006. **31**(26): p. 3061-9.

7.

Effect of physical therapy on the relation of kinesiophobia and outcome in patients with sciatica in primary care: a subgroup analysis from a randomized controlled trial.

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ABSTRACT

Background. A higher level of kinesiophobia seems to be associated with poor recovery in patients with sciatica.

Objective. To investigate the effect of physical therapy on the relation of kinesiophobia at baseline with outcome in patients with sciatica.

Design. A subgroup analysis from a randomized controlled trial.

Setting. Primary care.

Patients. A total 135 patients with acute sciatica.

Intervention. Patients were randomized to physical therapy plus general practitioners' care or to general practitioners' care alone.

Measurements. Kinesiophobia at baseline was measured with the Tampa Scale for Kinesiophobia (TSK) and a single substitute question for kinesiophobia (SQK). Pain and recovery were assessed at 3 and 12-months follow-up. Regression analysis was used to test for interaction between the level of kinesiophobia at baseline and treatment allocation. Subgroup results were calculated for patients 'suggestive of high fear of movement' and for patients 'suggestive of low fear of movement'.

Results. Physical therapy significantly interacted with kinesiophobia at baseline in the analysis with leg pain intensity at 12-months follow-up (interaction effect for TSK and SQK: $p=0.07$ and $p<0.01$, respectively). Of the 73 patients 'suggestive of high fear of movement', patients randomized to the physical therapy group non-significantly reported one point lower at a 0-10 scale of leg pain intensity at 12-months follow-up compared to the control group (1.8 vs 2.8). Physical therapy did not interact with kinesiophobia at baseline regarding any outcome at 3-months follow-up or recovery at 12-months follow-up.

Limitations. The post-hoc study design and relatively small sample size.

Conclusions. In these patients with sciatica, there is preliminary evidence that physical therapy may reduce the negative effect of kinesiophobia at baseline on reported leg pain intensity at 12-months follow-up.

INTRODUCTION

Sciatica is characterized by radiating leg pain and related disabilities.[1] It affects many people and has significant medical, social and economic impact. The annual prevalence as reported in nine epidemiologic studies ranges from 2.2-34%.[2] The natural course is generally favorable.[3,4] It is important to adequately inform the patient about the diagnosis and prognosis. The advice to stay active is recently reviewed as 'likely to be beneficial'.[1] A recent evidence-based clinical guideline of the North American Spine Society states that there is insufficient evidence to make recommendations for or against the use of physical therapy or structured exercise programs for patients with sciatica.[5]

We previously reported the clinical results of a randomized controlled trial (RCT) that compared general practitioners' (GPs) management alone with GPs' management plus physical therapy in patients with sciatica. We observed that additional physical therapy is effective with regard to global perceived recovery at 1-year follow-up, but not more cost-effective compared to GP care alone.[6,7]

In recent spine literature, increasing attention is paid to identifying subgroups of patients with specific prognostic profiles to offer targeted treatments with the aim to improve treatment effects and/or to better predict prognosis.[8] The presence of fear of movement might be such a subgroup characteristic.[9] The term kinesiophobia was introduced in 1990: this condition was described as an irrational and debilitating fear of physical movement resulting from a feeling of vulnerability to painful injury of re-injury.[10] Kinesiophobia, together with other psychological factors, is reported to play an important role in (the development of) chronic symptoms and their perception.[11] A recent study involving 466 patients with sciatica showed that kinesiophobia was associated with non-success at 2-year follow-up.[12] In theory, physical therapy may reduce fear of movement and improve outcome by informing the patient, by reassurance that movement will not harm, by guidance and promotion of mobility, by optimizing functional ability, by using the existing movement potential and patient tailored exercises. Patients with fear of movement may therefore form a plausible subgroup that especially benefits from physical therapy.

We hypothesized that physical therapy may reduce any negative effect of kinesiophobia on outcome. Therefore, the aim of the present study was to investigate the effect of physical therapy on the relation between kinesiophobia at baseline and leg pain severity and recovery at 3 and 12-months follow-up in patients with sciatica.

METHODS

Design Overview

The current study was a post-hoc analysis of a RCT comparing GP management alone with GP management plus physical therapy in patients with sciatica in primary care.[7,13] Details on the methods are described in the original publications.[6,7,13] The original trial was registered at www.controlled-trials.com (ISRCTN68857256). The Erasmus Medical Center Ethics Committee approved the procedures and design of the trial.

Setting and Participants

Between May 2003 and November 2004 participating GPs (n=112) invited patients with acute sciatica to participate in the trial. Most important inclusion criteria were radiating (pain) complaints in the leg below the knee of less than 6 weeks duration and with a severity of complaints scored above 3 on an 11-point numerical rating scale (0 = no complaints and 10 = maximum complaints).[7]

Randomization and Interventions

All patients received care from their GP according to clinical guidelines.[13] Physical therapy consisted of exercise therapy in combination with information and advice about sciatica. The treatment protocol was developed in a consensus meeting with the participating physical therapists.[7,13]

Fear of movement at baseline was measured using two questionnaires: 1) the Tampa Scale for Kinesiophobia (TSK), and 2) a newly devised substitute question to measure fear of movement on a numerical rating scale. The TSK is a validated questionnaire to measure fear of movement and consists of 17 items rated on a 4-point Likert scale.[10,14] The scores range from 17-68 points with higher scores indicating a higher level of kinesiophobia. Although the TSK may be valuable in daily clinical practice, it is time consuming to administer. Therefore, the investigators of the trial decided (during a consensus meeting) to apply one single question for measuring kinesiophobia. This question was introduced with the sentence *'You visited your general practitioner because of complaints in your back or leg'* followed by the question '*How much 'fear' do you have that these complaints would be increased by physical activity?'*. This question could be answered on an 11-point numerical rating scale ranging from 0 (no fear) to 10 (very much fear). Below, we refer to this question as Substitute Question Kinesiophobia (SQK). In a previous study we showed that this SQK may be feasible to replace the TSK for predicting outcome in patients with sciatica in primary care.[15]

Outcomes and Follow-up

Both recovery (global perceived effect) and leg pain intensity at 3 and 12-months follow-up were used as outcome measures. Global perceived effect was measured on a 7-point scale ranging from 1 (completely recovered) to 7 (vastly worsened).[16] This rating scale was dichotomized as recovery ('completely recovered' and 'much improved') and no recovery ('slightly improved' to 'worse than ever').[7] Leg pain intensity was scored on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (unbearable pain).[17]

Statistical Analysis

To test whether there is an interaction effect between the level of kinesiophobia at baseline and physical therapy we used regression analyses, with the outcomes recovery and leg pain intensity at 3 and 12-months follow-up. The regression analysis models contained as independent variables the treatment allocation (whether or not physical therapy), the level of kinesiophobia, and the interaction between them, and (according to the outcome measured) recovery or leg pain intensity as the dependent variable. The regression analysis with outcome leg pain intensity was adjusted for leg pain intensity at baseline. As the level of kinesiophobia was measured by two different questionnaires, all analyses were performed twice (with either TSK or SQK in the model). Basic statistical assumptions for linear regression were tested for the analysis with the outcome leg pain intensity, reported when violated, and handled according to up-to-date knowledge. Statistical significance for the interaction test was defined as $p < 0.10$, because of the lower power of the interaction test.[18]

In addition, for ease of clinical interpretation, descriptive statistics were calculated for patients 'suggestive of high fear of movement' and patients 'suggestive of low fear of movement'. In a highly cited Dutch study in chronic low back pain patients, the median TSK score of 37 was used as the cut-off for dividing the group into low responders (TSK ≤ 37) and high responders (TSK >37).[9] In accordance, the present study used the same cut-off point.[19-21] For both the patients 'suggestive of high fear of movement' and 'suggestive of low fear of movement', differences in leg pain intensity at 3 and 12-months follow-up between the randomization groups were assessed by using Student's t-test and differences in recovery were assessed by using the chi-square test.

Patients without complete questionnaires at 3 or 12-months follow-up were excluded from the analyses. At 3 and 12-months follow-up clinical outcomes were missing for 7% and 13% of the patients, respectively.[7] Four patients in the physical therapy group (6%) and 3 patients in the control group (4%) received surgery.[7] As these numbers of surgical intervention for sciatica were small, we did not correct for it in the analyses. Baseline dif-

ferences between patients with and without complete questionnaires were (depending on the type of variable) assessed by comparing means or percentages.

Role of the Funding Source

The Dutch Health Care Insurance Board (CvZ) funded the original RCT. The funding source had no involvement in the design, conduct, or reporting of results.

RESULTS

A total of 135 patients were included and randomized (Figure 1); of these, 67 received GP care plus physical therapy (intervention group) and 68 received GP care alone (Table 1). Patients in the intervention group reported a mean of 6.7 and 9.7 physical therapy treatments at 6 weeks and 12-weeks follow-up, respectively. At 3-months after randomization, 68% of the patients reported recovery (73% in the intervention group vs. 63% in the control group) and patients reported a mean leg pain intensity of 2.6 (2.3 in the intervention group vs. 2.8 in the control group). At 12-months after randomization, 73% of the patients reported recovery (82% in the intervention group vs. 63% in the control group) and patients reported a mean leg pain intensity of 2.1 (1.8 in the intervention group vs. 2.4 in the control group). The missing patients at 12-months follow-up had a significantly higher level of kinesiophobia at baseline according to the SQK compared to the non-missing patients (5.2 vs. 3.8, p=0.04). There was no significant difference in any of the other characteristics.

Table 1. Baseline characteristics of the study population[1]

	General Practitioners' care plus Physical Therapy (n=67)	General Practitioners' care (n=68)
Age in years	42.2 (9.6)	42.9 (11.9)
Male sex, no. (%)	29 (43)	41 (60)
Body mass index in kg/m^2	25.6 (4.1)	26.8 (4.9)
Symptom duration in days	12.1 (10.1)	14.2 (10.2)
TSK score (17 -68)[2]	39.0 (5.8)	41.0 (7.1)
High TSK (>37), no. (%)	38 (57)	48 (71)
SQK score (0-10)[3]	4.0 (2.6)	4.0 (2.8)
NRS leg pain score (0-10)[4]	6.3 (2.2)	6.3 (2.2)

[1] Values represent means (SD) unless otherwise indicated
[2] TSK = Tampa Scale for Kinesiophobia; higher scores indicate more kinesiophobia
[3] SQK = Substitute Question Kinesiophobia; higher scores indicate more kinesiophobia
[4] NRS = Numerical Rating Scale; higher scores indicate more pain

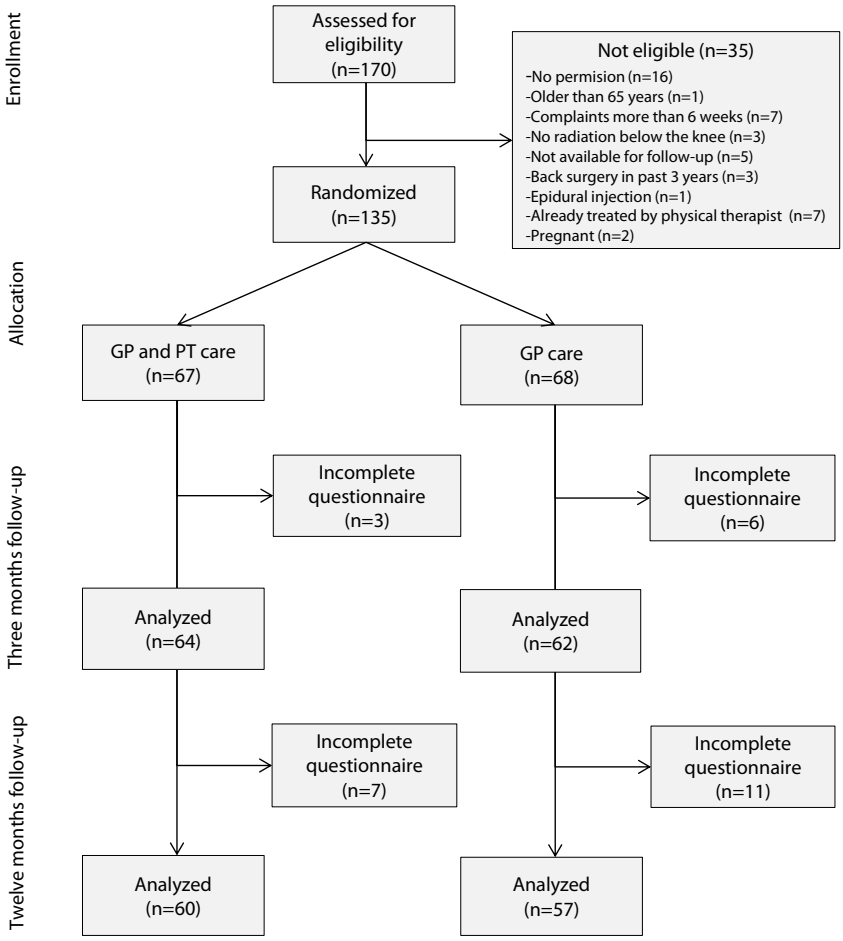


Figure 1. Flow chart representing participant enrollment, allocation and analysis throughout the study. GP care = General Practitioners' care; PT care = Physical Therapy care

Interaction effect

There was no interaction effect between the level of kinesiophobia at baseline (TSK and SQK) and treatment allocation (whether or not physical therapy) in the regression analyses predicting perceived recovery at 3 and 12-months follow-up (Table 2 and 4, respectively).

There was no interaction effect between kinesiophobia at baseline (TSK and SQK) and treatment allocation (whether or not physical therapy) in the regression analyses predicting leg pain intensity at 3-months follow-up (Table 3). Patients with higher levels of kinesiophobia at baseline reported higher leg pain intensity at 12-months follow-up

Table 2. Logistic Regression Analysis with Recovery at 3-Months Follow-up (n=126)

TSK	Beta (95% CI[1])	p-value	SQK	Beta (95% CI[1])	p-value
Randomization to PT[2]	2.7 (-2.4-7.7)	0.30	Randomization to PT[2]	0.1 (-1.4-1.5)	0.93
TSK[3]	0.0 (-0.1-0.1)	0.97	SQK[4]	-0.1 (-0.3-0.2)	0.59
Interaction term between TSK[3] and Randomization to PT[2]	-0.1 (-0.2-0.0)	0.23	Interaction term between SQK[4] and Randomization to PT[2]	-0.1 (-0.4-0.2)	0.37

[1] CI = Confidence Interval
[2] Randomization to PT = Treatment allocation to Physical Therapy additional to General Practitioners' care
[3] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia
[4] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia

Table 3. Linear Regression Analysis with Leg Pain Intensity at 3-Months Follow-up (n=126)

TSK	Beta (95% CI[1])	p-value	SQK	Beta (95% CI[1])	p-value
Randomization to PT[2]	3.1 (-2.8-9.1)	0.30	Randomization to PT[2]	0.4 (-1.2-2.0)	0.63
TSK[3]	0.1 (-0.0-0.2)	0.17	SQK[4]	0.2 (-0.0-0.5)	0.07
Interaction term between TSK[3] and Randomization to PT[2]	-0.1 (-0.2-0.1)	0.23	Interaction term between SQK[4] and Randomization to PT[2]	-0.2 (-0.6-0.1)	0.19
Baseline leg pain[5]	**0.3 (0.1-0.5)**	**<0.01**	Baseline leg pain[5]	**0.3 (0.1-0.5)**	**0.01**

[1] CI = Confidence Interval
[2] Randomization to PT = Treatment allocation to Physical Therapy additional to General Practitioners' care
[3] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia
[4] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia
[5] Leg pain severity on Numerical Rating Scale (0-10); higher scores indicates more pain

Table 4. Logistic Regression Analysis with Recovery at 12-Months Follow-up (n=117)

TSK	Beta (95% CI[1])	p-value	SQK	Beta (95% CI[1])	p-value
Randomization to PT[2]	0.8 (-5.1-6.8)	0.78	Randomization to PT[2]	-0.9 (-2.4-0.7)	0.30
TSK[3]	-0.1 (-0.2-0.1)	0.34	SQK[4]	-0.1 (-0.3-0.2)	0.52
Interaction term between TSK[3] and Randomization to PT[2]	0.0 (-0.2-0.1)	0.58	Interaction term between SQK[4] and Randomization to PT[2]	0.0 (-0.4-0.3)	0.84

[1] CI = Confidence Interval
[2] Randomization to PT = Treatment allocation to Physical Therapy additional to General Practitioners' care
[3] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia
[4] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia

($p<0.01$). However, treatment allocation to physical therapy showed a significant interaction with both the TSK score and the SQK score at baseline in the regression analysis predicting leg pain intensity at 12-months follow-up ($p=0.07$ and $p<0.01$, respectively) (Table 5).

Table 5. Linear Regression Analysis with Leg Pain Intensity at 12-Months Follow-up (n=117)

TSK	Beta (95% CI[1])	p-value	SQK	Beta (95% CI[1])	p-value
Randomization to PT[2]	4.0 (-1.0-9.0)	0.11	Randomization to PT[2]	0.8 (-0.5-2.1)	0.24
TSK[3]	**0.1 (0.0-0.2)**	**<0.01**	SQK[4]	**0.4 (0.2-0.6)**	**<0.01**
Interaction term between TSK[3] and Randomization to PT[2]	**-0.1 (-0.2-0.0)**	**0.07**	Interaction term between SQK[4] and Randomization to PT[2]	**-0.4 (-0.7- -0.1)**	**<0.01**
Baseline leg pain[5]	0.1 (-0.1-0.3)	0.20	Baseline leg pain[5]	0.1 (-0.1-0.3)	0.32

[1] CI = Confidence Interval
[2] Randomization to PT = Treatment allocation to Physical Therapy additional to General Practitioners' care
[3] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia
[4] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia
[5] Leg pain severity on Numerical Rating Scale (0-10); higher scores indicates more pain

High and low fear of movement

Patients classified as 'suggestive with low fear of movement' had a mean TSK score of 33.2 (± 3.1 standard deviation (±)) and mean SQK score of 2.9 (±2.4). Patients classified as 'suggestive with high fear of movement' had a mean TSK score of 43.9 (±4.4) and mean SQK score of 4.6 (±2.6). Table 6 presents the subgroup results of the patients 'suggestive of high fear of movement' at 3 and 12-months follow-up. Comparison of results between the treatment groups revealed non-significant results (although eyeballing showed a possible trend for better outcome results for the patients in the physical therapy group): Of the patients 'suggestive of high fear of movement' 72% of the patients in the physical therapy group reported being recovered at 3 months follow-up and 57% of the patients

Table 6. Subgroup results for the patients suggestive of high fear of movement (n=80 at 3 months / n=73 at 12 months)[1]

	General Practitioners' care plus Physical Therapy (n=36 at 3 mo./ 33 at 12 mo.)	General Practitioners' care (n=44 at 3 mo./ 40 at 12 mo.)
Recovery, 3 months, no. (%)	26 (72)	25 (57)
NRS leg pain score (0-10)[2], 3 months	2.3 (2.4)	3.1 (3.1)
SQK score (0-10)[3], 3 months	3.4 (3.1)	3.9 (3.2)
Recovery, 12 months, no. (%)	25 (76)	22 (55)
NRS leg pain score (0-10)[2], 12 months	1.8 (2.0)	2.8 (2.5)
TSK score (17 -68)[4], 12 months	37.4 (7.3)	37.4 (7.2)
SQK score (0-10)[3], 12 months	2.4 (2.6)	3.1 (2.8)

[1] Values represent means (SD) unless otherwise indicated
[2] Leg pain severity on Numerical Rating Scale (0-10); higher scores indicates more pain
[3] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia
[4] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia
The TSK score was not measured at 3 months follow-up

in the control group. A mean difference between the randomization groups of reported leg pain intensity at 3-months of 0.8 was seen in favor of the physical therapy group (2.3 vs 3.1). At 12-months follow-up 76% of the patients in the physical therapy group reported recovery compared to 55% of the patients in the control group. A mean difference of 1.0 in reported leg pain intensity at 12-months was seen in favor of the physical therapy group (1.8 vs 2.8). Appendix 1 presents the subgroup results of the patients 'suggestive of low fear of movement'.

DISCUSSION

Our study provides some indication that patients with a higher level of kinesiophobia at baseline may particularly benefit from physical therapy with regard to decreasing leg pain intensity at 12-months follow-up. The patients 'suggestive of high fear of movement' who were randomized to physical therapy non-significantly reported one point lower at the NRS scale at 12-months follow-up (1.8 vs 2.8). A significant result was only seen for the interaction term of physical therapy and kinesiophobia in the linear regression analysis with leg pain intensity at 12-months follow-up. Allocation to physical therapy did not interact with kinesiophobia at baseline with any outcome at 3-months follow-up, or with recovery at 12-months follow-up.

A limitation of the present study is the post-hoc study design, i.e. we did not a priori specify the study question but our interest arose in response to recent literature. Also, because a study question formulated post-hoc may complicate the interpretation of results, conformation of the present results is needed. Although multiplicity may introduce bias in subgroup analyses,[22] we think this is less relevant for our study because we limited our analyses to baseline kinesiophiobia only. Another limitation is the relative small sample size. The small sample size especially limits the interpretation of the additional subgroup analyses where patients were classified into one of four categories dependent on randomization group and the dichotomized scale of kinesiophobia.

Presenting results on patients classified as 'with kinesiophobia' or 'without kinesiophobia' eases clinical interpretation. However, important disadvantages are the loss of information by dichotomizing a continuous scale, and the difficult choice of the cut-off point. We decided to use the cut-off point most frequently reported in the literature. However, this cut-off point was based on a median TSK score in a different patient population (with chronic low back pain), resulting in 65% of patients of our population defined as 'suggestive of high fear of movement'. This high number of patients suggests that the

used cut-off point may have resulted in a too wide definition of 'high fear of movement', blurring the interpretation of results.

To our knowledge, this is the first study to investigate the effect of physical therapy on the relation between kinesiophobia and outcome in patients with sciatica in primary care. However, the relation between kinesiophobia at baseline and outcome in patients with sciatica has been studied in secondary care, especially in patients undergoing spine surgery. One study in 466 patients with sciatica of which 1/3 were treated surgically, showed an association between kinesiophobia and non-success.[12] Most, but not all, of the studies investigating the influence of kinesiophobia on outcome after lumbar disc surgery report an association between a higher level of kinesiophobia at baseline and worse outcomes after lumbar disc surgery.[23-27]

As treatment with physical therapy was most intensively given in the weeks after randomization, we would particularly have expected differences in results at 3-months follow-up instead of 12-months follow-up. This contradiction, the relatively small number of included patients and the post-hoc study design, make it difficult to draw firm conclusions on any clinical implications. However, the results from the present subgroup analysis show sufficient basis for further research on special treatment effects for patients with kinesiophobia. A larger sample size will be an important requirement for future research.

In conclusion, we found preliminary evidence that physical therapy may reduce the negative effect of a high level of kinesiophobia at baseline on reported leg pain intensity at 12-months follow-up in patients with sciatica. The patients 'suggestive of high fear of movement' who were randomized to physical therapy non-significantly reported one point lower at the NRS scale at 12-months follow-up (1.8 vs 2.8). No interaction effect was found with regard to recovery or leg pain intensity at 3-months follow-up or for recovery at 12-months follow-up.

REFERENCES

1. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
2. Konstantinou, K. and K.M. Dunn, *Sciatica: review of epidemiological studies and prevalence estimates.* Spine (Phila Pa 1976), 2008. **33**(22): p. 2464-72.
3. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-23.
4. Weber, H., I. Holme, and E. Amlie, *The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam.* Spine (Phila Pa 1976), 1993. **18**(11): p. 1433-8.
5. Kreiner, D.S., et al., *An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy.* Spine J, 2014. **14**(1): p. 180-91.
6. Luijsterburg, P.A., et al., *Cost-effectiveness of physical therapy and general practitioner care for sciatica.* Spine (Phila Pa 1976), 2007. **32**(18): p. 1942-8.
7. Luijsterburg, P.A., et al., *Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up.* Eur Spine J, 2008. **17**(4): p. 509-17.
8. Konstantinou, K., et al., *Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol.* BMC Musculoskelet Disord, 2012. **13**: p. 4.
9. Vlaeyen, J.W., et al., *Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance.* Pain, 1995. **62**(3): p. 363-72.
10. Kori, S.H., R.P. Miller, and D.D. Todd, *Kinesophobia: a new view of chronic pain behaviour.* Pain Manage, 1990. **Jan/Feb**: p. 35-43.
11. Monticone, M., et al., *Effect of a long-lasting multidisciplinary program on disability and fear-avoidance behaviors in patients with chronic low back pain: results of a randomized controlled trial.* Clin J Pain, 2013. **29**(11): p. 929-38.
12. Haugen, A.J., et al., *Prognostic factors for non-success in patients with sciatica and disc herniation.* BMC Musculoskelet Disord, 2012. **13**: p. 183.
13. Luijsterburg, P.A., et al., *Conservative treatment in patients with an acute lumbosacral radicular syndrome: design of a randomised clinical trial [ISRCTN68857256].* BMC Musculoskelet Disord, 2004. **5**(1): p. 39.
14. Swinkels-Meewisse, E.J., et al., *Psychometric properties of the Tampa Scale for Kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain.* Man Ther, 2003. **8**(1): p. 29-36.
15. Verwoerd, A.J., et al., *A single question was as predictive of outcome as the Tampa Scale for Kinesiophobia in people with sciatica: an observational study.* J Physiother, 2012. **58**(4): p. 249-54.
16. Bombardier, C., *Outcome assessments in the evaluation of treatment of spinal disorders: summary and general recommendations.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3100-3.
17. Collins, S.L., R.A. Moore, and H.J. McQuay, *The visual analogue pain intensity scale: what is moderate pain in millimetres?* Pain, 1997. **72**(1-2): p. 95-7.
18. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
19. Branstrom, H. and M. Fahlstrom, *Kinesiophobia in patients with chronic musculoskeletal pain: differences between men and women.* J Rehabil Med, 2008. **40**(5): p. 375-80.

20. Nijs, J., et al., *Chronic fatigue syndrome: lack of association between pain-related fear of movement and exercise capacity and disability.* Phys Ther, 2004. **84**(8): p. 696-705.
21. Back, M., et al., *The impact on kinesiophobia (fear of movement) by clinical variables for patients with coronary artery disease.* Int J Cardiol, 2013. **167**(2): p. 391-7.
22. Wang, R., et al., *Statistics in medicine—reporting of subgroup analyses in clinical trials.* N Engl J Med, 2007. **357**(21): p. 2189-94.
23. den Boer, J.J., et al., *Continued disability and pain after lumbar disc surgery: the role of cognitive-behavioral factors.* Pain, 2006. **123**(1-2): p. 45-52.
24. Ostelo, R.W., et al., *Residual complaints following lumbar disc surgery: prognostic indicators of outcome.* Pain, 2005. **114**(1-2): p. 177-85.
25. Svensson, G.L., et al., *High degree of kinesiophobia after lumbar disc herniation surgery: a cross-sectional study of 84 patients.* Acta Orthop, 2011. **82**(6): p. 732-6.
26. Archer, K.R., et al., *Early postoperative fear of movement predicts pain, disability, and physical health six months after spinal surgery for degenerative conditions.* Spine J, 2014. **14**(5): p. 759-67.
27. Johansson, A.C., et al., *A prospective study of cognitive behavioural factors as predictors of pain, disability and quality of life one year after lumbar disc surgery.* Disabil Rehabil, 2010. **32**(7): p. 521-9.

Appendix 1. Subgroup results for the patients suggestive of low fear of movement (n= 46 at 3 months / n= 44 at 12 months)[1]

	General Practitioners' care plus Physical Therapy (n=28 at 3 mo./ 27 at 12 mo.)	General Practitioners' care (n= 18 at 3 mo./ 17 at 12 mo.)
Recovery, 3 months, no. (%)	21 (75)	14 (78)
NRS leg pain score (0-10)[2], 3 months	2.3 (2.4)	2.1 (2.7)
SQK score (0-10)[3], 3 months	2.7 (2.9)	1.3 (1.8)
Recovery, 12 months, no. (%)	24 (89)	14 (82)
NRS leg pain score (0-10)[2], 12 months	1.7 (1.9)	1.5 (2.3)
TSK score (17 -68)[4], 12 months	32.4 (5.3)	30.7 (7.0)
SQK score (0-10)[3], 12 months	2.1 (2.4)	1.1 (2.3)

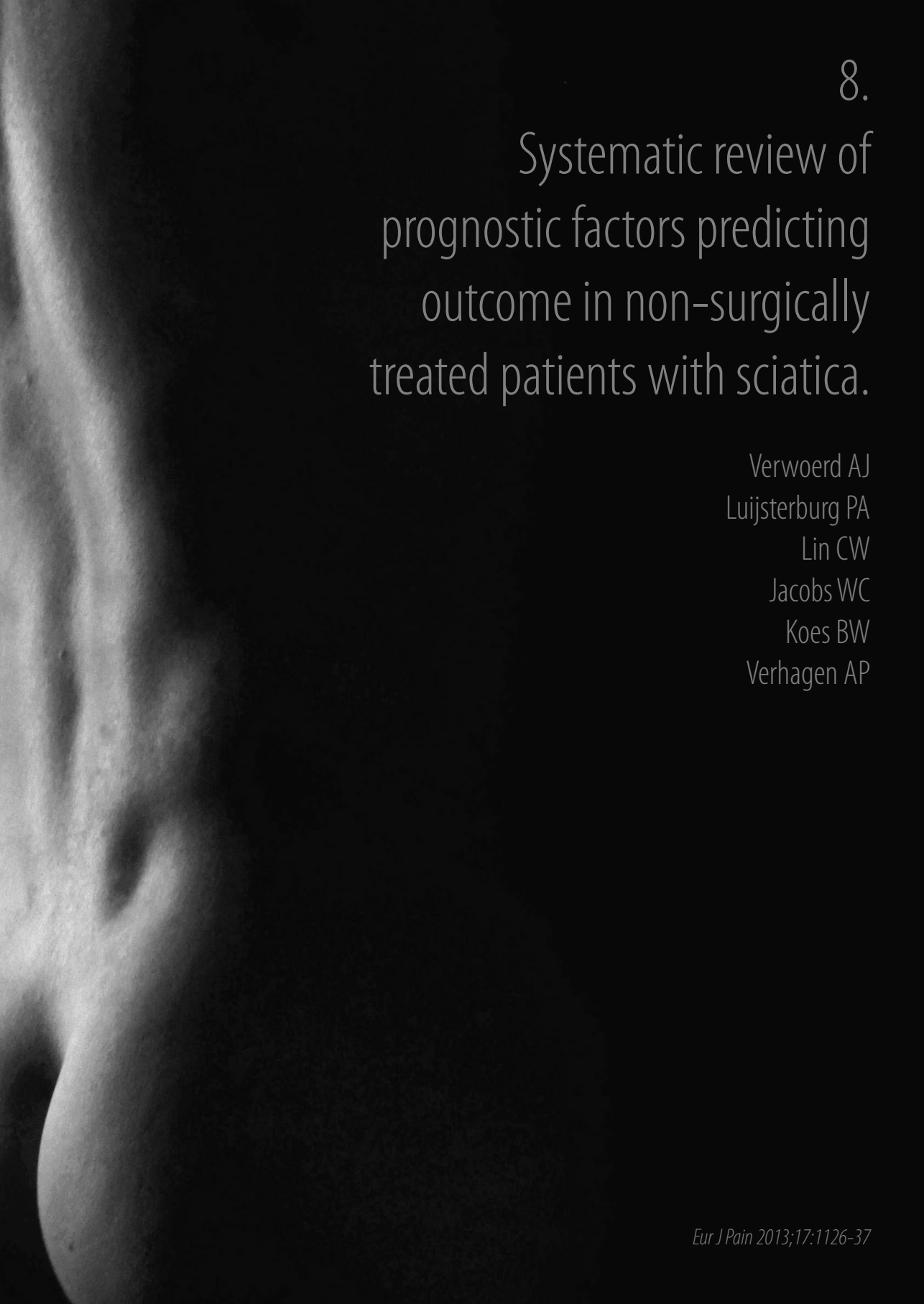
[1] Values represent means (SD) unless otherwise indicated

[2] Leg pain severity on Numerical Rating Scale (0-10); higher scores indicates more pain

[3] SQK = Substitute Question Kinesiophobia (0-10); higher scores indicate more kinesiophobia

[4] TSK = Tampa Scale for Kinesiophobia (17-68); higher scores indicate more kinesiophobia

The TSK score was not measured at 3 months follow-up



8.
Systematic review of prognostic factors predicting outcome in non-surgically treated patients with sciatica.

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ABSTRACT

Identification of prognostic factors for surgery in patients with sciatica is important to be able to predict surgery in an early stage. Identification of prognostic factors predicting persistent pain, disability and recovery are important for better understanding of the clinical course, to inform patient and physician and support decision making. Consequently, we aimed to systematically review prognostic factors predicting outcome in non-surgically treated patients with sciatica. A search of Medline, Embase, Web of Science and Cinahl, up to March 2012 was performed for prospective cohort studies on prognostic factors for non-surgically treated sciatica. Two reviewers independently selected studies for inclusion and assessed the risk of bias. Outcomes were pain, disability, recovery and surgery. A best evidence synthesis was carried out in order to assess and summarize the data. The initial search yielded 4392 articles of which 23 articles reporting on 14 original cohorts met the inclusion criteria. High clinical, methodological and statistical heterogeneity among studies was found. Reported evidence regarding prognostic factors predicting the outcome in sciatica is limited. The majority of factors that have been evaluated, e.g., age, body mass index, smoking and sensory disturbance, showed no association with outcome. The only positive association with strong evidence was found for leg pain intensity at baseline as prognostic factor for subsequent surgery.

Databases

- Medline, Embase, Web of Science and Cinahl

What does this study add?

- Evidence on prognostic factors predicting the outcome in non-surgically treated sciatica is sparse.
- The majority of factors that have been evaluated did not show an association with outcomes.
- Strong evidence was found for high leg pain intensity at baseline predicting subsequent back surgery.

INTRODUCTION

Sciatica is characterized by low-back related leg pain and related disabilities. Generally, definitions of sciatica include a distribution of the radiating pain to below the knee. The diagnosis of sciatica is primarily based on history and physical examination. Although there is discussion in literature on nomenclature of radiating pain in the leg, we used the term sciatica in this study because of its widespread use in the literature.[1] Prevalence rates of sciatica differ widely among studies. Partly due to differences in definition of sciatic symptoms, annual prevalence rates vary from 2.2% to 34%.[2] The most common cause of sciatica is a herniated lumbar disk.[1] The natural course is favourable in most patients[3-5] and if conservative therapy fails, surgery may be helpful. In carefully selected patients surgical discectomy gives faster relief of leg pain and a faster rate of perceived recovery compared to prolonged conservative treatment, but at 1 year follow-up rates of pain relief and of perceived recovery are similar for early surgery and prolonged conservative treatment.[4,6] Unfortunately, optimal selection of eligible patients for surgery is lacking.[6] There are indications that high leg pain intensity and more disability at baseline are prognostic factors for subsequent surgery[7], but this has not been systematically reviewed. Identification of prognostic factors for surgery is therefore important to be able to predict 'inevitable' surgery in an early stage in patients and therefore aim for faster relief of symptoms. Identification of prognostic factors predicting persistent pain, disability and recovery are important for better understanding of the clinical course, to inform patients and physicians and support decision-making in treatment and guidance of patients.

A systematic review published in 2003 reported the course of acute low back pain and sciatica and clinically important prognostic factors for these conditions.[8] Of the 15 included studies only one study included patients with sciatica. This study concerned the natural course of patients with sciatica and did not report on prognostic factors.[9] Another systematic review was published in 2011 and reported the prognostic factors in non-surgically treated sciatica.[10] Some prognostic factors were evaluated in multiple studies, but no one factor stood out as a prognostic factor. Most important observations were the heterogeneity of studies and the need for further research. Although the review was well conducted it was limited in focus. Only publications in English were included, single factor studies were excluded and surgery was not taken into account as outcome. We designed our systematic review with a more broad view on literature. The aim of our review was to systematically review and summarise the literature regarding the prognostic value of all possible prognostic factors for persistent pain, persistent disability, recovery and surgery in non-surgically treated patients with sciatica.

METHODS

Search strategy

We searched the electronic databases Medline, Embase, Web of Science, and Cinahl up to March 2012. We did not restrict searches to specific languages or time frame. The search strategy was developed in consultation with a medical librarian and used a variety of text words and MeSH terms to explore the most important key terms: sciatica and prognosis. The complete search strategies from all databases are available online (Appendix 1). A supplement search was done by bibliography screening and citation tracking of included articles.[11] Eligible studies were selected on title and abstract by two independent review authors (A.P.V. and A.J.H.V.). Full papers were retrieved and assessed if the abstract provided insufficient information.

Selection criteria

To be included, studies had to meet all of the following criteria: (1) the study had a prospective design with a follow-up period of at least 3 months; (2) the study population consisted of non-surgically treated, adult patients with sciatica; (3) the objective of the article was to assess prognostic factors predicting an outcome of interest; (4) outcomes of interest were severity of pain, disability, recovery or surgery; (5) sample size was at least 100 patients (complete cases). Solely return to work or receiving worker's compensation claim as outcome was not sufficient to be included. Studies with a population of mixed surgically and non-surgically treated patients that controlled for surgery in their analyses were also included. All criteria were applied independently by two independent review authors (A.P.V. and A.J.H.V.) to the full text of the articles that passed the first eligibility screening of the titles and abstract. A consensus meeting was planned to resolve disagreements. If disagreements persisted, a third review author (B.W.K.) was consulted.

Risk of bias

There is limited consensus on how to assess the methodological quality of prognosis studies.[12,13] We used a 21-item criteria list for risk of bias assessment for studies on prognostic factors (Appendix 2).[14] According to availability of sufficient information and the likelihood of bias, criteria could be scored positive, negative or unclear. The total quality score was assessed by adding the number of positively scored items together, so a maximum score of 21 could be obtained for each study. If articles were based on the same cohort, one quality score for the items regarding the cohort was given based on the information from all available included publications. Two review authors (W.C.H.J. and C.-W.C.L.) independently scored the quality of the studies. If no agreement could be reached during a consensus meeting, a third review author (A.P.V.) made the final decision. We pilot tested the risk of

bias assessment on three similar articles with presumed low, moderate and high quality regarding non-specific low back pain (these articles were not eligible for our review.[15]

Data extraction

Study characteristics extracted from eligible papers were source population, sample size, diagnostic criteria, inclusion and exclusion criteria, baseline characteristics like duration of complaints, all prognostic factors investigated, outcomes, duration and completeness of follow up, type of analysis and results. Outcomes extracted were the persistence or improvement of pain and disability, recovery and surgery after at least three months follow-up. Results from univariate or 'single factor' analysis (articles investigating one prognostic factor controlled for one or more confounding variables) were considered as a subgroup compared to results from multivariate prognostic models. If sufficient data was available we extracted or calculated odds ratios (ORs) with 95% confidence intervals (95% CI). We used standardized forms for data extraction to facilitate comparison. If more follow-up moments were available the latest follow-up was taken. We pilot tested data extraction on one article regarding non-specific low back pain. Two review authors (P.A.J.L. and A.J.H.V.) extracted the data. When consensus could not be reached, a third reviewer (A.P.V.) made the final decision.

Analysis

Inter-observer agreement of the risk of bias assessment was determined by the kappa statistic (less than 0.0 indicated poor; 0.0-0.2 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; and 0.81-1.0 almost perfect inter-observer agreement[16]). The cut-off point distinguishing a high- from low-quality study was set at the 50% of the maximum score (11 of 21 positive items). Additionally, as it is unlikely that the prognosis of sciatica is based on only one factor, results had to be derived from a multivariate prognostic model to be considered of high quality. Because statistical pooling was not possible, a level of evidence synthesis was performed.[15,17] For every factor with possible prognostic value (embedded in its own model) we defined a level of evidence: strong, moderate, limited or inconclusive.

We used the following levels of evidence:[17]

- Strong evidence: Consistent findings (≥80%) in at least 2 high-quality cohorts
- Moderate evidence: One high-quality cohort and consistent findings (≥80%) in one or more low-quality cohorts
- Limited evidence: Findings of one high-quality cohort or consistent findings in one or more low-quality cohorts
- Inconclusive evidence: Inconsistent findings irrespective of study quality
- No evidence: No studies

Finally, to increase statistical power, we combined the four outcomes 'low pain severity', 'improved disability', 'recovered' and 'no surgery' into a single outcome: 'favourable outcome'. A study only had to have one of the four single outcomes to count as the combined outcome.

RESULTS

Selection of studies

The initial search yielded 4392 articles (Medline 2214; Embase 1319; Web of Science 728; Cinahl 131). Duplicates were removed and 3150 articles remained (Fig. 1). After screening of titles and available abstracts, 168 full text articles were obtained. During the selection, the two review authors disagreed on 11 articles. Consensus was retrieved on 8 articles and for 3 articles the final decision was made by the third review author. Of the 168 full-text articles, 23 fulfilled all inclusion criteria and were included in our review and reported 14 original cohort studies.

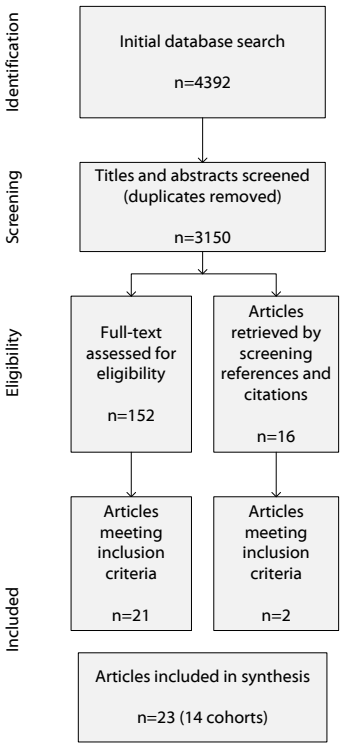

Figure 1. Flow chart of selection procedure.

Risk of bias

The two review authors scored in total 483 quality items and agreed on 351 (72.7%). The inter-observer reliability of scoring positive or not on the risk of bias assessment form was moderate (kappa statistic of 0.45).[16] Disagreement mainly occurred because of reading errors and/or differences in interpretation of items. Disagreement persisted in 12 items. The third review author (A.P.V.) made the final decision in these cases. Table 1 shows the results of the risk of bias assessments in subgroups of articles reporting on univariate or 'single-factor' analyses and results from articles presenting a multivariate prognostic model. Articles are presented in alphabetical order and articles based on the same cohort study are grouped together. Fourteen articles yielded a low risk of bias. The median score was 11 points. Only 3 articles[18-20] reported on the 'selection method of variables'. Nine of the 23 articles[7,20-27], representing 6 cohorts, reported results of a multivariate prognostic model. Almost none of the studies on prognostic models scored positive on the items that specially focused on performance and validation of prognostic models (item S, T and U). One of the articles evaluating a prognostic model[27] did not present odds ratios or resembling estimates for the multivariate prognostic model. And only one of the articles evaluating a prognostic model[23] did not violate the rule of at least ten cases per prognostic factor.[28] The four articles derived from the Maine Lumbar Spine Study[29] and the four articles derived from the SPORT trial[30] all evaluated a single prognostic factor.

Characteristics of included studies

Table 2 shows the main characteristics of the 23 included studies. Of the 14 included cohorts, two were population based[20,23], one cohort [3 articles[25-27]] reported on patients from primary care and 11 cohorts [18 articles[7,18,19,21,22,24,31-42]] on patients from secondary care. The diagnosis of sciatica in five cohorts was confirmed with diagnostic imaging [nine articles[7,18,19,22,35,38,39,41,42]], seven cohorts based the diagnosis primarily on clinical criteria [12 articles[21,24-27,31-34,36,37,40]] and two cohorts on self-reported presence of back pain radiating to the leg.[20,23] Length of follow-up ranged from 3 months to 10 years. We denoted these differences in study population as clinical and methodological heterogeneity. All included papers were published in the English language.

Appendix 3 gives an overview of the prognostic factors, outcomes and results per included article. Of the univariate analyses, only the significant results were reported, and of the multivariate prognostic models, the results of all variables retained in the final model were reported. In the univariate and 'single-factor' studies different types of analysis were used like t-tests, repeated measurement analysis and logistic regression analysis. We denoted these differences in statistical approach as statistical heterogeneity. Three cohorts [four articles[18,22,33,37]] reported on a mixed population consisting of surgically and non-surgically treated patients and controlled for surgery in their analyses. Conclusions made by authors

Table 1. Risk of bias of the 23 included articles representing 14 cohort studies

Cohort	Article	Prognostic factor(s)	Outcome[1]	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
Univariate analysis or 'single factor' analysis																								
	Albert et al, 2012	Centralization	P/D	-	-	+	+	+	-	+	+	-	+	+	+	+	-	-	+	-	-	-	-	-
Maine Lumbar Spine Study (Keller et al., 1996)	Atlas et al, 1996	QTFC-classification[2]	P	-	+	-	+	-	-	-	+	?	+	+	+	-	+	-	+	-	-	-	-	-
	Atlas et al, 2000	Workers compensation	P/D/R					-	-	+	+	-	+	+	+	+	+	-	+	-	+	-	-	-
	Atlas et al, 2006	Workers compensation	P/R					+	-	+	+	-	+	+	+	+	+	+	+	-	+	-	-	-
	Edwards et al, 2007	SF-36 mental health	P/D/R					-	+	+	+	-	+	-	+	+	-	-	+	-	-	-	-	-
'SPORT' trial (Birkmeyer et al., 2012)	Atlas et al, 2009	Workers compensation	P/D/R	-	+	+	+	-	-	+	+	-	+	+	+	+	+	+	+	-	+	-	-	-
	Freedman et al, 2011	Diabetes	P/D					+	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-	-
	Olson et al, 2011	Educational attainment	P/D/R					+	-	+	-	-	+	+	+	+	+	-	+	?	-	-	-	-
	Rihn et al, 2011	Symptom duration	P/D/R					+	-	+	+	-	-	+	+	+	+	-	+	-	-	-	-	-
	Bush et al, 1992	Gender / disc bulges on MRI	S	-	-	-	+	-	-	+	-	-	+	+	-	-	+	-	-	-	-	-	-	-
	Jacobsen et al, 2012	COMT Met-allele	P/D	-	-	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	-	-	-
	Karppinen et al, 2008	IL6 haplotype	P/D	-	-	+	+	+	-	-	+	?	+	+	+	+	+	-	-	+	-	-	-	-
	Rasmussen et al, 2008	Compensation claim	P/D/R	+	+	-	+	-	-	+	+	-	-	+	+	+	+	+	-	-	+	-	-	-
	Suri et al, 2011	Age	P/D	+	-	+	+	-	+	-	+	-	-	+	+	+	-	+	+	-	+	-	-	-

Table 1. Risk of bias of the 23 included articles representing 14 cohort studies (continued)

Cohort	Article	Prognostic factor(s)	Outcome[1]	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
Multivariate prognostic models																								
	Jensen et al, 2007	MRI variables (like disk contour)	R	-	+	+	+	+	-	+	+	-	-	+	+	+	+	-	-	-	+	-	-	-
	Miranda et al, 2002	Clinical variables (like age)	P	-	-	-	+	-	-	+	-	-	-	+	+	-	+	+	-	+	+	-	-	-
'Sciatica trial' (Peul et al., 2005)	Peul et al, 2008a	Clinical + MRI variables	S	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	-	-	+	+	+	-
	Peul et al, 2008b	Clinical + MRI variables	R					+	-	+	+	?	-	+	+	+	+	+	-	-	+	-	-	-
	Tubach et al, 2004	Clinical variables	R	-	+	-	+	+	-	+	+	-	-	+	-	-	+	-	+	-	+	-	-	-
	Valls et al, 2001	Clinical + CT variables	S	-	+	?	+	+	-	+	-	-	+	+	+	+	+	+	-	-	+	-	-	-
(Vroomen et al., 1999)	Vroomen et al, 2000	Clinical variables	S	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	-	-	+	+	-	-
	Vroomen et al, 2002a	Clinical variables	R					+	-	+	+	-	?	+	-	-	+	+	-	-	+	-	+	-
	Vroomen et al, 2002b	MRI variables	R					-	-	+	+	-	-	+	+	+	-	-	-	-	-	-	-	-
Total (out of maximum 23 points)				5	17	10	23	14	5	18	18	1	12	22	20	17	19	10	11	3	13	2	2	0

Positive (+) when the criteria are fulfilled in the article (sufficient information available and small likelihood of bias)
Negative (-) when the criteria are not fulfilled in the article (not sufficient information available or high likelihood of bias)
Question mark (?) when it is not clear if the criteria is fulfilled
A) Inception cohort?
B) Source population well described?
C) Inclusion and exclusion criteria well described?
D) Prospective design?
E) Number of drop-outs ≤20% or adequate dealt with?
F) Information on how is dealt with missing data?
G) All prognostic factors in model described?
H) Standardized or valid prognostic factors?
I) Linearity assumption studied (or not relevant)?
J) No dichotomization of prognostic variables?
K) Data presentation of prognostic factors?
L) Description of clinical relevant outcome measures?
M) Standardized or valid outcome measurements?
N) Data presentation of important outcome measures?
O) Presentation of univariate crude estimates?
P) Sufficient numbers of subjects per variable?
Q) Selection method of variables explained?
R) Presentation of multivariate estimates?
S) Information about performance?
T) Internal validation?
U) External validation?

[1] P = Pain; D = Disability; R = Recovery and S = Surgery
[2] QTFC classification means Quebec Task Force Classification for Spinal Disorder

Table 2. Characteristics of the 23 included articles representing 14 cohort studies

Cohort	Author, year of publication	Country, primary or secondary care	No. patients	Radiological or clinical diagnosis	Participants (e.g. sex, age and duration of complaints if available for the population of interest)	Follow-up
	Albert et al, 2012	Denmark, secondary care	165	Clinical	Acute, sub-acute and chronic sciatica; 52% male, mean age = 45.	1 year
Maine Lumbar Spine Study (Keller et al., 1996)	Atlas et al, 1996	USA, secondary care	154	Clinical and partly radiological	Acute, sub-acute and chronic sciatica.	1 year
	Atlas et al, 2000	USA, secondary care	150	Clinical	Acute, sub-acute and chronic sciatica.	4 years
	Atlas et al, 2006	USA, secondary care	394	Clinical	Acute, sub-acute and chronic sciatica, and work eligible. Mixed surgically and non-surgically treated population, analyses were controlled for surgery.	5-10 years
	Edwards et al, 2007	USA, secondary care	441	Clinical	Acute, sub-acute and chronic sciatica. Mixed surgically and non-surgically treated population, analyses were controlled for surgery.	3, 6, 12, 24, and 36 months
'SPORT' trial (Birkmeyer et al., 2002)	Atlas et al, 2009	USA, secondary care	347	Radiological	Subacute and chronic sciatica due to lumbar disc herniation, surgical candidates and work eligible; 61% males, mean age = 41.	2 years
	Freedman et al, 2011	USA, secondary care	393	Radiological	Sciatica due to lumbar disc herniation.	1, 2, 3, and 4 years
	Olson et al, 2011	USA, secondary care	397	Radiological	Subacute and chronic sciatica due to lumbar disc herniation and surgical candidates.	6 weeks, 3, 6 months, 1, 2, 3 and 4 years
	Rihn et al, 2011	USA, secondary care	404	Radiological	Subacute and chronic sciatica due to lumbar disc herniation.	4 years

Table 2. Characteristics of the 23 included articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Country, primary or secondary care	No. patients	Radiological or clinical diagnosis	Participants (e.g. sex, age and duration of complaints if available for the population of interest)	Follow-up
	Bush et al, 1992	UK, secondary care	165	Clinical	Subacute and chronic sciatica, surgical candidates; 69% male; mean age = 41, average duration of symptoms 4.2 months.	1 year
	Jacobsen et al, 2012	Norway, secondary care	258	Radiological	Sciatica due to lumbar disc herniation; 53% male, mean age = 41. Mixed surgically and non-surgically treated population, analyses were controlled for surgery (45% of patients).	6 weeks, 6 and 12 months
	Karppinen et al, 2008	Finland, secondary care	153	Radiological	Acute, subacute and chronic sciatica; 60% males, mean age = 44, mean duration 2.5 months.	1, 2 and 3 years
	Rasmussen et al, 2008	Denmark, secondary care	1243	Clinical	Acute and subacute sciatica; 55% males, mean age = 45.0.	1 year
	Suri et al, 2011	USA, secondary care	133	Radiological	Acute and subacute sciatica due to lumbar disk herniation; 67% males, mean age = 54, mean duration 4.9 weeks.	6 months
	Jensen et al, 2007	Denmark, secondary care	154	Clinical	Acute, subacute and chronic sciatica; 55% male, mean age = 45.	14 months
	Miranda et al, 2002	Finland, employees of a large forest industry company	327	Clinical (self-reported)	Forest industry workers that answered on a questionnaire having low back pain radiating below the knee for more than 30 days the preceding 12 months; 73% males, mean age = 45.	1 year
'Sciatica trial' (Peul et al., 2005)	Peul et al, 2008a	The Netherlands, secondary care	142	Radiological	Subacute sciatica due to lumbar disc herniation and surgical candidates; 68% male.	1 year
	Peul et al, 2008b	The Netherlands, secondary care	283	Radiological	Subacute sciatica due to lumbar disc herniation and surgical candidates; 66% male, mean age = 42.6. Mixed surgically and non-surgically treated population, analyses were controlled for surgery (64% of patients).	1 year

Table 2. Characteristics of the 23 included articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Country, primary or secondary care	No. patients	Radiological or clinical diagnosis	Participants (e.g. sex, age and duration of complaints if available for the population of interest)	Follow-up
	Tubach et al, 2004	France, workers from electricity and gas company 1991	622	Clinical (self-reported)	Employees that answered on a questionnaire to have had low back pain radiating to the leg at least 1 day during the previous year; 84% males.	2 years
	Valls et al, 2001	France, secondary care	134	Clinical and/or radiological	Acute, subacute and chronic sciatica; 51% males, mean age = 46.	11 to 24 months
(Vroomen et al., 1999)	Vroomen et al, 2000	The Netherlands, primary care	183	Clinical	Acute and subacute sciatica; 56% males, mean age = 46.	6 months
	Vroomen et al, 2002a	The Netherlands, primary care	183	Clinical	Acute and subacute sciatica; 56% males, mean age = 46.	3 months
	Vroomen et al, 2002b	The Netherlands, primary care	133	Clinical	Acute and subacute sciatica; 55% males.	3 months

on prognostic factors in articles not reporting odds ratios were (abbreviated) reported in the last column of Appendix 3.

Level of evidence

Table 3 gives an overview of results per prognostic variable and level of evidence per outcome if the prognostic variable was evaluated in at least two different cohort studies. **Disability** was not used as an outcome in any of the multivariate prognostic models and was therefore not present in the table. When results from both univariate and multivariate analyses were reported, only the multivariate results were taken into account.

Single factor studies: No single-factor analysis could be included in the level of evidence synthesis because there were no two different cohort studies that reported ORs or resembling estimates per prognostic factor.

Prognostic models: Regarding the outcome **surgery**, we found strong evidence that no prognostic association could be found for age, gender, smoking, previous low back pain or sciatica, physical exercise, pain on sitting, crossed leg-raising test, sensory disturbance, motor loss, ankle and knee tendon reflex differences, Kemp's sign (provocation of radicular leg pain by ipsilateral passive lateroflexion and extension of the lumbar spine), finger-floor distance, and level of lumbar disk herniation seen on magnetic resonance imaging (MRI). Strong evidence was also found for intensity of leg pain being a prognostic factor for subsequent back surgery. An OR of 1.72 with a 95% CI of 1.11-2.67 per 20 mm increase on a 0-100mm visual analogue scale (VAS) for pain intensity in the leg was found in a model predicting surgery in the subsequent 12 months[7] and an OR of 1.91 with an 95% CI of 1.09-3.36 per 20 mm increase on the same scale was found in another model predicting surgery in the subsequent 6 months.[25] Regarding **recovery**, strong evidence was found that no prognostic association was found for age, body mass index (BMI), smoking, increase on coughing/sneezing/straining, pain on sitting, slow start of symptoms, leg pain intensity, sensory disturbance, Kemp's sign and finger-floor distance. Concerning severity of **pain**, only limited or no evidence was found.

Favourable outcome

A 'favourable outcome' was defined as 'low pain severity', 'improved disability', 'recovered' or 'no surgery'. Strong evidence for not having found an association with favourable outcome was revealed for age, gender, BMI, smoking, previous low back pain or sciatica, physical exercise, increase on coughing/sneezing/straining, pain on sitting, physically demanding job, crossed leg-raising test, sensory disturbance, motor loss, ankle and knee tendon reflex differences, Kemp's sign, finger-floor distance, and level of disc herniation.

Table 3. Level of evidence for each prognostic factor, at least reported in two different cohort studies. Disability was not used as an outcome in any of the multivariate prognostic models and is therefore not present in the table.

Prognostic factor	Outcome	Positive association (+)	No association	Negative association (-)	Level of evidence
Age	Pain		(Miranda et al., 2002)		Limited
	Recovery		***(Peul et al., 2008b)*** (Tubach et al., 2004) **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a) (Valls et al., 2001) (Vroomen et al., 2000)**		Strong
Male gender	Pain		(Miranda et al., 2002)		Limited
	Recovery	***(Peul et al., 2008b)***	(Tubach et al., 2004) **(Vroomen et al., 2002a)**		Inconclusive
	Surgery		**(Peul et al., 2008a) (Valls et al., 2001) (Vroomen et al., 2000)**		Strong
BMI	Pain		(Miranda et al., 2002)		Limited
	Recovery		***(Peul et al., 2008b)*** (Tubach et al., 2004) **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a)**		Limited
Height	Pain		(Miranda et al., 2002)		Limited
	Recovery		(Tubach et al., 2004)		Limited
	Surgery		**(Valls et al., 2001)**		Limited
Smoking	Pain		(Miranda et al., 2002)[1]		Limited
	Recovery		***(Peul et al., 2008b)*** (Tubach et al., 2004) **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a) (Vroomen et al., 2000)**		Strong
Previous low back pain or sciatica	Pain		(Miranda et al., 2002)		Limited
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery		**(Valls et al., 2001) (Vroomen et al., 2000)**		Strong
Job dissatisfaction	Pain			(Miranda et al., 2002)	Limited
	Recovery		(Tubach et al., 2004)		Limited
	Surgery				No
Physical exercise / sports	Pain		(Miranda et al., 2002)		Limited
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery		**(Valls et al., 2001) (Vroomen et al., 2000)**		Strong

Table 3. Level of evidence for each prognostic factor, at least reported in two different cohort studies. Disability was not used as an outcome in any of the multivariate prognostic models and is therefore not present in the table. (continued)

Prognostic factor	Outcome	Positive association (+)	No association	Negative association (-)	Level of evidence
Increase on coughing, sneezing or straining	Pain				No
	Recovery		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery	**(Vroomen et al., 2000)**	**(Peul et al., 2008a)** **(Valls et al., 2001)**		Inconclusive
Pain on sitting	Pain				No
	Recovery		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a)** **(Vroomen et al., 2000)**		Strong
Slowly start of symptoms	Pain				No
	Recovered		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery	**(Vroomen et al., 2000)**	**(Peul et al., 2008a)**		Inconclusive
Duration of symptoms	Pain				No
	Recovery	**(Vroomen et al., 2002a)**			Limited
	Surgery		**(Valls et al., 2001)**		Limited
Disability	Pain				No
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery	**(Peul et al., 2008a)**			Limited
Leg pain intensity	Pain				No
	Recovery		***(Peul et al., 2008b)*** (Tubach et al., 2004) **(Vroomen et al., 2002a)**		Strong
	Surgery	**(Peul et al., 2008a)** **(Vroomen et al., 2000)**			Strong
Mental Stress[2]	Pain		(Miranda et al., 2002)		Limited
	Recovery		**(Vroomen et al., 2002a)**	(Tubach et al., 2004)	Inconclusive
	Surgery		**(Vroomen et al., 2000)**		Limited
Driving a car	Pain		(Miranda et al., 2002)		Limited
	Recovery		(Tubach et al., 2004)[3]		Limited
	Surgery				No
Physically demanding job	Pain		(Miranda et al., 2002)		Limited
	Recovery		***(Peul et al., 2008b)***		Limited
	Surgery		**(Valls et al., 2001)**		Limited

Table 3. Level of evidence for each prognostic factor, at least reported in two different cohort studies. Disability was not used as an outcome in any of the multivariate prognostic models and is therefore not present in the table. (continued)

Prognostic factor	Outcome	Positive association (+)	No association	Negative association (-)	Level of evidence
Mentally demanding job	Pain				No
	Recovery		***(Peul et al., 2008b)***		Limited
	Surgery	**(Vroomen et al., 2000)**	**(Peul et al., 2008a)**		Inconclusive
Job dissatisfaction	Pain			(Miranda et al., 2002)	Limited
	Recovery		(Tubach et al., 2004)		Limited
	Surgery				No
Twisting at work	Pain		(Miranda et al., 2002)		Limited
	Recovery		(Tubach et al., 2004)		Limited
	Surgery				No
Bending at work	Pain		(Miranda et al., 2002)		Limited
	Recovery		(Tubach et al., 2004)		Limited
	Surgery				No
Straight leg-raising test	Pain				No
	Recovery		***(Peul et al., 2008b)***	**(Vroomen et al., 2002a)**	Inconclusive
	Surgery	**(Valls et al., 2001)**	**(Peul et al., 2008a)** **(Vroomen et al., 2000)**		Inconclusive
Crossed leg-raising test	Pain				No
	Recovery		***(Peul et al., 2008b)***		Limited
	Surgery		**(Peul et al., 2008a)** **(Vroomen et al., 2000)**		Strong
Sensory disturbance	Pain				No
	Recovery		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a)** **(Valls et al., 2001)** **(Vroomen et al., 2000)**		Strong
Motor loss	Pain				No
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery		**(Valls et al., 2001)** **(Vroomen et al., 2000)**		Strong
Ankle tendon reflex difference	Pain				No
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery		**(Vroomen et al., 2000)** **(Valls et al., 2001)**		Strong

Table 3. Level of evidence for each prognostic factor, at least reported in two different cohort studies. Disability was not used as an outcome in any of the multivariate prognostic models and is therefore not present in the table. (continued)

Prognostic factor	Outcome	Positive association (+)	No association	Negative association (-)	Level of evidence
Knee tendon reflex difference	Pain				No
	Recovery		**(Vroomen et al., 2002a)**		Limited
	Surgery		**(Valls et al., 2001)** **(Vroomen et al., 2000)**		Strong
Kemp's sign	Pain				No
	Recovery		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a)** **(Vroomen et al., 2000)**		Strong
Finger-floor distance > 24-30 cm	Pain				No
	Recovery		***(Peul et al., 2008b)*** **(Vroomen et al., 2002a)**		Strong
	Surgery		**(Peul et al., 2008a)** **(Vroomen et al., 2000)**		Strong
Nerve root compression	Pain				No
	Recovery	(Vroomen et al., 2002b)	**(Jensen et al., 2007)**		Inconclusive
	Surgery				No
Disk contour (sequester/ protrusion/ extrusion/ bigger size of herniation)[4]	Pain				No
	Recovery	**(Jensen et al., 2007)**	***(Peul et al., 2008b)***		Inconclusive
	Surgery	**(Valls et al., 2001)**	**(Peul et al., 2008a)**		Inconclusive
Location of the disk herniation (foraminal)	Pain				No
	Recovery		**(Jensen et al., 2007)**	(Vroomen et al., 2002b)	Inconclusive
	Surgery		**(Valls et al., 2001)**		Limited
Level of disk herniation	Pain				No
	Recovery		***(Peul et al., 2008b)***		Limited
	Surgery		**(Peul et al., 2008a)** **(Valls et al., 2001)**		Strong

Results with a high quality and derived from a prognostic model are in **bold**

Results from a mixed surgically and non-surgically treated population that was controlled for surgery are in *italic*

[1]Being an ex-smoker was a prognostic factor for persistent sciatic pain

[2]SF-36 mental health (Edwards et al., 2007), mental stress defined in four categories (Miranda et al., 2002), psychosomatic well being score (Tubach et al., 2004) and worrying about health (Vroomen et al., 2000, 2002a) were defined as 'mental stress'

[3] Driving a car more than 2h/day less than once a week was a prognostic factor for recovery

[4] Every study divided 'disk contour' in its own, different categories

No factors were found that showed a positive or negative relationship with favourable outcome with strong or moderate evidence.

DISCUSSION

Our study shows that high pain intensity in the leg at baseline predicts subsequent surgery for sciatica (strong evidence). ORs were 1.72 (95%CI 1.11-2.67) and 1.91 (95%CI 1.09-3.36) per 20 mm increase on the VAS at baseline in two different prognostic models predicting surgery at 12 and 6 months follow-up, respectively. There was strong evidence that no association with surgery could be found for age, gender, smoking, previous low back pain or sciatica, physical exercise, pain on sitting, crossed leg-raising test, sensory disturbance, motor loss, ankle and knee tendon reflex differences, Kemp's sign, finger-floor distance, and level of disc herniation on MRI. Concerning recovery, there was strong evidence that no association could be found for age, BMI, smoking, increase on coughing/sneezing/straining, pain on sitting, slowly start of symptoms, pain intensity, sensory disturbance, Kemp's sign, and finger-floor distance. Other factors revealed limited, inconclusive or no evidence. Concerning severity of pain and disability, no strong evidence was found. Overall, the evidence on prognostic factors predicting the outcome in non-surgically treated sciatica is only limited and studies on prognostic factors for the outcome of sciatica are clinically, methodologically and statistically heterogeneous.

Our study shows that several factors that may have been ascribed prognostic influence and may have been used in daily clinical practice (e.g., age, BMI, smoking and sensory disturbance) did not show an association with outcome. This finding may influence thoughts in the process of clinical decision making on sciatica. Another implication of our systematic review is that more research on prognostic factors in non-surgically treated sciatica is necessary. Especially, studies with large sample sizes and a focus on primary care are needed. However, all but one of the factors that have been evaluated in our review showed not being associated with prognosis. Therefore, developing a clinically useful prognostic model for patients with sciatica could be difficult. The lack of a prognostic model for patients with sciatica negatively impacts clinical decision making and the development of such a prognostic model to bring the care for patients with sciatica to a higher level almost seems to be a dead-end road.

A previous review also systematically reviewed prognostic factors in non-surgically treated sciatica.[10] Although the global aims of our reviews were similar, important differences were apparent in design of both reviews. Due to these differences and due to our more extended search we included 14 cohort studies instead of 8, and only 3 of the

cohorts were included in both systematic reviews. Four studies[43-46] were not included in our review because they had less than 100 patients in the analysis and one study[47] was not included as it used a retrospective chart review. Nevertheless, our overall conclusion on the heterogeneity of studies is the same, and our conclusions are partly in concordance in terms of the associations with prognostic value of variables. No level of evidence synthesis was performed in the review of Ashworth et al, but from the results, it can be concluded that strong evidence for no association with poor outcome was found for age, gender, BMI, smoking, previous sciatica, level of disc herniation and heaviness of work. Evaluating an association with favourable outcome in our systematic review also revealed strong evidence that no association could be found for the same factors, and additionally for physical exercise, increase on coughing/sneezing/straining, pain on sitting, crossed leg-raising test, sensory disturbance, motor loss, ankle and knee tendon reflex differences, Kemp's sign, finger-floor distance.

Publication bias should always be considered in a systematic review. In the present study the sensitive search strategy, the absence of a language restriction and the inclusion of 'single-factor' studies may have limited this bias. Indications for 'inevitable' surgery in patients with sciatica and back surgery rates differ widely among countries.[48] One difficulty in predicting surgery in patients with sciatica is that different indications for surgery are used. Our study found consistent evidence that high pain intensity in the leg was predictive of surgery, but other factors that may predict surgery may vary between settings. Multiple testing bias and not complying to the rule of 10 cases per eligible variable in multivariable analysis may be other important biases.[28] This may partly be caused by the relatively small sample sizes of the included cohorts that may have limited the power of the analyses. As most studies were secondary analysis of data from a randomized controlled trial evaluating effectiveness of treatment, studies were not optimally designed for evaluating prognostic factors and bias was introduced because assessors were often not blinded to the prognostic factors evaluated. Included populations in our systematic review varied from employees of a company that answered having low back pain radiating to below the knee on a questionnaire, to highly selected secondary care patients eligible for back surgery. Also, follow-up times ranged widely among studies and for the outcome 'favourable outcome' the 4 different outcomes of interest were combined. Although it was our motivated choice to derive levels of evidence from combining these distinct populations, this may have contributed to wide variations in results. It is important to acknowledge that there is a big difference between evidence for a lack of effect and lack of evidence for an effect. There is no clear definition when to state evidence-based that there is a lack of effect as effects may change when the number of included patients are raised or other subgroups may be included. Therefore, we are reserved concluding a lack of effect with high evidence.

CONCLUSION

Studies on prognostic factors for the outcome of non-surgically treated sciatica show clinical, methodological and statistical heterogeneity. Evidence on prognostic factors predicting the outcome in non-surgically treated sciatica is limited. The majority of factors that have been evaluated showed no association with outcome at follow-up. However, strong evidence was found for high leg pain intensity at baseline predicting subsequent surgery.

REFERENCES

1. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
2. Konstantinou, K. and K.M. Dunn, *Sciatica: review of epidemiological studies and prevalence estimates.* Spine (Phila Pa 1976), 2008. **33**(22): p. 2464-72.
3. Luijsterburg, P.A., et al., *Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up.* Eur Spine J, 2008. **17**(4): p. 509-17.
4. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
5. Vroomen, P.C., et al., *Lack of effectiveness of bed rest for sciatica.* N Engl J Med, 1999. **340**(6): p. 418-23.
6. Gibson, J.N. and G. Waddell, *Surgical interventions for lumbar disc prolapse: updated Cochrane Review.* Spine (Phila Pa 1976), 2007. **32**(16): p. 1735-47.
7. Peul, W.C., et al., *Improving prediction of "inevitable" surgery during non-surgical treatment of sciatica.* Pain, 2008a. **138**(3): p. 571-576.
8. Pengel, L.H., et al., *Acute low back pain: systematic review of its prognosis.* BMJ, 2003. **327**(7410): p. 323.
9. Weber, H., I. Holme, and E. Amlie, *The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam.* Spine (Phila Pa 1976), 1993. **18**(11): p. 1433-8.
10. Ashworth, J., K. Konstantinou, and K.M. Dunn, *Prognostic factors in non-surgically treated sciatica: A systematic review.* BMC Musculoskelet Disord, 2011. **12**: p. 208.
11. Hayden, J.A., et al., *Systematic reviews of low back pain prognosis had variable methods and results: guidance for future prognosis reviews.* J Clin Epidemiol, 2009. **62**(8): p. 781-796 e1.
12. Altman, D.G., *Systematic reviews of evaluations of prognostic variables.* BMJ, 2001. **323**(7306): p. 224-8.
13. Hayden, J.A., P. Cote, and C. Bombardier, *Evaluation of the quality of prognosis studies in systematic reviews.* Ann Intern Med, 2006. **144**(6): p. 427-37.
14. Van Oort, L., et al., *Preliminary state of development of prediction models for primary care physical therapy; a systematic review.* J Clin Epidemiol, 2012. **65**(12): p. 1257-66.
15. van Tulder, M.W., et al., *Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders.* Spine (Phila Pa 1976), 1997. **22**(20): p. 2323-30.
16. Landis, J.R. and G.G. Koch, *The measurement of observer agreement for categorical data.* Biometrics, 1977. **33**(1): p. 159-74.
17. Scholten-Peeters, G.G., et al., *Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies.* Pain, 2003. **104**(1-2): p. 303-22.
18. Jacobsen, L.M., et al., *The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation.* Eur J Pain, 2012. **16**(7): p. 1064-69.
19. Karppinen, J., et al., *Is the interleukin-6 haplotype a prognostic factor for sciatica?* Eur J Pain, 2008. **12**(8): p. 1018-1025.
20. Miranda, H., et al., *Individual factors, occupational loading, and physical exercise as predictors of sciatic pain.* Spine (Phila Pa 1976), 2002. **27**(10): p. 1102-1109.

21. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
22. Peul, W.C., et al., *Influence of gender and other prognostic factors on outcome of sciatica.* Pain, 2008b. **138**(1): p. 180-91.
23. Tubach, F., J. Beaute, and A. Leclerc, *Natural history and prognostic indicators of sciatica.* J Clin Epidemiol, 2004. **57**(2): p. 174-179.
24. Valls, I., et al., *Factors predicting radical treatment after in-hospital conservative management of disk-related sciatica.* Joint Bone Spine, 2001. **68**(1): p. 50-8.
25. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *When does the patient with a disc herniation undergo lumbosacral discectomy?* J Neurol Neurosurg Psychiatry, 2000. **68**(1): p. 75-9.
26. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002a. **52**(475): p. 119-123.
27. Vroomen, P.C., J.T. Wilmink, and M.C. de Krom, *Prognostic value of MRI findings in sciatica.* Neuroradiology, 2002b. **44**(1): p. 59-63.
28. Peduzzi, P., et al., *A simulation study of the number of events per variable in logistic regression analysis.* J Clin Epidemiol, 1996. **49**(12): p. 1373-9.
29. Keller, R.B., et al., *The Maine Lumbar Spine Study, Part I. Background and concepts.* Spine (Phila Pa 1976), 1996. **21**(15): p. 1769-76.
30. Birkmeyer, N.J., et al., *Design of the Spine Patient outcomes Research Trial (SPORT).* Spine (Phila Pa 1976), 2002. **27**(12): p. 1361-72.
31. Albert, H.B., E. Hauge, and C. Manniche, *Centralization in patients with sciatica: are pain responses to repeated movement and positioning associated with outcome or types of disc lesions?* Eur Spine J, 2012. **21**(4): p. 630-6.
32. Atlas, S.J., et al., *Long-term disability and return to work among patients who have a herniated lumbar disc: the effect of disability compensation.* J Bone Joint Surg Am, 2000. **82**(1): p. 4-15.
33. Atlas, S.J., et al., *The impact of disability compensation on long-term treatment outcomes of patients with sciatica due to a lumbar disc herniation.* Spine (Phila Pa 1976), 2006. **31**(26): p. 3061-3069.
34. Atlas, S.J., et al., *The Quebec Task Force classification for Spinal Disorders and the severity, treatment, and outcomes of sciatica and lumbar spinal stenosis.* Spine (Phila Pa 1976), 1996. **21**(24): p. 2885-2892.
35. Atlas, S.J., et al., *The impact of workers' compensation on outcomes of surgical and nonoperative therapy for patients with a lumbar disc herniation: SPORT.* Spine (Phila Pa 1976), 2009. **35**(1): p. 89-97.
36. Bush, K., et al., *The natural history of sciatica associated with disc pathology. A prospective study with clinical and independent radiologic follow-up.* Spine (Phila Pa 1976), 1992. **17**(10): p. 1205-12.
37. Edwards, R.R., et al., *Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes.* Pain, 2007. **130**(1-2): p. 47-55.
38. Freedman, M.K., et al., *The impact of diabetes on the outcomes of surgical and nonsurgical treatment of patients in the spine patient outcomes research trial.* Spine (Phila Pa 1976), 2011. **36**(4): p. 290-307.
39. Olson, P.R., et al., *Lumbar disc herniation in the Spine Patient Outcomes Research Trial: does educational attainment impact outcome?* Spine (Phila Pa 1976), 2011. **36**(26): p. 2324-32.
40. Rasmussen, C., et al., *Poor outcome in patients with spine-related leg or arm pain who are involved in compensation claims: a prospective study of patients in the secondary care sector.* Scand J Rheumatol, 2008. **37**(6): p. 462-8.

41. Rihn, J.A., et al., *Duration of symptoms resulting from lumbar disc herniation: effect on treatment outcomes: analysis of the Spine Patient Outcomes Research Trial (SPORT).* J Bone Joint Surg Am, 2011. **93**(20): p. 1906-1914.
42. Suri, P., et al., *Nonsurgical treatment of lumbar disk herniation: are outcomes different in older adults?* J Am Geriatr Soc, 2011. **59**(3): p. 423-9.
43. Balague, F., et al., *Recovery of severe sciatica.* Spine (Phila Pa 1976), 1999. **24**(23): p. 2516-2524.
44. Beauvais, C., et al., *Prognostic value of early computed tomography in radiculopathy due to lumbar intervertebral disk herniation. A prospective study.* Joint Bone Spine, 2003. **70**(2): p. 134-139.
45. Hasenbring, M., et al., *Risk factors of chronicity in lumbar disc patients. A prospective investigation of biologic, psychologic, and social predictors of therapy outcome.* Spine (Phila Pa 1976), 1994. **19**(24): p. 2759-2765.
46. Komori, H., et al., *Factors predicting the prognosis of lumbar radiculopathy due to disc herniation.* J Orthop Sci, 2002. **7**(1): p. 56-61.
47. Carragee, E.J. and D.H. Kim, *A prospective analysis of magnetic resonance imaging findings in patients with sciatica and lumbar disc herniation. Correlation of outcomes with disc fragment and canal morphology.* Spine (Phila Pa 1976), 1997. **22**(14): p. 1650-1660.
48. Cherkin, D.C., et al., *An international comparison of back surgery rates.* Spine (Phila Pa 1976), 1994. **19**(11): p. 1201-6.

Appendix 1: Full details of the search strategy

Pubmed
(sciatic neuropathy[mesh] OR sciatic neuropath*[tw] OR sciatic neuralgi*[tw] OR sciatic pain*[tw] OR sciatic hernia*[tw] OR sciatic paraly*[tw] OR sciatic paresthe*[tw] OR sciatic paraesthe*[tw] OR sciatica[tw] OR sciatics[tw] OR ischialg*[tw] OR piriformis[tw] OR ((intervertebral disk displac*[tw] OR herniated disk*[tw] OR slipped disk*[tw] OR prolapsed disk*[tw] OR disk prolap*[tw] OR disk hernia*[tw] OR intervertebral disc displac*[tw] OR herniated disc*[tw] OR slipped disc*[tw] OR prolapsed disc*[tw] OR disc prolap*[tw] OR disc hernia*[tw] OR radicular syndr*[tw] OR radiculopath*[tw]) AND (lumbosacral[tw] OR lumbal[tw] OR lumbar[tw]))) AND (determinant*[tw] OR prognosis[mesh] OR prognos*[tw] OR survival analysis[mesh] OR surviv*[tw] OR comorbid*[tw] OR predict*[tw] OR forecast*[tw] OR foretell*[tw] OR prophe*[tw]) AND (quality of health care[mesh] OR quality*[tw] OR outcome*[tw]) NOT (animals[mesh] NOT humans[mesh]) NOT (case report*[tw] OR editorial*[tw] OR letter*[tw])

Embase
((sciatic NEAR/1 neuropath*):ti,ab,de OR (sciatic* NEAR/3 (neuralgi* OR pain* OR hernia* OR paraly* OR paresthe* OR paraesthe*)):ti,ab,de OR sciatica:ti,ab,de OR sciatics:ti,ab,de OR ischialg*:ti,ab,de OR piriformis:ti,ab,de OR 'lumbar disk hernia':ti,ab,de OR (('intervertebral disk hernia'/syn OR ((hernia* OR slipped OR prolaps*) NEAR/3 (disk* OR disc*)):ti,ab,de OR (radicular NEAR/1 syndr*):ti,ab,de OR radiculopath*:ti,ab,de) AND (lumbosacral:ti,ab,de OR lumba*:ti,ab,de))) AND (determinant*:ti,ab,de OR prognos*:ti,ab,de OR survival/exp OR surviv*:ti,ab,de OR comorbid*:ti,ab,de OR predict*:ti,ab,de OR forecast*:ti,ab,de OR foretell*:ti,ab,de OR prophe*:ti,ab,de) NOT (animals/exp NOT humans/exp) NOT ((case NEAR/1 report*):ti,ab,de OR editorial*:ti,ab,de OR letter*:ti,ab,de)

Web of Science
((sciatic NEAR/1 neuropath*) OR (sciatic* NEAR/3 (neuralgi* OR pain* OR hernia* OR paraly* OR paresthe* OR paraesthe*)) OR sciatica OR sciatics OR ischialg* OR piriformis OR 'lumbar disk hernia' OR ((((hernia* OR slipped OR prolaps*) NEAR/3 (disk* OR disc*)) OR (radicular NEAR/1 syndr*) OR radiculopath*) AND (lumbosacral OR lumba*))) AND (determinant* OR prognos* OR survival/exp OR surviv* OR comorbid* OR predict* OR forecast* OR foretell* OR prophe*) NOT (animal* NOT human*) NOT ((case NEAR/1 report*) OR editorial* OR letter*)

Cinahl
(MH sciatic neuropathy OR sciatic neuropath* OR sciatic neuralgi* OR sciatic pain* OR sciatic hernia* OR sciatic paraly* OR sciatic paresthe* OR sciatic paraesthe* OR sciatica OR sciatics OR ischialg* OR piriformis OR ((intervertebral disk displac* OR herniated disk* OR slipped disk* OR prolapsed disk* OR disk prolap* OR disk hernia* OR intervertebral disc displac* OR herniated disc* OR slipped disc* OR prolapsed disc* OR disc prolap* OR disc hernia* OR radicular syndr* OR radiculopath*) AND (lumbosacral OR lumbal OR lumbar))) AND (determinant* OR MH prognosis OR prognos* OR MH survival analysis OR surviv* OR comorbid* OR predict* OR forecast* OR foretell* OR prophe*) AND (MH quality of health care OR quality* OR outcome*) NOT (MH animals NOT MH humans) NOT (case report* OR editorial* OR letter*)

Appendix 2: 21-item criteria list for risk of bias assessment for studies on prognostic factors.[14]

Criteria		Score
Study design		
a)	Inception cohort	+ / - / ?
b)	Source population	+ / - / ?
c)	Inclusion and exclusion criteria	+ / - / ?
d)	Prospective design	+ / - / ?
Study attrition		
e)	Number of drop-outs	+ / - / ?
f)	Information given on method how is dealt with missing data	+ / - / ?
Prognostic factors		
g)	All prognostic factors described used to develop the model	+ / - / ?
h)	Standardized or valid measurements	+ / - / ?
i)	Linearity assumption studied	+ / - / ?
j)	No dichotomization of prognostic variables	+ / - / ?
k)	Data presentation of all prognostic factors	+ / - / ?
Outcome measures		
l)	Description of outcome measures used	+ / - / ?
m)	Standardized or valid measurements	+ / - / ?
n)	Data presentation of most important outcome measures	+ / - / ?
Analysis		
o)	Presentation of univariate crude estimates	+ / - / ?
p)	Sufficient numbers of subjects per variable	+ / - / ?
q)	Selection method of variables explained	+ / - / ?
r)	Presentation of multivariate estimates	+ / - / ?
Clinical performance / validity		
s)	Clinical performance	+ / - / ?
t)	Internal validation	+ / - / ?
u)	External validation	+ / - / ?

Study participation

a) Inception cohort: **positive** when patients were identified at an early uniform point (inception cohort) in the course of their complaints (e.g. first point at which symptoms were first noticed or first consultation at general practice). **Also positive** in case of a heterogeneous population (survival cohort) for which subgroups of patients were identified and analysed (first episode of complaints or first consultation at general practice). **Negative** when no inception cohort was used.

b) Source population: **positive** when population was described in terms of sampling frame (primary care, general population, physiotherapy practice) and recruitment procedure (place and time-period of recruitment and type of methods used to identify the sample). **Negative** when not both of these features are given. **Also negative** when it is likely that the recruitment procedure led to selection of participants that are systematically different from eligible non-participants.

c) Inclusion and exclusion criteria: **positive** when criteria were formulated for at least 3 out of 4 of the (for the study) most relevant characteristics, mostly:
   1. Age or sex
   2. Relevant co-morbidity
   3. Duration of complaints
   4. Severity of complaints

   Negative when ≤2 criteria were formulated. **Also negative** when it is likely that the criteria used for inclusion/exclusion led to selection of participants that are systematically different from eligible non-participants.

d) Prospective design: **positive** when a prospective design was used. **Also positive** in case of a historical cohort of which the determinants (prognostic factors) are measured before the outcome was determined. Negative if a historical cohort is used, considering prognostic factors at time zero which are not related to the primary research question for which the cohort is created or in case of an ambispective design.

Study attrition

e) Drop-outs: **positive** when total number of drop-outs (loss to follow-up) was ≤20%. **Also positive** when appropriate procedures were used to deal with missing values (e.g. use of multiple imputation). **Negative** when the total number of drop-outs exceeds the 20% cut-off point and no appropriate procedures were used to deal with missing values.

f) **Positive** if method is described. **Negative** if not.

Prognostic factor measurement

g) **Positive** when the article describes at least one of the following clinically relevant potential prognostic factors at baseline:
   1. Physical/disease factors (e.g. severity of pain, range of motion, duration of complaints, localization of complaints)
   2. Psychosocial factors (e.g. live events, anxiety, depression)
   3. Sociodemographic factors, other than gender and age (e.g. employment status, occupation, co-morbidity)

   Negative when the article does not describe at least one of the factors mentioned above at baseline.

h) Standardized or valid measurements: **positive** if at least one of the factors of g), excluding age and gender, are measured in a standardized, valid and reliable way.

i) **Positive** if studied (and accounted for if necessary) or not relevant (in case of no continuous predictors used), **negative** if not.

j) **Positive** if a continuous prognostic variable isn't dichotomized or dichotomization is sensible to do. **Negative** if prognostic variable is dichotomized.

k) Data presentation of most important prognostic factors: **positive** when frequencies, percentages or mean (and range, standard deviation or CI), or median (and range) are reported for all prognostic factors in the final model. In all other cases: **negative**.

Outcome

l) Clinical relevant outcome measure(s): **positive** if pain, function, recovery and/or surgery are an outcome measure. In all other cases: **negative**.

m) Standardized or valid measurements: **positive** if one or more of the main outcome measures are measured in a standardized, valid and reliable way. In all other cases: **negative**.

n) Data presentation of most important outcome measures: **positive** if frequencies, percentages or mean (and range, standard deviation or CI), or median (and range) are reported for one or more of the main outcome measures for the most important follow-up measurements. In all other cases: **negative**.

Analysis

o) Univariate crude estimates presented: **positive** if univariate crude estimates (RR, OR, HRR) between prognostic factors separately and outcome are provided. **Negative** if only p-values or wrong association values (Spearman, Pearson, sensitivity) are given, or if no tests are performed at all.

p) Sufficient numbers of subjects per variable: **positive** if it is mentioned (or easy derivable) that the number of cases (and non-cases) in the multivariate analysis was at least 10 times the number of independent variables that were put in the multivariate analysis. In all other cases and if no multivariate analysis was done: **negative**.

q) **Positive** if references are used to explain the selection method of variables. **Also positive** if an appropriate rationale is given. **Negative** if not.

r) Multivariate estimates presented: **positive** if multivariate estimates (with CI or p-values) are presented of all prognostic factors that are part of the final clinical prediction rule. **Negative** if not.

Clinical performance / validity

s) Performance measurement: **positive** if the study provides information about performance measurement (e.g. discrimination, calibration, explained variance). In all other cases: **negative**.

t) Internal validation: **positive** if appropriate techniques are used to assess internal validity of the prognostic model (e.g. cross-validation or bootstrapping). In all other cases: **negative**.

u) External validation: **positive** if the prognostic model is tested in a different population. **Negative** if not.

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
				Univariate or 'single factor' analysis			
	Albert et al, 2012	Centralization, peripheralization and no effect	A) RDQ[1] B) Improvement in leg pain	ANCOVA (controlled for gender, age and treatment (symptom-guided exercises or sham exercises))	-	-	('Centralization was associated with improvement in activity limitation and leg pain')
Maine Lumbar Spine Study (Keller et al., 1996)	Atlas et al, 1996	1) Quebec Task Force Classification category 2, 3, 4 and 6 2) Duration of symptoms 3) Working status	Improvement of leg or back pain	(Mantel-Haenszel trend test) Odds ratios	1) OR 4->2 = 2.29 (95%CI 1.19–4.39) OR 6->2 = 4.79 (95%CI 1.34-17.20) 2+3) no OR's were calculable	-	
	Atlas et al, 2000	Receiving workers' compensation	A) Relief from pain in the low back B) Relief from pain in the lower limb C) Mean change in modified score of RDQ[1] D) Quality of life (QoL) at least moderately improved E) Satisfied with current state of back symptoms	-A, B, D and E: Odds ratios -C: t-test (-Multivariate models)	Pain relief low back: OR = 0.3 (0.1-0.5) Pain relief lower limb: OR = 0.4 (0.2-0.8) QoL: OR = 0.4 (0.2-0.9) Satisfaction: OR = 0.4 (0.2-0.8)	-	('After adjustment for independent predictors of outcome…patients who had been receiving Workers' Compensation were less likely to report relief of pain and were less satisfied with their current state (OR = 0.4-0.5, all $p \leq 0.05$) 'Data not shown.)
	Atlas et al, 2006	Receiving workers' compensation	A) Improvement in the patients' predominant symptom (either low back or leg pain reported at baseline) B) Satisfaction with the patients' current state	Logistic regression models (controlled for age, gender, and initial treatment (surgical or non-surgical care))	-	-	('Individuals initially receiving workers' compensation had worse disability and quality of life outcomes')

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Edwards et al, 2007	SF-36 mental health[2]	A) Sciatica symptom frequency[3] B) RDQ[1] C) SF-36 bodily pain[4] D) SF-36 physical function[5]	Multivariate repeated-measures analyses (Generalized Estimating Equations model) (controlled for initial treatment (surgical versus non-surgical), workers' compensation status, age, gender, baseline value of outcome measure, and interactions and time-varying prospective predictors)	-	-	('In most analyses, symptoms of depression and anxiety were significant independent predictors of worse pain and function after controlling for relevant covariates.')
'SPORT' trial (Birkmeyer et al., 2002)	Atlas et al, 2009	Receiving workers´ compensation	A) SF-36 bodily pain[4] B) SF-36 physical function[5] C) Modified ODI[6] D) Sciatica bothersome index[7] E) Satisfaction with symptoms F) Self-rated major improvement	Longitudinal regression models	-	-	('Patients treated nonoperatively reported similar pain, function and satisfaction over time regardless of workers' compensation status.')
	Freedman et al, 2011	Diabetes	A) SF-36 bodily pain[4] B) SF-36 physical function[5] C) ODI[6]	Wald tests of areas under the curve (controlled for age, gender, BMI, baseline score for SF-36 and ODI, and center)	-	-	('Outcomes for nonoperative treatment were not different between patients with diabetes and patients without diabetes for BP, PF, or ODI')

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Olson et al, 2011	Educational attainment (high school or less, some college, and college degree or above)	A) SF-36 bodily pain[4] B) SF-36 physical function[5] C)MODEMS version of the ODI[6] D) Sciatica Bothersomeness Index[7] E) Low Back Pain Bothersomeness Scale[8]	Mixed-effects longitudinal regression model (controlled for covariates associated with missed visits and treatment received)	-	-	('Higher levels of education were associated with significantly greater overall improvement in BP, PF and ODI')
	Rihn et al, 2011	Symptoms for 6 months or less (versus more than 6 months)	A) SF-36 bodily pain[4] B) SF-36 physical function[5] C) ODI[6] D) Sciatica Bothersomeness Scale[7] E) Low Back Pain Bothersomeness Index[8] F) Leg Pain Bothersomeness Scale[9] G) Satisfaction with symptoms H) Self-rated health trend	Longitudinal regression model?	-	-	('Increased symptom duration due to lumbar disc herniation is related to worse outcomes')
	Bush et al, 1992	1) Female gender, 2) Disc bulges (versus disc herniation)	Surgery	T-tests and chi-square tests	-	-	
	Jacobsen et al, 2012	COMT rs4680 Met allele (Met/Met, Val/Met and Val/Val genotype)	A) Pain in activity (VAS)[10] B) McGill pain score[11] C) ODI[6]	Repeated measure ANOVA (controlled for age, gender, smoking status and treatment (surgery versus conservative), if they were statistical significant)	-	-	('The functional COMT Val 158Met SNP contributes to long lasting low back pain, sciatica and disability.')

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Karppinen et al, 2008	Interleukin-6 haplotype GGGA	A) Days with back pain B) Days with leg pain C) Back pain intensity (VAS)[10] D) Leg pain intensity (VAS)[10] E) ODI[4]	Repeated measures analysis of variance (controlled for physical work load)	-	-	('The IL6 haplotype GGGA predicted the number of days with back or leg pain and also sickness absence.')
	Rasmussen et al, 2008	Having a compensation claim	A) No global improvement (unchanged, somewhat worse, or much worse) B) Back pain not reduced (VAS)[10] C) Leg pain not reduced (VAS)[10] D) Disability not improved E) Analgesics intake not reduced	Univariate and multivariate logistic regression (controlled for disability, intensity of back pain and duration of leg pain)	No improvement: OR = 4.1 (3.0-5.7) Back pain not reduced: OR = 3.7 (2.7-5.0) Leg pain not reduced: OR = 3.8 (2.8-5.2) Disability not improved: OR = 3.5 (2.6-4.8) Analgesic intake not reduced: OR = 3.6 (2.6-5.0)	**No improvement: OR = 4.2 (2.8-6.2)** Other outcome measures: not tested	
	Suri et al, 2011	Age <60 years (versus ≥ 60 years)	A) ODI[6] (change scores) B) Leg pain intensity (VAS)[10] C) Back pain intensity (VAS)[10]	Univariate and multivariate regression analysis (controlled for gender, race, work status, prior LBP, tobacco history, comorbidity, duration of symptoms, baseline severity, midlumbar disk herniation, foraminal/ extraforaminal disk herniation, and disk extrusion/sequestration.	-	-	('Outcomes were not worse in older adults (age≥60 years) as compared to younger adults (age<60 years.')

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
				Multivariate prognostic models			
	Jensen et al, 2007	MRI findings: 1) disk contour (6 categories); 2) location of herniation (5 categories); 3) nerve root (4 categories); 4) disk signal (4 categories); 5) disk height (4 categories); 6) high-intensity zone; 7) central stenosis; 8) lateral stenosis; 9) foraminal stenosis.	Recovery (defined as absence of sciatic leg pain and a RDQ[1] score of 3 or less)	Univariate and multivariate logistic regression analysis (method: forward stepwise, and controlled (forced) for age, sex and (conservative) treatment	Disk contour (Ref.: no protrusion): Broad-based protrusion: OR = 15.6 (1.8-131.5) Extrusion: OR = 8.0 (1.4-47.2)	Disk contour (ref.: no protrusion) Bulge: OR = 0.9 (0.2-3.4) Focal protrusion: OR = 4.6 (0.8-25.6) **Broad-based protrusion: OR = 22.9 (2.5-209.1)** **Extrusion: OR = 8.7 (1.5-49.5)** Location of herniation (ref.: central location) No herniation (normal or bulge): OR = 4.4 (0.5-42.1) Lateral: OR = 0.6 (0.1-2.7) Root compromise: OR = 0.4 (0.1-1.3) Age group (45+/<45): OR = 1.3 (0.6-2.6) **Male gender: OR = 2.3 (1.1-4.7)** Treatment: OR = 0.8 (0.4-1.7)	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Miranda et al, 2002	1) gender; 2) age (4 categories); 3) height (4 categories); 4) BMI (4 categories); 5) mental stress (4 categories); 6) smoking (3 categories); 7) driving a car (3 categories); 8) previous low back injuries; 9) amount of twisting movements of the trunk during a workday (3 categories); 10) working with the trunk forward flexed (4 categories); 11) working with a hand above shoulder level (3 categories); 12) working in a sitting position (3 categories); 13) working in kneeling or squatting position (3 categories); 14) daily lifting of loads (5 categories); 15) operating a motor vehicle (4 categories); 16) physical strenuousness of work (3 categories); 17) job satisfaction (3 categories); 18) overload at work (3 categories); 19) risk of accident at work (3 categories); 20) frequency of physical exercise (3 categories); 21-36) 26 different sports (all with 3 categories)	Persistent, severe sciatic pain (more than 30 days on both the baseline and 1-year questionnaire)	Multivariate logistic regression analysis (controlled for gender and age and those variables with a significance level $P \leq 0.05$ in the age- and gender-adjusted analysis)	-	Female gender: OR = 1.0 (0.6–1.8) Age (ref: <35y) 35–44 y: OR = 1.1 (0.3–4.1) 45–54 y: OR = 2.1 (0.6–7.5) ≥55 y: OR = 2.0 (0.5–7.9) Smoking (ref: nonsmoker) **Ex-smoker: OR = 2.3 (1.3–4.3)** Current smoker: OR = 1.0 (0.5–1.9) Mental stress (ref: not at all) Only little: OR = 1.8 (0.7–4.5) To some extent: OR = 0.9 (0.3–2.1) Rather much or much: OR = 1.6 (0.6–4.3) Jogging (ref: not at all or only little) **Moderately or actively: OR = 3.9 (1.4–10.7)** Job satisfaction (ref: rather or very satisfied) Not satisfied but not dissatisfied either: OR = 1.6 (0.9–2.9) **Rather or very dissatisfied: OR = 2.8 (1.2-6.7)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
'Sciatica Trial' (Peul et al., 2005)	Peul et al, 2008a	1) gender; 2) age ≥ 40; 3) intellectual job; 4) housewife; 5) spouse/partner; 6) children; 7) smoking; 8) BMI; 9) slowly start sciatica; 10) sciatica provoked by sitting; 11) coughing, sneeze; 12) straight leg raising; 13) crossed leg raising; 14) Kemp's sign; 15) finger-floor distance > 30cm; 16) Bragard's test; 17) sensory disturbance; 18) MRI-level herniation L5S1; 19) MRI-sequester; 20) mild preference surgery; 21) RDQ; 22) VAS-leg pain; 23) RDQ difference (T2W-T0); 23) VAS difference (T2W-T0)	Surgery	Univariate and multivariate logistic regression analysis (method: backward stepwise)	Kemp's sign: OR = 2.8 (1.3-5.8) Mild preference surgery: OR = 0.5 (0.2-1.0) RDQ (per 3 points): OR = 2.1 (1.2-3.5) VAS-leg pain (per 20 mm): OR = 1.7 (1.1-2.6)	**RDQ (per 3 points): OR = 1.8 (1.2-2.9)** **VAS-leg pain (per 20 mm): OR = 1.7 (1.1-2.7)** Gender, age, intellectual job, housewife, body mass index, Kemp's sign, mild preference surgery: non-significant	
	Peul et al, 2008b	1) surgery; 2) timing surgery after randomization (3 categories); 3) gender; 4) age ≥ 40, 5) mentally demanding job; 6) physical job; 7) housewife; 8) spouse/partner; 9) children; 10) smoking; 11) body mass index; 12) start sciatica (slow increase); 13) sciatica provoked by sitting; 14) sciatica provoked by coughing, sneeze; 15) VAS leg pain ≥ 70 mm 16) straight leg raising; 17) crossed leg raising; 18) Kemp's sign; 19) finger-floor distance > 30cm; 20) Bragard's test; 21) sensory disturbance; 22) MRI-level herniation; 23) MRI-sequester; 24) preference surgery	Unsatisfactory outcome (defined as no complete or no near complete recovery on a 7-point Likert scale)	Univariate and multivariate log rank analysis	Female gender: OR =3.3 (1.7-6.3) Housewife: OR = 3.3 (1.3-8.4) Bragard's test: OR = 3.8 (1.9-7.5)	Surgery: OR = 0.5 (0.2-1.0) **Female gender: OR = 2.8 (1.4-5.7)** Mentally demanding job: OR = 1.1 (0.4-2.5) Housewife: OR = 1.7 (0.5-5.7) Smoking: OR = 2.0 (1.0-4.1) Sciatica provoked by sitting: OR = 1.3 (0.5-3.2) Crossed leg-raising test: OR =1.8 (0.8-3.8) **Bragard's test: OR = 2.7 (1.3-5.6)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Tubach et al, 2004	1) gender; 2) age (3 categories); 3) height (2 categories); 4) BMI (4 categories); 5) smoking habits; 6) a hobby of home repair or renovation; 7) employment grade (3 categories); 8) standing >2hrs/day (4 categories); 9) carrying heavy loads >2hrs/day (4 categories); 10) driving >2hrs/day (4 categories); 11) pulling or pushing heavy loads at work (4 categories); 12) twisting at work (4 categories); 13) bending backward or forward at work (4 categories); 14) visit to physician; 15) physiotherapy; 16) sick leave; 17) pain intensity (VAS) (3 categories); 18) long-lasting LBP; 19) sciatica the year before; 20) psychosomatic well being score; 21) depression score; 22) job satisfaction (3 categories)	Persistence or recurrence of sciatica (based on the question 'Have you suffered from sciatica during the previous year?')	Pearson's chi-square test and multivariate logistic regression (controlled for gender and those variables with a significance level $P \leq 0.20$ in the univariate analysis)	-	Female gender: OR = 1.4 (0.7-2.7) Carrying loads> 10kg (ref: never) **Less than once a week: OR = 1.7 (1.0-3.0)** More than once a week: OR = 1.2 (0.7-2.2) Every day: OR = 1.5 (0.8-2.8) Driving > 2hrs/day (ref: never) **Less than once a week: OR = 2.4 (1.2-4.9)** More than once a week: OR = 1.8 (1.0-3.3) Every day: OR = 1.0 (0.6-1.6) Home repair > 1 h a week: OR =1.3 (0.8-2.2) Visit to medical practitioner: OR = 0.9 (0.5-1.4) Sick leave for low back pain: OR = 1.4 (0.8-2.3) Pain intensity (ref: low) Intermediate: OR = 1.1 (0.6-1.8) High: OR = 1.2 (0.7-2.1) **High psychosomatic score: OR = 1.7 (1.1-2.6)** High depression score: OR = 0.9 (0.6-1.4) Job satisfaction (ref: high) Intermediate: OR = 1.5 (0.9-2.6) Low: OR = 1.1 (0.7-1.8) Long lasting back pain: OR = 1.2 (0.8-1.8) **Sciatica one year before baseline: OR = 1.9 (1.2-2.9)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Valls et al, 2001	1) age; 2) height; 3) weight; 4) gender; 5) manual occupation; 6) physical activities; 7) history of spinal disorders; 8) nature of prior spinal symptoms (3 categories); 9) precipitating factor (3 categories); 10) duration (3 categories); 11) lumbar support; 12) epidural glucocorticoid injections; 13) good compliance to rest; 14) nerve root pain distribution (6 categories); 15) exacerbated by straining; 16) antalgic posture; 17) schöber's index; 18) nerve root pain upon finger pressure on paraspinal area; 19) limitation of range of motion at the lumbar spine (3 categories); 20) straight leg-raising test (in degrees and dichotomized); 21) motor loss; 22) hypoesthesia; 23) deep tendon reflexes knee; 24) deep tendon reflexes ankle; 25) plain radiographs changes (3 categories); 26) facet joint osteoarthritis; 27) computed tomography done; 28) location of the herniation (6 categories); 29) level of the herniation; 30) size of the herniation; 31) time of CT relative to the hospital stay (3 categories); 32) hospital stay length; 33) epidural glucocorticoid injections	Nucleolysis or surgery	Odds ratios (univariate) (Kruskal-Wallis test), and multivariate logistic regression analysis (controlled for those variables with a significance level $P < 0.05$ in the univariate analysis)	Symptom duration > 1 month: OR = 3.3 (1.3-8.5) Use of a lumbar support prior to admission: OR = 2.7 (1.2-6.2) History of epidural glucocorticoid injection: 1.2 vs 0.9, p = 0.005 (no OR given) Positive straight leg-raising test: OR = 9.4 (1.2-187) Disc herniation size of at least 50% of the spinal canal diameter: OR = 7.9 (1.5-77.1)	Symptom duration > 1 month: OR = 2.6 (1.0-4.2) **Use of a lumbar support prior to admission: OR = 2.8 (1.2-4.4)** **Positive straight leg-raising test: OR = 9.9 (7.0-12.8)** Other variables were non-significant When imaging data were included (n=89): **Disc herniation size of at least 50% of the spinal canal diameter: OR = 15.7 (12.7-18.6)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
(Vroomen et al., 1999)	Vroomen et al, 2000	1) age; 2) gender; 3) high education level; 4) living alone; 5) mentally demanding job; 6) previous episodes of pain in the leg; 7) previous episodes of low back pain; 8) family history; 9) co-morbidity; 10) smoking; 11) sports activities; 12) exercised back or abdominal muscles; 13) more pain in the leg than back; 14) sudden onset of pain; 15) cause of pain known; 16) pain worse in the evening or night; 17) paroxysmal pain; 18) pain already improving; 19) typically dermatomal pain distribution; 20) more pain on coughing/sneezing/straining; 21) more pain on sitting; 22) numbness in the leg; 23) paraesthesias in the leg; 24) cold feeling in the leg; 25) worrying about health; 26) intensity of pain in the leg (VAS scale); 27) complaints considered severe by the physician; 28) pain rating index of McGill pain questionnaire for sensory and affective dimensions; 29) difficulty putting on sock/ stockings; 30) pain while dressing; 31) finger-floor distance; 32) paresis; 33) hypaesthesia; 34) hypalgesia; 35) ankle tendon reflex difference; 36) knee tendon reflex difference; 37) straight leg-raising test; 38) reversed straight leg-raising test; 39) crossed straight leg-raising test; 40) Kemp sign; 41) Naffziger sign	Surgery	Univariate and multivariate logistic regression analysis (method: backward stepwise)	Mentally demanding job: OR = 3.8 (1.7-8.6) Sudden onset: OR = 0.3 (0.1-0.7) More pain on coughing/ sneezing /straining: OR = 5.3 (2.0-13.6) Pain intensity in the leg (VAS): OR = 1.0 (1.0-1.1) Reversed SLR-test: OR =2.5 (1.1-5.8)	**Mentally demanding job: OR = 4.0 (1.5-10.3)** **Sudden onset: OR = 0.2 (0.1-0.7)** **More pain on coughing/ sneezing /straining: OR = 4.3 (1.5-12.4)** Difficulty putting on socks/ stockings: OR = 2.3 (0.9-6.0) **VAS-leg pain (1mm): OR = 1.0 (1.0-1.1)** **Reversed SLR-test: OR = 3.2 (1.2-8.9)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Vroomen et al, 2002a	Set A: 1) age; 2) gender; 3) tertiary education; 4) living alone; 5) employed; 6) previous sciatica; 7) previous low back pain; 8) family history; 9) comorbidity; 10) smokers; 11) active in sporting activities; 12) has exercised abdominals; 13) BMI; 14) Revised Oswestry score; 15) RDQ score; 16) McGill Pain score; Set B: 17) leg pain greater than back pain; 18) sudden onset of pain; 19) cause of pain known; 20) pain worse at night; 21) paroxysmal pain; 22) pain already improving; 23) observer's opinion; 24) typically dermatomal pain; 25) increased pain on pressure; 26) pain on sitting; 27) decreased pain on lying down; 28) decreased pain when upright; 29) subjective weakness; 30) subjective sensory loss; 31) cold sensations; 32) paraesthesias in the leg; 33) urinary problems; 34) health worries; Set C: 35) decreased lordosis; 36) finger-to-floor distance > 24cm; 37) paresis; 38) hypaesthesia; 39) hypalgesia; 40) ankle tendon reflex difference; 41) knee tendon reflex difference; 42) straight leg-raising test; 43) reversed straight leg-raising test; 44) valleix points; 45) Kemp sign present; 46) Naffziger sign present	Favourable outcome (defined as no eventual surgery or no lack of improvement)	Univariate, and multivariate logistic regression analysis (Set A was modelled first, then set B, incorporating the predictive variables from model of set A, and then the same was done for set C. Analysis were controlled for treatment (bed rest versus watchful-waiting) received)	Duration of pain 30 days or less: OR = 0.3 (0.1-0.6) Already improving at baseline: OR = 2.9 (1.2-6.9) More pain on increase of pressure: OR = 0.5 (0.2-1.0) Positive straight leg-raising test: OR = 0.4 (0.2-0.9) Positive reversed straight leg-raising test: OR = 0.5 (0.2-0.97)	**Duration of pain 30 days or less: OR = 0.1 (0.05-0.2)** Already improving at baseline: non-significant More pain on increase of pressure: non-significant **Positive straight leg-raising test: OR = 0.4 (0.1-0.9)** **Positive reversed straight leg-raising test: OR = 0.4 (0.2-0.9)**	

Appendix 3: Overview of the prognostic factors and outcomes of the included 23 articles representing 14 cohort studies (continued)

Cohort	Author, year of publication	Prognostic factors investigated	Outcome	Type of analysis	Significant univariate results (Crude estimates and 95% Confidence intervals (CI's))	Multivariate results (Adjusted Odds Ratios (OR's) and 95% CI)	Comments (authors' conclusion for results not reported)
	Vroomen et al, 2002b	MRI findings: 1) nerve root compression; 2) disc herniation; 3) annular rupture; 4) root ganglion compression; 5) compression of root in axilla; 6) compression of root in shoulder; 7) compression of root in dural sac; 8) medial disc herniation; 9) mediolateral disc herniation; 10) foraminal disc herniation	Favourable outcome (improvement or strong improvement)	Odds ratios (univariate), and multivariate logistic regression analysis	**Nerve root compression: OR = 3.3 (1.1-9.8)** **Annular rupture: OR = 3. 5 (1.2-10.5)** **Foraminal disc herniation: OR = 0.2 (0.1-0.7)** -		('The logistic regression analysis, in which surgery was treated as a confounding and effect-modifying variable, provided identical estimates of predictive value and statistical significance to the results of the univariate analysis')

[1] RDQ means Roland Morris Disability Questionnaire [0-24]. Higher scores indicate more disability.
[2] SF-36 mental health [0-100]. Higher scores indicate better mental health.
[3] Sciatica symptom frequency [0-24]. Higher scores indicate more frequent symptoms.
[4] SF-36 bodily pain [0-100]. Higher scores indicate less pain.
[5] SF-36 physical function [0-100]. Higher scores indicate better function.
[6] ODI means Oswestry Disability Index [0-100]. Higher scores indicate more severe symptoms.
[7] Sciatica bothersome index/scale [0-24]. Higher scores indicate more severe symptoms.
[8] Low back pain bothersomeness index/scale [0-6]. Higher scores indicate more severe symptoms.
[9] Leg pain bothersomeness scale [0-6]. Higher scores indicate more severe symptoms.
[10] VAS mean visual analogue scale [0-10 or 0-100]. Higher scores indicate more pain.
[11] McGill pain score; results in seven words describing the quality and intensity of pain.

9. Prognostic value of magnetic resonance imaging findings in patients with sciatica.

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ABSTRACT

Background context: Magnetic resonance imaging (MRI) findings may have prognostic value in patients with intense sciatica and intuitively help to identify subgroups of patients that might benefit more from either early surgery or a strategy of prolonged conservative care.

Purpose: To determine the prognostic value of MRI variables to predict outcome in patients with sciatica and whether MRI facilitates the decision-making between early surgery and prolonged conservative care in sciatica.

Study design: Prospective observational evaluation of patients enrolled in a randomized trial with 1-year follow-up.

Patient sample: A total of 283 sciatica patients randomized to surgery, or prolonged conservative care with surgery if needed.

Outcome measures: Recovery was registered on a 7-point Likert scale. Complete/near complete recovery was considered to be a satisfactory outcome. Leg pain severity was measured on a 0-100 mm visual analogue scale.

Methods: Multiple MRI characteristics of the degenerated disc herniation were scored. Cox models were used to study the influence of MRI variables on rate of recovery, and linear mixed models to determine the predictive value of MRI variables for leg pain severity during follow-up. Interaction of each MRI predictor with treatment allocation was tested. There were no study-specific conflicts of interest.

Results: Baseline MRI variables associated with less leg pain severity were the reader's assessment of presence of nerve root compression ($p<0.001$), and assessment of extrusion as compared to protrusion of the disc herniation ($p=0.006$). Both variables tended to associate, but not significantly, with satisfactory outcome during follow-up (hazard ratio [HR] 1.45; 95% confidence interval [CI] 0.93-2.24 and HR 1.24; 95% CI 0.96-1.61, respectively). The size of disc herniation at baseline was not associated with outcome. There was no significant change between the effects between treatment groups.

Conclusions: MRI assessment of the presence of nerve root compression and extrusion of a herniated disc at baseline was associated with less leg pain during 1-year follow-up, irrespective of a surgical or conservative treatment. MRI was not demonstrated to be helpful in the decision-making process regarding early surgery versus prolonged conservative care.

INTRODUCTION

Sciatica, also called sciatic neuralgia or lumbosacral radicular syndrome, is the most common neurological spine disease. It is usually caused by the frequently occurring degenerative disc disease resulting in compression or irritation of a nerve root by herniating disc material. The estimated annual prevalence rate is reported to be between 2.2% and 34%.[1] Differences in study populations and definition of sciatic symptoms explain most of the variation of reported prevalence estimates. The natural history of sciatica is favorable, with spontaneous resolution of the leg pain within 8 weeks in 60-80% of patients experiencing their first episode of sciatica.[2,3] Patients with severe symptoms who fail to respond to conservative care for at least 6-8 weeks have an indication for magnetic resonance imaging (MRI).[3] However, despite the guidelines many patients in Western Society seem to receive earlier MRI, often without any indication for surgery. When severe symptoms persist, surgery as a treatment modality is considered and MRI is used to assess whether a herniated disc with nerve root compression is indeed present, and what surgical approach is the most optimal. For instance, surgery for a mediolateral sequestrated herniated disc at L4-L5 needs a completely different method than an intraforaminally located contained herniated disc at L5-S1, while both disc herniations give rise to a neurologically identical nerve root syndrome of L5. Patients who fail on conservative care and in whom clinical findings correspond well to imaging findings may qualify for surgery. Despite this common algorithm, surgical treatment rates for lumbar discectomy vary widely between countries and even within countries.[3,4] This may (in part) be due to a lack of a clear definition of sciatica, a paucity of evidence on the value of diagnostic and therapeutic interventions, and a lack of clear clinical guidelines.[3]

Earlier, our group reported the results of a randomized controlled trial (RCT) designed to define optimal timing of surgery for patients with sciatica.[5] The trial showed that patients recover twice as fast after early surgery as compared to a strategy of prolonged conservative care. Furthermore, 39% of patients in the conservative group were still operated within the 1-year follow-up. Despite the apparent benefit of surgery, effectiveness analysis found no differences in the final outcome after 1-year, thereby supporting a conservative approach with surgery only if needed.[5] However, because the success of this approach may differ between subgroups of patients, it is important to identify individuals that may benefit more from either early surgery or a strategy of prolonged conservative care. Our group also evaluated whether MRI at baseline could have predicted surgery in patients assigned to the conservative group of the trial and concluded that MRI at baseline was unable to distinguish between patients who did and did not undergo delayed surgery.[6] In another study we evaluated the influence of clinical determinants on the rate of recovery in all patients included in the RCT and found female

gender, a positive Bragard's sign, and the crossed straight-leg-raise test to be predictive of an unsatisfactory outcome.[7] The present study aims to assess 1) the predictive value of various MRI variables for satisfactory outcome during 1-year follow-up and 2) whether MRI facilitates decision-making between early surgery and prolonged conservative care in patients with herniated disc related sciatica.

METHODS

Study population

Patients for this study were participants in the Sciatica Trial: a multicenter RCT in patients with sciatica persisting for 6-12 weeks. Patients were aged 18-65 years and were included only if they had a dermatomal pattern of pain distribution with concomitant neurological disturbances that correlated to the same nerve root being affected on MRI. An early surgery strategy was compared with prolonged conservative care for an additional 6 months followed by surgery for patients who did not improve, or who had an urge for surgery earlier because of aggravating symptoms.[5,8] The Medical Ethics committees at the 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients.

MRI protocol and Image evaluation

MRI scans were performed at all 9 participating hospitals using standardized protocols tailored to a 1.5 Tesla scanner. Sagittal T1 and transversal T1 spin echo images of the lumbar spine were acquired. In addition, T2-weighted sagittal and axial series, and contrast-enhanced (gadolinium) T1 fat suppressed images were obtained. Two experienced neuroradiologists (BK and GL) and one neurosurgeon (CV) independently evaluated all MR images. The readers were not provided any clinical information and had not been involved in the selection or care of the included patients. Each reader was given a manual containing definitions of imaging characteristics based on the recommendations from the combined task forces of the North American Spine Society, the American Society of Spine Radiology, and the American Society of Neuroradiology for classification of lumbar disc pathology in order to standardize the nomenclature.[9] Vertebral endplate signal changes were defined according to the criteria of Modic et al.[10,11] Before the start of the study, the readers met in person to evaluate and refine the standardized definitions. After reaching final consensus, standardized case record forms with these final definitions were used to evaluate the images (Appendix 1). The presence of nerve root compression and clinically relevant characteristics of the disc level and disc herniation (e.g. size, location and morphology) were scored for the disc level with the most severe nerve root compression. Based on the literature and clinical practice, we selected 9 MRI

variables from this standardized case record form as being the most relevant to test their association with clinical outcome during the 1-year follow-up.

For assessment of the presence of nerve root compression on MRI at baseline a 4-point scale was used: 'Definite about the presence', 'Probable about the presence' if there was some doubt but the probability was >50%, 'Possible about the presence' if there was reason to consider but the probability was <50%, and 'Definite about the absence'. The first two categories were combined and categorized as 'Assessed as having nerve root compression' and the last two categories were combined and categorized as 'Assessed as not having nerve root compression'.

Outcomes

Outcome measures included a 7-point Likert self-rating scale of global perceived recovery, based on the question how the patient experienced recovery compared to baseline (answers ranged from 'Completely recovered' to 'Much worse'),[12] the Roland Disability Questionnaire (RDQ) for Sciatica (scores ranged from 0-23, with higher scores indicating worse functional status),[13] and the 0-100-mm visual analogue scale (VAS) for leg and back pain (with 0 representing no pain, and 100 the worst pain ever experienced).[14] These outcome measures were assessed at baseline and at 2, 4, 8, 12, 26, 38 and 52 weeks.

Statistical Analysis

The majority opinion of the three readers regarding the MRI characteristics (answer independently given by a minimum of 2 out of 3 readers) was used in the analysis. Details on the interobserver agreement for the MRI findings are already published.[15]

Perceived recovery was defined as 'Complete' or 'Nearly complete disappearance of symptoms' on the patient-reported 7-point Likert scale for global perceived recovery, while a score in the remaining five categories was marked as a poor or unsatisfactory outcome and defined as 'No recovery'.[5,8] Cox proportional hazards models were used to study the relationship between MRI variables and time until perceived recovery (as determined by the prescheduled moments of outcome registration during follow-up).

Multivariate linear mixed effects models were used to study the relationship between MRI variables and leg pain severity during follow-up. In both the Cox proportional hazards models and the linear mixed regression models, all univariate relationships between MRI variables and outcome were also adjusted for the randomization arm. Additionally, when an MRI variable proved to significantly predict perceived recovery or leg

pain severity during follow-up, differences in RDQ score and VAS back pain determined at 1-year between the subcategories of this variable were assessed using Student's t-test.

Effect modification of each MRI predictor was tested in the Cox proportional hazards models and the linear mixed regression models containing the treatment allocation, the MRI predictor and the interaction between them. We prespecified that when a predictor shows a significant interaction we would enter this predictor in a repeated measurements analysis for the RDQ for sciatica and the VAS for back pain, to test whether the interaction also holds in linear mixed regression models. Statistical significance was defined as a p-value <0.05.

RESULTS

Of the 599 patients screened for the Sciatica Trial, 283 patients were randomized.[5] No significant baseline differences were found between the 141 patients randomized to early surgery and the 142 patients randomized to prolonged conservative care (Table 1).[5] Of the patients assigned to early surgery 10% were assessed not to have nerve root compression on MRI at baseline compared to 8% of the patients assigned to receive prolonged conservative care. In both treatment groups 3 (2.1%) patients had a bulging disc instead of disc herniation. Of the 141 patients assigned to receive early surgical treatment, 16 recovered before surgery could be performed. Of the 142 patients assigned to prolonged conservative care, 55 (39%) underwent surgery during the first year. In the early-surgery group, 3.2% of patients had recurrent sciatica leading to a second surgical intervention, as compared to 1.8% of patients in the conservative-treatment group who underwent surgery. Complications occurred in 1.6% of all surgical patients, consisting of two dural tears and one wound hematoma. All complications resolved spontaneously. At 1-year follow-up patients reported a mean score of 10.8 on the VAS for leg pain (mean score of 11.0 for patients in the early-surgery group, and 10.6 in the conservative-treatment group) and 84% of the patients reported to be recovered (86% in the early-surgery group and 83% in the prolonged conservative care group).

Rate of recovery according to baseline MRI characteristics

Patients assessed to have nerve root compression on baseline MRI tended to have a higher, but non-significant, rate of recovery compared to patients in whom no nerve root compression was assessed on MRI (hazard ratio [HR] adjusted for treatment allocation 1.45; 95% confidence interval [CI] 0.93-2.24). However, only 9% of the included patients were not assessed as having nerve root compression on MRI. Table 2 shows the rate of recovery according to characteristics of the affected disc level or herniated disc on

Table 1. Baseline characteristics of the study population.

	Early surgery group (n=141)	Prolonged conservative treatment group (n=142)
Age (in years)	41.7±10.0	43.4±9.6
Male sex	89 (63)	97 (68)
Body mass index[1]	25.9±4.1	25.5±3.3
Duration of sciatica (in weeks)	9.4±2.4	9.5±2.2
Smoking	57 (40)	52 (37)
Suspected disc level and type of displacement on MRI		
L3L4 Herniation	6 (4)	4 (3)
L4L5 Herniation	63 (45)	51 (36)
L4L5 Bulging	2 (1)	1 (1)
L5S1 Herniation	69 (49)	84 (59)
L5S1 Bulging	1 (1)	2 (1)
MRI assessed nerve root compression		
Definite: no doubt about the presence of nerve root compression	90 (64)	102 (72)
Probable: some doubt but probability > 50%	37 (26)	29 (20)
Possible: reason to consider but probability < 50%	11 (8)	10 (7)
Definitely no root compression	3 (2)	1 (1)
Sensory loss	92 (65)	105 (74)
Abnormal reflexes[2]	89 (63)	101 (71)
Muscle weakness[3]	103 (73)	115 (81)
Disturbed neurological tests[4]	131 (93)	129 (91)
Roland Disability score[5]	16.5±4.4	16.1±3.9
VAS leg pain in mm[6]	67.3±19.6	64.4±21.2
VAS back pain in mm[6]	34.0±29.6	30.8±27.7

Values are n (%) or means ± SD

No significant baseline differences observed in the intention-to-treat group

[1] Body mass index is the weight in kilograms divided by the square of the height in meters

[2] Reflexes were rated as abnormal if absent, less than the other side, or in case of an extensor plantar response (Babinski sign).

[3] Muscle strength was considered normal in case of MRC Grade 5 whereas Grade 4 or less was rated abnormal.

[4] Six neurological tests were performed (Lasègue's sign, Crossed straight-leg raising, Kemp's sign, Bragard's Sign, walking on heels and walking on toes). One or more disturbed tests was considered to be an abnormal result.

[5] The Roland Disability Questionnaire for Sciatica is a disease-specific disability scale that measures the functional status of patients with pain in the leg or back. Scores range from 0-23, with higher scores indicating worse functional status.

[6] The intensity of pain is indicated on a horizontal 100 mm visual analogue scale (VAS) with 0 representing no pain and 100 the worst pain ever experienced.

Table 2. Association between baseline MRI findings and rate of recovery during the first year after randomization.

	Comparison (%)	Subgroup effect HR (95% CI)	Subgroup effect HR adjusted for treatment allocation (95% CI)[1]	P-value of adjusted HR	P-value group interaction[2]
Presence of nerve root compression	Yes (91) vs. No (9)	1.34 (0.87-2.08)	1.45 (0.93-2.24)	0.10	0.92
Disc level disc herniation	L5S1 (55) vs. L3L4 or L4L5 (45)	0.96 (0.75-1.22)	1.02 (0.80-1.31)	0.88	0.87
Size of the disc herniation	Size > 50% (21) vs. size < 50% in relation to spinal canal (79)	1.02 (0.75-1.38)	1.09 (0.80-1.48)	0.60	0.37
Location of the disc herniation	Central and/or subarticular (91) vs. foraminal and/or extraforaminal (9)	1.07 (0.70-1.64)	1.08 (0.71-1.66)	0.72	0.68
Morphology of the disc herniation	Extrusion (64) vs. protrusion (36)	1.15 (0.89-1.49)	1.24 (0.96-1.61)	0.10	0.26
Absence of epidural fat adjacent to the dural sac or surrounding the nerve root sheath	Completely (60) vs. partly or not disappeared (40)	1.01 (0.79-1.30)	1.08 (0.84-1.39)	0.54	0.95
Presence of impaired discs on other disc levels	Yes (79) vs. no (21)	1.13 (0.83-1.53)	1.08 (0.80-1.47)	0.61	0.54
Presence of Vertebral Endplate Signal Changes at the disc level of the herniated disc	Present (33) vs. absent (67)	1.15 (0.89-1.51)	1.12 (0.86-1.46)	0.42	0.51
Presence of Schmorl's nodules (herniation of the disc into the vertebral-body endplate) at the disc level of the herniated disc	Present (5) vs. absent (95)	1.24 (0.71-2.17)	1.34 (0.77-2.35)	0.31	0.55

Recovery was defined as 'Complete' or 'Nearly' complete disappearance of symptoms on a 7-point Likert scale.

HR; hazard ratio. CI; confidence interval.

[1] Treatment strategies were randomized allocation to early surgery vs. prolonged conservative care

[2] Tests whether the hazard ratio of early surgery vs. prolonged conservative care is different between the subgroups analysed.

baseline MRI. Patients assessed at baseline to have a large herniated disc (size >50% in relation to spinal canal) did not report a significantly higher rate of recovery compared to patients with a smaller disc herniation (HR 1.09; 95% CI 0.80-1.48). Patients who were assessed with an extrusion as the herniation form tended to have a higher, but non-significant, rate of recovery compared to patients with a protrusion as the herniation form (HR 1.24, 95% CI 0.96-1.61). For all MRI variables investigated, p-values for group interaction were non-significant (all p-values for interaction >0.26).

Leg pain severity according to baseline MRI characteristics

Table 3 presents leg pain severity according to baseline MRI characteristics. Patients assessed to have nerve root compression on baseline MRI reported significantly less leg pain severity during follow-up compared to patients who had no nerve root compression on baseline MRI (estimate of reduction of VAS leg pain of 11.69, 95% CI 5.87-17.50). Similarly, patients assessed to have nerve root compression on baseline MRI also reported a more favorable RDQ score (3.0 vs. 7.4, p=0.01) and a lower VAS back pain score (13.8 vs. 29.7, p=0.02) during follow-up. Patients with extrusions at baseline reported less leg pain compared to patients with protrusions (estimate of reduction of VAS leg pain of 4.98, 95% CI 1.42-8.54). Patients assessed with extrusions as the herniation form on baseline MRI did not report a significantly more favorable RDQ score at follow-up (2.9 vs. 4.3, p=0.07); however, these latter patients reported a lower VAS back pain score at follow-up (12.9 vs. 20.2, p=0.02). Other characteristics of the affected disc level or herniated disc on baseline MRI showed no relationship with leg pain severity (Table 3). For all MRI variables investigated, none showed an interaction with treatment allocation (all p-values for interaction >0.22).

DISCUSSION

Main results

In this patient group, the size of disc herniation at baseline did not influence outcome during the 1-year follow-up. However, patients with nerve root compression seen on baseline MRI reported less leg pain during follow-up compared to patients with no depicted nerve root compression, irrespective of surgical or conservative treatment. In accordance with clinical observations, patients without a clear compressive etiology of their severe sciatic symptoms experience more persistent leg pain. Apparently, a non-compressive etiology of sciatica seems more difficult to resolve. Patients assessed with an extrusion reported less leg pain during follow-up as compared to patients with a protrusion; again, irrespective of a surgical or conservative treatment. Furthermore, no interaction was found between assigned treatment and baseline MRI findings for

Table 3. Repeated measures analysis of baseline MRI findings for less leg severity during 1-year follow-up.

	Comparison (%)	Estimate (95% CI)	Estimate adjusted for treatment allocation (95% CI)[1]	P-value of adjusted estimate	P-value group Interaction[2]
Presence of nerve root compression	Yes (91) vs. No (9)	11.11 (5.04-17.18)	11.69 (5.87-17.50)	**<0.001**	0.58
Disc level disc herniation	L5S1 (55) vs. L3L4 or L4L5 (45)	1.26 (-2.29-4.81)	2.21 (-1.21-5.64)	0.21	0.60
Size of disc herniation	Size > 50% (21) vs. size < 50% in relation to spinal canal (79)	0.38 (-4.06-4.82)	0.82 (-3.46-5.11)	0.71	0.86
Location of the disc herniation	Central and/or subarticular (91) vs. foraminal and/or extraforaminal (9)	3.66 (-2.55-9.87)	3.51 (-2.48-9.49)	0.25	0.70
Morphology of disc herniation	Extrusion (64) vs. protrusion (36)	4.57 (0.89-8.25)	4.98 (1.42-8.54)	**0.006**	0.24
Absence of epidural fat adjacent to the dural sac or surrounding the nerve root sheath	Completely (59) vs. partly or not disappeared (41)	1.81 (-1.77-5.39)	2.74 (-0.74-6.21)	0.12	0.29
Presence of impaired discs on other disc levels	Yes (79) vs. no (21)	1.36 (-2.99-5.71)	1.04 (-3.18-5.25)	0.99	0.41
Presence of vertebral endplate signal changes at the disc level of the herniated disc	Present (33) vs. absent (67)	-0.92 (-4.66-2.82)	-0.07 (-3.69-3.55)	0.97	0.96
Presence of Schmorl's nodules (herniation of the disc into the vertebral-body endplate) at the disc level of the herniated disc	Present (5) vs. absent (95)	-0.15 (-8.45-8.15)	1.50 (-6.52-9.52)	0.71	0.22

CI; confidence interval

[1] Treatment strategies were randomized allocation to early surgery vs. prolonged conservative care

[2] Tests whether the estimate of randomized allocation to early surgery vs. prolonged conservative care differs between the subgroups analyzed

recovery or persisting leg pain. This indicates that, while some baseline MRI findings were informative in predicting leg pain severity during the first year after diagnosis, they are unable to predict which patients may benefit from either early surgery or prolonged conservative care.

Comparison with literature

Earlier studies examined the prognostic value of various MRI characteristics.[16] However, difficulties may arise when correlating MRI findings with prognosis, as the treatment choice following the MRI findings may reflect patient prognosis, and the preference of both the practice community and physician. From a clinical viewpoint, we expected a larger size disc herniation at baseline to be associated with a better outcome in a surgically treated cohort during follow-up, and less so in the conservatively treated patients. However, the presence of large disc herniations (present in 21% of our included patients) showed no prognostic value, irrespective of surgical or prolonged conservative treatment. This is in concordance with a study in surgically treated patients and another in non-surgically treated patients, both of which showed no correlation between size of the disc herniation and outcome.[17,18] In contrast, another retrospective cohort study showed that patients with a thecal sac compression of 1/3 or more had greater surgical treatment effect than those with small disc herniations, although for conservatively treated patients no differences in outcome were seen.[19] Overall, differences in the prognostic value of MRI characteristics between studies may be largely explained by differences in study design, study population, sample size and treatment received. The discrepancy between studies regarding disc herniation size may be caused by the interpretation of small and large disc herniations; this largely depends on the reviewer and how it is measured. The method in which the size is correlated to the width of the canal seems the most reliable; however, the level at which the size of the canal is determined has considerable influence on the measurement of the size of the bulging disc. Moreover, it is debatable whether the size of the bony canal should be measured, or the size of the canal minus the flaval ligament. Morphometric studies would benefit from clear guidelines on this topic.

Recent studies support the theory of a multifactorial etiologic origin of sciatica in which spinal nerve irritation may result from both compressive and non-compressive causes.[20,21] Therefore, as with other diseases, differences in etiology of sciatica may (theoretically) result in different outcomes. For example, a non-compressive (possibly inflammatory) cause of sciatica may be more difficult to resolve spontaneously. The present study in 283 patients, as well as two earlier studies, support this theory and found a better prognosis for patients with clear nerve root compression on MRI.[17,22] However, two other studies found no significant association for nerve root compression.[23,24] Another

(retrospective) cohort observed better surgical outcomes for patients with nerve root compression, whereas the outcomes in the non-surgical groups were similar.[19] Again, these differences in observed prognostic value of the presence of nerve root compression may be largely explained by differences in study design, study population, sample size and treatment received.

Different classification methods for morphology of disc herniations are used, thereby complicating comparisons between studies. A recent systematic review evaluating the probability of spontaneous regression among different types of lumber herniated discs, found a rate of spontaneous regression of 96% for disc sequestration, 70% for disc extrusion and 41% for disc protrusion.[25] The higher rate of spontaneous regression of disc extrusions compared to disc protrusions, may indicate a better prognosis for extruded disc herniations in conservatively treated patients. In surgically treated patients it is feasible that decompression of the nerve is more impressive in case of an extrusion. In the present study, the finding of a better prognosis for patients assessed with an extruded disc (present in 64% of the included patients) tends to support these theories. Moreover, another study in conservatively treated patients, and two studies in surgically treated patients, also found better outcome results for patients with extrusions.[23,26,27] However, another study (retrospective cohort, 61% had disc surgery) observed no different outcomes between different disc morphology groups.[19] Again, the way in which the disc extrusion or protrusion is determined, has a strong influence on the outcome. However, until clear guidelines become available, no firm conclusions can be drawn. Moreover, it is noteworthy that the size of the herniated disc is not associated with outcome, whereas the presence of extrusion does; perhaps there is an association between size and extrusion?

For the presence of both nerve root compression and of an extruded disc, clear and significant results were seen for their prognostic value on the outcome 'leg pain severity' during follow-up. However, results for the outcome 'recovery' were not significant (although a tendency was found as both p-values were 0.10). We have no clear explanation for this discrepancy between outcome measures.

The present study demonstrates that the MRI parameters studied are not helpful in the decision-making process of early surgery vs. prolonged conservative care. Even for the MRI variables indicating possibly more benefit from surgery (i.e. large disc herniation and extruded disc) there was no interaction with treatment allocation. A similar study in the same patient population showed that only the history item on the presence of 'sciatica provoked by sitting' showed interaction with the timing of surgery and thus influenced the rate of recovery.[28] Thus, unfortunately, we have to conclude that clinical

and MRI characteristics are minimally informative in determining which patients might fare better with early surgery as compared to a strategy of prolonged conservative care.

It seems that the threshold is lowering with regard to making an MRI in patients with low back pain.[29] In addition, with improvements in the resolution of imaging studies, more and smaller abnormalities will probably be detected which may be clinically irrelevant,[30] but may create the potential for overestimation of the prevalence of surgically amenable diseases in the lumbar spine.[31] Disc herniations on MRI are observed in 28-76% of persons without any symptoms.[32,33] The marked increase in rates of lumbar spine surgery has partly been linked to the increased availability of advanced diagnostic imaging techniques.[30,31] Moreover, spine imaging may have an adverse effect, i.e. telling patients they have an imaging abnormality can lead to unintended harm related to disease labelling.[34,35] The present study adds that, within this highly selected population of patients with 6-12 weeks herniated disc related sciatica, MRI has no value in the decision-making between early surgery and prolonged conservative care. Patients with clear sciatic symptoms and, on MRI, a severe disc herniation with clear nerve root compression might still benefit from conservative care. Even those abnormalities (seen on MRI) that do match clinical symptoms may well resolve spontaneously.

Study limitations

The main drawback of the present study was the selection of patients from neurological outpatient clinics after referral by primary care physicians; therefore, also due to the stringent inclusion criteria, there was less MRI contrast between patients. Although the trial had a pragmatic study design, the patients were highly selected and had a monodermatomal pain problem leading to a clear-cut sciatica condition. However, in daily practice, for most patients the neurological syndrome is less clear, so that MRIs may not show nerve root compression or present very small herniated discs. In reality (i.e. outside RCTs), there is considerable contrast between groups of similar pain patients with disc-related nerve root compression and those without morphological nerve root problems. Although, hypothetically, in MRI studies this contrast will lead to a better MRI discrimination, this has not yet proven. If the sciatica is not intense, or the MRI findings are not consistent with clear-cut nerve root compression, we advise to withhold from surgery.

Furthermore, the present results should be interpreted carefully since the power analysis performed during planning of the clinical outcome study was based on how many patients would be required to detect a difference in clinical outcome between early surgery and prolonged conservative care for sciatica. No separate power analysis was

performed for the present study. Also, as some MRI characteristics were present in only 5-9% of the patients, a larger study population would have been desirable.

In conclusion, the size of disc herniation assessed at baseline did not influence outcome during 1-year follow-up. In this highly selected study population, baseline MRI findings were not helpful in determining which patients might fare better with early surgery as compared to a strategy of prolonged conservative care. Only the assessed presence of nerve root compression and disc morphology (disc extrusion) on MRI may be informative to predict the patient's prognosis in sciatica, and might even lead to greater contrast in outcome among a 'regular' outpatient population. If the sciatica is not intense, or the MRI findings are not consistent with clear-cut nerve root compression, the authors advise to withhold from surgery.

REFERENCES

1. Konstantinou, K. and K.M. Dunn, *Sciatica: review of epidemiological studies and prevalence estimates.* Spine (Phila Pa 1976), 2008. **33**(22): p. 2464-72.
2. Vroomen, P.C., et al., *Conservative treatment of sciatica: a systematic review.* J Spinal Disord, 2000. **13**(6): p. 463-9.
3. Koes, B.W., M.W. van Tulder, and W.C. Peul, *Diagnosis and treatment of sciatica.* BMJ, 2007. **334**(7607): p. 1313-7.
4. Cherkin, D.C., et al., *An international comparison of back surgery rates.* Spine (Phila Pa 1976), 1994. **19**(11): p. 1201-6.
5. Peul, W.C., et al., *Surgery versus prolonged conservative treatment for sciatica.* N Engl J Med, 2007. **356**(22): p. 2245-56.
6. el Barzouhi, A., et al., *Predictive value of MRI in decision making for disc surgery for sciatica.* J Neurosurg Spine, 2013. **19**(6): p. 678-87.
7. Peul, W.C., et al., *Influence of gender and other prognostic factors on outcome of sciatica.* Pain, 2008. **138**(1): p. 180-91.
8. Peul, W.C., et al., *Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial [ISRCT 26872154].* BMC Musculoskelet Disord, 2005. 6: p. 8.
9. Fardon, D.F. and P.C. Milette, *Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology.* Spine (Phila Pa 1976), 2001. **26**(5): p. E93-E113.
10. Modic, M.T., et al., *Imaging of degenerative disk disease.* Radiology, 1988. **168**(1): p. 177-86.
11. Modic, M.T., et al., *Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging.* Radiology, 1988. **166**(1 Pt 1): p. 193-9.
12. Bombardier, C., *Outcome assessments in the evaluation of treatment of spinal disorders: summary and general recommendations.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3100-3.
13. Patrick, D.L., et al., *Assessing health-related quality of life in patients with sciatica.* Spine (Phila Pa 1976), 1995. **20**(17): p. 1899-908; discussion 1909.
14. Collins, S.L., R.A. Moore, and H.J. McQuay, *The visual analogue pain intensity scale: what is moderate pain in millimetres?* Pain, 1997. **72**(1-2): p. 95-7.
15. El Barzouhi, A., et al., *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PLoS One, 2013. **8**(7): p. e68411.
16. Verwoerd, A.J., et al., *Systematic review of prognostic factors predicting outcome in non-surgically treated patients with sciatica.* Eur J Pain, 2013. **17**(8): p. 1126-37.
17. Halldin, K., et al., *Three-dimensional radiological classification of lumbar disc herniation in relation to surgical outcome.* Int Orthop, 2009. **33**(3): p. 725-30.
18. Oland, G. and T.G. Hoff, *Intraspinal cross-section areas measured on myelography—computed tomography. The relation to outcome in nonoperated lumbar disc herniation.* Spine (Phila Pa 1976), 1996. **21**(17): p. 1985-9; discussion 1990.
19. Lurie, J.D., et al., *Magnetic resonance imaging predictors of surgical outcome in patients with lumbar intervertebral disc herniation.* Spine (Phila Pa 1976), 2013. **38**(14): p. 1216-25.
20. Cuellar, J.M., et al., *Cytokine expression in the epidural space: a model of noncompressive disc herniation-induced inflammation.* Spine (Phila Pa 1976), 2013. **38**(1): p. 17-23.
21. Di Martino, A., L. Merlini, and C. Faldini, *Autoimmunity in intervertebral disc herniation: from bench to bedside.* Expert Opin Ther Targets, 2013. **17**(12): p. 1461-70.

22. Vroomen, P.C., J.T. Wilmink, and K.M. de, *Prognostic value of MRI findings in sciatica.* Neuroradiology, 2002. **44**(1): p. 59-63.
23. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
24. Modic, M.T., et al., *Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome.* Radiology, 2005. **237**(2): p. 597-604.
25. Chiu, C.C., et al., *The probability of spontaneous regression of lumbar herniated disc: a systematic review.* Clin Rehabil, 2015. **29**(2): p. 184-95.
26. Folman, Y., et al., *Late results of surgery for herniated lumbar disk as related to duration of preoperative symptoms and type of herniation.* Surg Neurol, 2008. **70**(4): p. 398-401; discussion 401-2.
27. Dewing, C.B., et al., *The outcomes of lumbar microdiscectomy in a young, active population: correlation by herniation type and level.* Spine (Phila Pa 1976), 2008. **33**(1): p. 33-8.
28. Peul, W.C., et al., *Timing of surgery for sciatica: subgroup analysis alongside a randomized trial.* Eur Spine J, 2009. **18**(4): p. 538-45.
29. Chou, R., et al., *Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians.* Ann Intern Med, 2011. **154**(3): p. 181-9.
30. Deyo, R.A., *Magnetic resonance imaging of the lumbar spine. Terrific test or tar baby?* N Engl J Med, 1994. **331**(2): p. 115-6.
31. Lurie, J.D., N.J. Birkmeyer, and J.N. Weinstein, *Rates of advanced spinal imaging and spine surgery.* Spine (Phila Pa 1976), 2003. **28**(6): p. 616-20.
32. Boos, N., et al., *1995 Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations.* Spine (Phila Pa 1976), 1995. **20**(24): p. 2613-25.
33. Jensen, M.C., et al., *Magnetic resonance imaging of the lumbar spine in people without back pain.* N Engl J Med, 1994. **331**(2): p. 69-73.
34. Fisher, E.S. and H.G. Welch, *Avoiding the unintended consequences of growth in medical care: how might more be worse?* JAMA, 1999. **281**(5): p. 446-53.
35. Webster, B.S., et al., *Iatrogenic consequences of early magnetic resonance imaging in acute, work-related, disabling low back pain.* Spine (Phila Pa 1976), 2013. **38**(22): p. 1939-46.

Appendix 1. Form for the baseline MRI

MRI variable	Type	Categories
Disc level that most likely caused the lumbosacral radicular syndrome of the patient	Disc level	1. L2L3 2. L3L4 3. L4L5 4. L5S1 5. Not applicable, all disc levels have a normal disc contour: no disc extension beyond the normal margins of the intervertebral disc space at any disc level
	Disc contour at this disc level	1. Bulging: presence of disc tissue circumferentially (50-100%) beyond the edges of the ring apophyses 2. Herniation: localized displacement of disc material beyond the normal margins of the intervertebral disc space 3. Not applicable, all disc levels have a normal disc contour: no disc extension beyond the normal margins of the intervertebral disc space at any disc level
	Certainty about the presence of this disc herniation	1. Definite about the presence: no doubt about the presence 2. Probable about the presence: some doubt but likelihood > 50% 3. Possible about the presence: reason to consider but likelihood < 50% 4. Definite about the absence: no doubt about the absence
	Loss of disc height (distance between the planes of the end-plates of the vertebrae craniad and caudad to the disc) at this disc level	1. Yes 2. No
	Spinal canal stenosis	1. Yes 2. No
	Absence of epidural fat adjacent to the dural sac or surrounding the nerve root sheath	1. Yes, completely disappeared 2. Yes, partly disappeared 3. No disappearance
	Flattening of the ventrolateral angle of the dural sac or the emerging root sheath	1. Yes 2. No

Appendix 1. Form for the baseline MRI (continued)

MRI variable	Type	Categories
	Presence of impaired discs on other disc levels	1. Yes: presence of disc extension(s) beyond the normal margins of the intervertebral disc space at other disc levels 2. No: absence of disc extension(s) beyond the normal margins of the intervertebral disc space at other disc levels
If a herniation at the disc level is considered	Side of this disc herniation	1. Right 2. Left 3. Right and left
	Location on axial view of this disc herniation	1. Central zone: zone within the vertebral canal between sagittal planes through the medial edges of each facet 2. Sub-articular zone: zone, within the vertebral canal, sagittally between the plane of the medial edges of the pedicles and the plane of the medial edges of the facets, and coronally between the planes of the posterior surfaces of the vertebral bodies and the under anterior surfaces of the superior facets. 3. Foraminal zone: zone between planes passing through the medial and lateral edges of the pedicles 4. Extra-foraminal zone: the zone beyond the sagittal plane of the lateral edges of the pedicles, having no well-defined lateral border.
	Size of this disc herniation in relation to spinal canal	1. Large stenosing: size >75% of the spinal canal 2. Large: size 75-50% of the spinal canal 3. Average: size 25-50% of the spinal canal 4. Small: size <25% of the spinal canal
	Form disc herniation	1. Protrusion: localized displacement of disc material beyond the intervertebral disc space, with the base against the disc of origin broader than any other dimension of the protrusion. 2. Extrusion: localized displacement of disc material beyond the intervertebral disc space, with the base against the disc of origin narrower than any one distance between the edges of the disc material beyond the disc space measured in the same plane, or when no continuity exists between the disc material beyond the disc space and that within the disc space.

Appendix 1. Form for the baseline MRI (continued)

MRI variable	Type	Categories
	Gadolineum enhancement of the intervertebral disc herniation	1. No enhancement 2. Any edge enhancement 3. Complete circumferential enhancement 4. Diffuse staining
Nerve root compression	Probability of nerve root compression	1. Definite about the presence: no doubt about the presence 2. Probable about the presence: some doubt but likelihood > 50% 3. Possible about the presence: reason to consider but likelihood < 50% 4. Definitely no clinical relevant nerve root compression
	If nerve root compression present, which nerve root is affected	1. L3 2. L4 3. L5 4. S1
	Side nerve root compression	1. Right 2. Left
	Gadolineum enhancement of the affected nerve root	1. No enhancement 2. Yes, mild enhancement 3. Yes, strong enhancement
Separate for every end plate from level L2-L3 through L5-S1	Presence of vertebral end plate changes (VESC) and its extent	1. No VESC 2. VESC type I: mild, moderate or severe 3. VESC type II: mild, moderate or severe 4. VESC type III: mild, moderate or severe 5. Mixed VESC type I/II: mild, moderate or severe 6. Mixed VESC type II/III: mild, moderate or severe
	Presence of Schmorl's nodes (herniation of the disc into the vertebral-body end plate)	1. Yes 2. No

10.
General discussion.

In this thesis we aimed to gain insight into unknown elements of the diagnostic process and prognosis of patients with sciatica. The previous chapters report on the findings of each study that was conducted to achieve this objective. This chapter presents an overview of the main findings emerging from this thesis and discusses how to interpret these results in the context of existing literature and in light of some important methodological issues. Subsequently, implications for future research and clinical practice are discussed.

KEY FINDINGS

- In randomized controlled trials of conservative treatments, there is an inconsistent and interchangeable use of available terms used to describe radiating leg pain or symptoms
- No adequate set of history items and physical examination tests are known that can accurately predict the presence of a disc herniation on magnetic resonance imaging (MRI)
- It may be feasible to replace the Tampa Scale for Kinesiophobia by a single substitute question to predict clinical outcome in patients with sciatica
- There is preliminary evidence that physical therapy may reduce the negative effect of kinesiophobia found at baseline, on reported leg pain intensity at 1-year follow-up
- Evidence on prognostic factors in sciatica is limited
- Nerve root compression and extrusion of a herniated disc on baseline MRI seem to be associated with less leg pain during 1-year follow-up, irrespective of a surgical or conservative treatment

DISCUSSION OF THE MAIN FINDINGS

Terminology

Systematic reviews of scientific literature are essential to evidence-based medicine. These reviews aim to provide an accurate and reliable summary of current literature and are, therefore, the starting point for discussing further research and clinical implications.[1] We found that there was an inconsistent and interchangeable use of possible terms used to describe radiating leg pain or symptoms in randomized controlled trials of conservative treatments (Chapter 3). This finding is in concordance with a structured literature review that found a wide variation in the number and type of eligibility criteria used in randomized clinical trials involving radiculopathy due to lumbar herniated disc.[2]

In practice, it seems that no specific nomenclature on radiating leg pain associated with back pain, is widely accepted and internationally applied. This complicates and hampers both communication in clinical practice and comparison in research.

Diagnosis

Validation of a diagnostic model

Sciatica is diagnosed based on history taking and physical examination. However, a Cochrane review revealed poor diagnostic accuracy of most of the physical tests when used in isolation.[3] Only a few studies have determined the diagnostic accuracy of history taking.[4-6] Moreover, only one study included in the Cochrane review was performed among primary care patients and this study found that their newly developed diagnostic model showed a good discrimination.[5] However, because this model was not validated, (either internally or externally) the results might be overoptimistic. We aimed to validate this diagnostic model of history items in 395 patients with severe sciatica in a selected secondary care population of surgical candidates (Chapter 4). Unfortunately, the diagnostic model showed a 'failed discrimination' in this external validation. This remarkable discrepancy in diagnostic accuracy might be explained by the differences in study populations; however, this finding also indicates the instability of the diagnostic models for sciatica.

A new diagnostic model

Therefore, we developed a new diagnostic model based on six history items selected from the literature and tested the performance of this model in the same population of 395 patients with severe disabling radicular leg pain of 6-12 weeks duration (Chapter 4.) Three of the included variables were also included in the previously published model (age, pain worse in leg than in back, and pain worse on coughing, sneezing, or straining).[5] However, this multivariate logistic regression analysis of six history items preselected from the literature, also revealed poor diagnostic accuracy. The results were disappointing. Thus, the evidence on which to base an optimal diagnostic trajectory of history taking and physical examination in patients with sciatica, remains weak.

Methodological issues

Entire books have been written on the development of models and reflect the wide scope of methodological issues related to modelling.[7,8] It is difficult to summarize the complex and continuing diagnostic process of sciatica into one diagnostic model. The time-dependent factors (patients are reviewed by their physician more than once because treatment is initially conservative; however, this may also be referred to as a prognostic factor), all other information received during consultation and the physi-

cian's experience are difficult to include in a clinically useful and concise diagnostic model. Secondly, as very few studies have investigated the diagnostic value of history items, the basis on which to select variables from the literature to build a model, is weak. Moreover, discussion regarding the 'gold' standard of MRI in the diagnosis of sciatica due to disc herniation is ongoing. A meta-analysis of five studies on the diagnostic accuracy of MRI to identify disc herniation showed a sensitivity of 75% and a specificity of 77% compared with findings at surgery.[9] Although studies with operative findings as reference standard probably do not suffer from misclassification bias, they are prone to selection and verification bias because these patients were already selected as surgical candidates during a comprehensive process. Also, bias may be introduced because it is difficult to review operative findings completely blinded from the pre-operative information. Another issue that warrants discussion is the difference between sciatica and nerve root compression. Various studies support the theory of a multifactorial etiologic origin of sciatica in which spinal nerve irritation may result from compressive and non-compressive etiologies (Chapter 2). Of patients with sciatica complaints, 20-47% have no compressive etiology on MRI.[10,11] Studies aiming to report on patients with sciatica in general, using the presence of nerve root compression as an inclusion criteria or outcome (as in diagnostic studies), exclude this important subgroup of patients with sciatica who have no nerve root compression on MRI. Nevertheless, almost half of the studies on conservative treatments in primary care that used the term 'sciatica' included imaging results as eligibility criteria (Chapter 3).

Diagnostic accuracy of single history items

As stated, because few studies have investigated the diagnostic accuracy of history items, the basis for selection of history items from the literature to develop a diagnostic model was somewhat weak. Therefore, we explored the diagnostic accuracy of 20 history items for the presence of lumbosacral nerve root compression or disc herniation on MRI in the same secondary care population (Chapters 4 and 5). We found significant associations of nerve root compression with the variables 'male sex', 'pain worse in leg than in back', 'a non-sudden onset' and 'worsening of leg pain on coughing, sneezing or straining'. Significant association with the presence of a herniated disc was found for the variables 'body mass index <30,' 'a non-sudden onset', 'sensory loss' and 'worsening of leg pain on coughing, sneezing or straining'. These findings contribute to the literature regarding the selection of variables for future diagnostic models.

Dichotomizing answer options

In addition to our aim to gain insight into unknown elements of the diagnostic process, we tested the influence on diagnostic accuracy of variations in dichotomizing the answer options (regarding the location of worsening of pain) of the question whether pain

worsens during coughing, sneezing or straining. This was tested in the same population of 395 selected secondary care patients with the assessed presence of nerve root compression and disc herniation on MRI as outcome measure. The question as to whether pain worsens during coughing, sneezing or straining could be answered on a 4-point scale: no worsening of pain, worsening of back pain, worsening of leg pain, worsening of back and leg pain. We showed that the diagnostic accuracy of the history item on 'worsening of pain on coughing, sneezing or straining' only changed into significant values when the answer option was further narrowed to worsening of **leg** pain, instead of worsening of pain in general (Chapter 5). This finding is in line with the theory that coughing, sneezing or straining increases pressure which results in more irritation or mechanical compression of the nerve root, leading to more radiating pain in the leg but not in the back. The short report on these results highlights the importance of the formulation of answer options in history taking. Preferably, dichotomization of answer options should be avoided to prevent loss of information.[12,13] In addition, the kind of analyses planned to answer a study question should (preferably) be pre-specified in the study protocol and, accordingly, decisions on the number and type of answer options should be defined. For post-hoc analyses (as in our study), dichotomizing answer options may be a good alternative. However, our study highlights the importance of discussion regarding the choice of dichotomization. Therefore, we recommend that decisions about answer options should be made in a consensus meeting of the research team and, where possible, by also consulting the existing literature.

Prognosis

What is known?

One of the questions frequently asked by patients is: 'When will I be totally recovered?' We attempted to gain more insight into the prognosis of sciatica by systematically reviewing prognostic factors in non-surgically treated sciatica (Chapter 8). The only consistent and significant prognostic factor found was leg pain intensity at baseline, which predicted subsequent surgery. Strong evidence that no association could be found was observed for age, body mass index, smoking, sensory disturbance and several other factors (Chapter 8). Strong evidence was defined as 'consistent findings (≥80%) of at least two high-quality cohorts'.[14] This definition of strong evidence includes the important issues on quality assessment of studies and validation of results which, in general, is necessary before clinical implications can be drawn from a study. However, evidence for the absence of an association is difficult to prove; for example, in a relatively large study population a significant (but small) association may still be found. Moreover, in our systematic review, the comparison of studies was limited by clinical, methodological and statistical heterogeneity. The inconsistent and often interchangeable use of differ-

ent terms to describe radiating leg pain (Chapter 3) was also partly responsible for this heterogeneity.

Overall, evidence on the prognostic factors in sciatica is limited. We are not yet able to validly predict prognosis for patients with sciatica on the basis of baseline characteristics. More research is required on prognostic factors for sciatica. However, in our literature review, for all but one of the factors that were labelled 'with strong evidence', no association with prognosis could be found. Developing a clinically useful prognostic model for patients with sciatica could prove to be difficult. Therefore, studies with large sample sizes (power) are needed. In addition, despite the clinical relevance of giving patients valid information on prognosis in primary care, we could identify only one cohort which included primary care patients. Therefore, we also recommend that more studies take place in primary care.

Single question on kinesiophobia

In an observational study of 135 patients with sciatica in primary care, we found that a single question on kinesiophobia was as predictive of outcome as the validated Tampa Scale for Kinesiophobia as a whole (Chapter 6). The unique substitute question was: 'You visited your general practitioner because of complaints in your back or leg. How much 'fear' do you have that these complaints would be increased by physical activity?' (score range from 0 = no fear, to 10 = very much fear). Two substitute questions for other validated questionnaires did not consistently predict outcome at 1-year follow-up. To our knowledge, this is the first study to compare these validated questionnaires with newly-devised single substitute questions. However, the exploratory design of the present study has inherent limitations. Further extensive psychometric testing on the unique substitute question for kinesiophobia is needed before any clinical implication can be made. Moreover, the relatively small sample size may have limited the power of the analysis, and generalizability to other patient populations may also be limited. Nevertheless, we think that these exploratory results are promising and that the clinical relevance of time-saving and utility of such a single question on kinesiophobia is high. Therefore, we recommend additional research on this topic, particularly studies that focus on psychometric testing.

Prognostic value of MRI

Furthermore, in 283 patients with severe sciatica in secondary care, we found that MRI assessment of the presence of nerve root compression and extrusion of a herniated disc at baseline was positively associated with less leg pain during 1-year follow-up, irrespective of a surgical or conservative treatment (Chapter 9). Seven other MRI characteristics, including the size of disc herniation, did not correlate to outcome during 1-year follow-

up. In advance, we hypothesized that the treatment effect of surgery would be greater for a large disc herniation compared to a small disc herniation. However, we found no effect of size of disc herniation on outcome, irrespective of a surgical or conservative treatment. This finding is in concordance with two other studies[15,16]; however, another (retrospective) study found a greater surgical treatment effect for patients with large disc herniations and no differences in outcome for the conservatively treated patients.[17] These inconsistencies might be attributed to differences in study design, study population, sample size and treatment received. In addition, differences in definitions used to assess the presence of an MRI variable (e.g. disc herniation size) may have also influenced the study results. Overall, it seems that patients with clear sciatic symptoms and a large disc herniation on MRI may still benefit from conservative care, and the size of disc herniation does not seem to be associated with outcome.

In the literature there is inconsistency about the value of MRI findings as a prognostic factor: in concordance with our finding, some studies found a positive prognostic value for the presence of nerve root compression[15,18] whereas others did not.[19,20] The same applies to disc extrusion: three studies found a positive prognostic value for the presence of an extruded disc as in our study[15,19,21] whereas one study did not.[17] Again, differences in study design, study population, sample size and treatment received may explain the inconsistencies found. A recent systematic review reported higher rates of spontaneous regression of disc extrusion compared to disc protrusion (96% for disc sequestration, 70% for disc extrusion and 41% for disc protrusion).[22] This may explain the positive influence of the presence of a disc extrusion on outcome compared to the presence of a disc protrusion. The worse prognosis for patients without lumbosacral nerve root compression on MRI (compared to patients with nerve root compression on MRI) may be caused by a more difficult resolution of a non-compressive etiology of sciatica. These patients seem to form a specific subgroup of patients with a different pathophysiologic mechanism and a different prognosis. We hypothesize that an inflammatory component may play an important role in these patients.[23,24] Further research may reveal the exact cause of their non-compressive sciatic symptoms; it is also important to establish whether these patients may benefit from a special treatment plan, perhaps interfering with this causal mechanism.

Subgrouping

MRI variables

Identifying subgroups of patients with specific prognostic profiles has recently gained more attention in spine literature.[25] The aim of this identification is to improve treatment effects by offering targeted treatments and/or to better predict prognosis. The above-

mentioned study on MRI predictors in 283 patients with severe sciatica (Chapter 9) is an example of this type of search. Patients with nerve root compression on MRI had a better outcome than patients without nerve root compression on MRI. In this trial of patients with severe sciatica due to disc herniation on MRI, 9% of the patients were assessed as not having nerve root compression on MRI. In other study populations, percentages up to 47% of patients without nerve root compromise on MRI, despite sciatica symptoms, are reported.[10] This important subgroup of patients with sciatica but without nerve root compression on MRI arouses interest. Why does this subgroup have a worse prognosis? What causes the nerve root irritation, as there was no compressive etiology? What is the role of inflammatory factors? How best to treat these patients? Further research on this subgroup of patients may reveal the answers to these important questions. Again, we hypothesize that an inflammatory component may play an important role.[23,24] In addition, one may hypothesize, for example, that a high 'anti-inflammatory' dose of a non-steroidal anti-inflammatory drug (NSAID) may be especially effective for these patients. However, evidence for an inflammatory role in these patients is difficult to obtain, as patients without nerve root compression on MRI do not have an indication to be operated and examination of extirpated herniated disc specimens for inflammation is therefore not possible in these patients. Although there is a modest search to depict inflammation on lumbar MRI, results from these exploratory studies are not yet clinically useful.[10,26] The fact that inflammation is not yet quantifiable[27] or visible on imaging, complicates clinical research. First, more fundamental research on the inflammatory role in sciatica is necessary.

Kinesiophobia and physical therapy

Another interesting subgroup of patients are the patients with kinesiopobia. In a study including 466 patients with sciatica, a higher level of kinesiophobia (on a continuous scale) was associated with non-success at 2-year follow-up.[28] In 135 patients with sciatica in primary care, we found preliminary evidence that physical therapy may reduce the negative effect of kinesiophobia at baseline on reported leg pain intensity at 1-year follow-up (Chapter 7). In the analysis with leg pain intensity at 1-year follow-up, physical therapy significantly interacted with kinesiophobia at baseline (interaction effect for Tampa Scale for Kinesiophobia and a single substitute question for kinesiophobia: $p=0.07$ and $p<0.01$, respectively). In a subgroup analysis of 73 patients classified as 'suggestive of high fear of movement', patients randomized to the physical therapy group (non-significantly) reported one point lower on a 0-10 scale of leg pain intensity at 1-year follow-up compared to the control group (1.8 vs 2.8). However, in the same study, no significant effect was found regarding any outcome at 3-month follow-up or recovery at 1-year follow-up. However, confirmation of these results is necessary because the study was not specifically designed for this research question and the post-hoc analysis

may complicate the interpretation of results. Another limitation of this study was the relatively small sample size, making it difficult to find significant associations when comparing treatment results for the subgroup of patients defined as suggestive of high fear of movement. To our knowledge, this is the first study to investigate subgroup effects according to the level of kinesiophobia.

Biases

As described above, important findings may result from subgroup analyses. However, subgroup analyses may be limited by an increased risk of bias and, therefore, regularly trigger a discussion as to whether the subgroup effect is actually spurious or a real subgroup effect.[29] Most well-known is the multi-testing bias which increases the chance of false-positive findings. Therefore, subgroup analyses should be limited to only a few analyses (as few as possible) and to only plausible study questions.[30] This was also applicable for the subgroup analyses described in Chapter 7 (examining the effect of physical therapy on the relation between kinesiophobia and outcome) and Chapter 9 (examining the prognostic value of MRI findings). In addition, subgroup analysis should preferably be pre-specified in the study protocol of the main study.[30] With regard to this multiplicity problem and other potential biases influencing the interpretation of results, checklists for judging the credibility of subgroup analyses are proposed.[29,31-33] A systematic review tested the credibility of authors' claims of subgroup effects by applying 11 predefined criteria and found a usually low credibility of most subgroup claims in randomized controlled trials.[34] Other studies showed similar results.[33] The checklists for judging the credibility of subgroup effects are specifically defined for judging 'the extent to which a clinician should believe and act on the results of subgroup analyses' and therefore are relatively strict and comprehensive.[31] Subgroup analyses can also be initiated for other objectives. For example, subgroup analyses may be especially valuable in generating hypotheses for further research and may be a first step in the aim to achieve improvement of overall treatment effects. Nevertheless, risks of bias should be minimized and checklists on the credibility of subgroup analysis should provide a clear framework to achieve this. Overall, as for sciatica, little is known about subgroups of patients who potentially may benefit from an individualized treatment plan; therefore, subgroup analyses may be of great value for research in patients with sciatica.

NEED FOR FURTHER RESEARCH

The neurological syndrome of sciatica was already recognized in ancient times. In 1934 Mixter and Barr revolutionized the understanding of sciatica by asserting that sciatica was caused by a herniated disc pressing against a nerve root.[35] However, evidence is

still limited for different clinical aspects of sciatica. We have a long way to go before we obtain complete and reliable answers to the following questions: which term to use and when? (Chapter 3), how best to diagnose? (Chapters 4 and 5), which is the best treatment to offer? (reviewed in Chapter 2), and what is the prognosis? (Chapter 8). Answers to these questions are essential for an evidence-based clinical practice regarding sciatica. In conclusion, despite the long history of sciatica and its high incidence and burden, the clinical evidence related to sciatica is more limited than one might expect. Therefore, further research on sciatica may be prioritized.

RECOMMENDATIONS FOR RESEARCH

Terminology

Firstly, no common nomenclature on radiating leg pain associated with back pain has been widely recognized as authoritative, or has been widely accepted in clinical practice (Chapter 3). A lack of generally accepted nomenclature generates diluted study results. Therefore, it is important to consider approaches on how to reach more consensus and how to subsequently adhere to a single nomenclature, as this may prevent miscommunication and ease comparison between studies. A Delphi Study among professionals and experts from various disciplines and various countries may help to achieve consensus on nomenclature.[36]

Primary care

Very few studies on the diagnosis and prognosis of sciatica have been performed in primary care (Chapters 4 and 8). However, in many countries, patients first contact their general practitioner for a diagnosis of their symptoms. Also, patients are mainly treated in primary care. Despite the fact that diagnosing and informing about prognosis will mainly take place in a primary care setting, studies on the diagnosis and prognosis are rarely performed in this setting. Therefore, we recommend more studies on the diagnosis and prognosis of sciatica in large primary care populations.

Substitute question kinesiophobia

It is shown that it may be feasible to replace the Tampa Scale for Kinesiophobia by a single substitute question to predict outcome in patients with sciatica (Chapter 6). However, extensive psychometric testing of the substitute question is necessary before any clinical implication can be made. Especially further testing of the reliability, validity, and responsiveness is necessary to establish whether this substitute question may be useful in daily clinical practice. Taking into account the promising results of our explorative

study and the clinical relevance of our question, it seems worthwhile to initiate further research to establish the clinical usefulness of the substitute question for kinesiophobia.

Prognosis

Evidence on prognostic factors for sciatica is limited (chapter 8). The Dutch Spine Surgery Registry (http://dssr.clinicalaudit.nl/) collects information regarding patients with back surgery since December 2013. Before surgery and during a 2-year follow-up, patients are surveyed with validated questionnaires. The primary aim of this registry is to improve quality of back surgery. However, one may also extract information from this large observational cohort on which patients did benefit and which patients did not benefit from surgery.[37] Linkage with the Swedish Spine Register[38] would strongly enlarge the number of patients in this observational cohort and enables comparisons between both countries. Expansion of this registry to all patients with sciatica, operatively or non-operatively treated, would even give information on prognosis for all kind of subgroups of patients and may give insight in which patients benefit most from certain treatments. Identification of subgroups of patients may eventually result in better overall treatment effects in patients with sciatica.

Subgrouping

The importance of identifying subgroups of patients with sciatica to personalize treatments according to specific characteristics of such a subgroup is highlighted in recent literature. We found that kinesiophobia (Chapter 7) and the presence of nerve root compression or an extruded disc on MRI (Chapter 9) may form such a specific subgroup. The preliminary evidence that physical therapy may reduce the negative effect of baseline kinesiophobia on reported leg pain intensity at 1-year follow-up needs to be validated in other patient populations. In the present study, patients were treated with regular physical therapy (as a black box). In future studies one might consider a more specifically described physical therapy treatment, for instance combined with cognitive behavioral aspects related to kinesiophobia. More research needs to focus on patients with sciatica without nerve root compression on MRI. As prognosis is worse for these patients (compared to patients with nerve root compression) (Chapter 9), questions arise regarding the pathophysiologic process and, theoretically, a different treatment plan may be more appropriate for these patients.

RECOMMENDATIONS FOR CLINICAL PRACTICE

In the Netherlands, widely supported guidelines on sciatica for primary care[39] and secondary care[40] are available. Although complete and reliable evidence-based answers

are not available for many of the clinical questions related to sciatica, guidelines with best-available evidence are important to support clinical practice. The information presented in this thesis regarding the diagnosis and prognosis of sciatica may contribute to these guidelines. Although attempts to develop a clinically relevant and valid diagnostic model have been (until now) unsuccessful (Chapters 4 and 5), the single history items with a significant diagnostic accuracy for the presence of nerve root compression on MRI, may be helpful in guiding history taking according to the best-available evidence.

Regarding providing information to patients about their prognosis, it is known that the natural course in patients with sciatica is generally favorable, with an improvement of symptoms in about 75% of patients within 3 months.[41,42] The present thesis also shows that it is difficult to predict the prognosis for individual patients (Chapter 8). In addition, according to the availability of imaging results, patients may be informed that the size of disc herniation does not seem to influence outcome, whereas the presence of nerve root compression or an extruded disc seems to be positively associated with outcome (Chapter 9).

REFERENCES

1. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**(7): p. e1000100.
2. Genevay, S., S.J. Atlas, and J.N. Katz, *Variation in eligibility criteria from studies of radiculopathy due to a herniated disc and of neurogenic claudication due to lumbar spinal stenosis: a structured literature review.* Spine (Phila Pa 1976), 2010. **35**(7): p. 803-11.
3. van der Windt, D.A., et al., *Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain.* Cochrane Database Syst Rev, 2010(2): p. CD007431.
4. Coster, S., S.F. de Bruijn, and D.L. Tavy, *Diagnostic value of history, physical examination and needle electromyography in diagnosing lumbosacral radiculopathy.* J Neurol, 2010. **257**(3): p. 332-7.
5. Vroomen, P.C., et al., *Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression.* J Neurol Neurosurg Psychiatry, 2002. **72**(5): p. 630-4.
6. Vucetic, N., et al., *Diagnosis and prognosis in lumbar disc herniation.* Clin Orthop Relat Res, 1999(361): p. 116-22.
7. Knottnerus, J.A. and F. Buntix., *The Evidence Base of Clinical Diagnosis: Theory and Methods of Diagnostic Research* 2011: Wiley-Blackwell.
8. Steyerberg, E.W., *Clinical prediction models: A practical approach to development, validation, and updating* 2009: Springer-Verlag New York Inc.
9. Wassenaar, M., et al., *Magnetic resonance imaging for diagnosing lumbar spinal pathology in adult patients with low back pain or sciatica: a diagnostic systematic review.* Eur Spine J, 2012. **21**(2): p. 220-7.
10. Sirvanci, M., et al., *Value of perineural edema/inflammation detected by fat saturation sequences in lumbar magnetic resonance imaging of patients with unilateral sciatica.* Acta Radiol, 2009. **50**(2): p. 205-11.
11. Verwoerd, A.J., et al., *Diagnostic accuracy of history taking to assess lumbosacral nerve root compression.* Spine J, 2013. **14**(9): p. 2028-37
12. Rifkin, R.D., *Maximum Shannon information content of diagnostic medical testing. Including application to multiple non-independent tests.* Med Decis Making, 1985. **5**(2): p. 179-90.
13. Shinkins, B. and R. Perera, *Diagnostic uncertainty: dichotomies are not the answer.* Br J Gen Pract, 2013. **63**(608): p. 122-3.
14. Scholten-Peeters, G.G., et al., *Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies.* Pain, 2003. **104**(1-2): p. 303-22.
15. Halldin, K., et al., *Three-dimensional radiological classification of lumbar disc herniation in relation to surgical outcome.* Int Orthop, 2009. **33**(3): p. 725-30.
16. Oland, G. and T.G. Hoff, *Intraspinal cross-section areas measured on myelography—computed tomography. The relation to outcome in nonoperated lumbar disc herniation.* Spine (Phila Pa 1976), 1996. **21**(17): p. 1985-9; discussion 1990.
17. Lurie, J.D., et al., *Magnetic resonance imaging predictors of surgical outcome in patients with lumbar intervertebral disc herniation.* Spine (Phila Pa 1976), 2013. **38**(14): p. 1216-25.
18. Vroomen, P.C., J.T. Wilmink, and M.C. de Krom, *Prognostic value of MRI findings in sciatica.* Neuroradiology, 2002. **44**(1): p. 59-63.
19. Jensen, T.S., et al., *Magnetic resonance imaging findings as predictors of clinical outcome in patients with sciatica receiving active conservative treatment.* J Manipulative Physiol Ther, 2007. **30**(2): p. 98-108.
20. Modic, M.T., et al., *Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome.* Radiology, 2005. **237**(2): p. 597-604.

21. Dewing, C.B., et al., *The outcomes of lumbar microdiscectomy in a young, active population: correlation by herniation type and level.* Spine (Phila Pa 1976), 2008. **33**(1): p. 33-8.
22. Chiu, C.C., et al., *The probability of spontaneous regression of lumbar herniated disc: a systematic review.* Clin Rehabil, 2015. **29**(2): p. 184-95.
23. Cuellar, J.M., et al., *Cytokine expression in the epidural space: a model of noncompressive disc herniation-induced inflammation.* Spine (Phila Pa 1976), 2013. **38**(1): p. 17-23.
24. Di Martino, A., L. Merlini, and C. Faldini, *Autoimmunity in intervertebral disc herniation: from bench to bedside.* Expert Opin Ther Targets, 2013. **17**(12): p. 1461-70.
25. Konstantinou, K., et al., *Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol.* BMC Musculoskelet Disord, 2012. **13**: p. 4.
26. Saifuddin, A., R. Mitchell, and B.A. Taylor, *Extradural inflammation associated with annular tears: demonstration with gadolinium-enhanced lumbar spine MRI.* Eur Spine J, 1999. **8**(1): p. 34-9.
27. Gebhardt, K., et al., *The course of high-sensitive C-reactive protein in correlation with pain and clinical function in patients with acute lumbosciatic pain and chronic low back pain - a 6 months prospective longitudinal study.* Eur J Pain, 2006. **10**(8): p. 711-9.
28. Haugen, A.J., et al., *Prognostic factors for non-success in patients with sciatica and disc herniation.* BMC Musculoskelet Disord, 2012. **13**: p. 183.
29. Sun, X., et al., *Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses.* BMJ, 2010. **340**: p. c117.
30. Kasenda, B., et al., *Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications.* BMJ, 2014. **349**: p. g4539.
31. Oxman, A.D. and G.H. Guyatt, *A consumer's guide to subgroup analyses.* Ann Intern Med, 1992. **116**(1): p. 78-84.
32. Sun, X., et al., *How to use a subgroup analysis: users' guide to the medical literature.* JAMA, 2014. **311**(4): p. 405-11.
33. Wang, R., et al., *Statistics in medicine—reporting of subgroup analyses in clinical trials.* N Engl J Med, 2007. **357**(21): p. 2189-94.
34. Sun, X., et al., *Credibility of claims of subgroup effects in randomised controlled trials: systematic review.* BMJ, 2012. **344**: p. e1553.
35. Mixter, W.J. and J.S. Barr, *Rupture of the Intervertebral Disc with Involvement of the Spinal Canal.* N Engl J Med 1934. **211**: p. 210-215.
36. Stanton, T.R., et al., *A modified Delphi approach to standardize low back pain recurrence terminology.* Eur Spine J, 2011. **20**(5): p. 744-52.
37. Sigmundsson, F.G., et al., *Prognostic factors in lumbar spinal stenosis surgery.* Acta Orthop, 2012. **83**(5): p. 536-42.
38. Stromqvist, B., et al., *The Swedish Spine Register: development, design and utility.* Eur Spine J, 2009. **18 Suppl 3**: p. 294-304.
39. Mens, J.M.A., et al., *NHG-Standaard Lumbosacraal radiculair syndroom.* Huisarts Wet, 2005. **48**(4): p. 171-8.
40. Kwaliteitsinstituut voor de Gezondheidszorg CBO, *Richtlijn Lumbosacraal Radiculair Syndroom* 2008, www.neurologie.nl.
41. Vroomen, P.C., M.C. de Krom, and J.A. Knottnerus, *Predicting the outcome of sciatica at short-term follow-up.* Br J Gen Pract, 2002. **52**(475): p. 119-23.
42. Weber, H., I. Holme, and E. Amlie, *The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam.* Spine (Phila Pa 1976), 1993. **18**(11): p. 1433-8.

Summary

SUMMARY

Chapter 1 gives an introduction about clinical aspects of sciatica, the motivation of our study aims and the outline of this thesis. Sciatica is one of the most common lumbar spine disorders with a life time incidence of 12 to 40%. The most common cause of sciatica is a herniated disc. Other causes of sciatica are non-compressive irritation of the nerve root (such as infection), lumbar stenosis, or (rarely) a tumor. Sciatica is associated with significant morbidity. Back problems rank, certainly in the industrialized countries, as one of the most costly and ubiquitous medical problems. Despite this heavy burden, the diagnostic process of sciatica and prediction of prognosis is insufficiently evidence-based. The main objective of this thesis is to reveal unknown elements related to the diagnosis and prognosis of sciatica.

What is recently discussed in the literature regarding clinical aspects of sciatica? A clinical review.

Chapter 2 discusses the literature on new developments regarding sciatica. Recent studies support the theory of a multifactor etiologic origin in which spinal nerve irritation may result from compressive and non-compressive causes. It is not known which combination of history items and physical examination tests most accurately predict the presence of a disc herniation on Magnetic Resonance Imaging (MRI). Discussion is ongoing regarding the role of MRI in sciatica. The role of MRI is essential for patients with alarming symptoms and for patients who are potential candidates for lumbar disc surgery, but seems to have limited value for other indications in sciatica.

About 75% of patients with sciatica improve within 3 months. In the absence of alarming symptoms, treatment should be conservative in at least the first 6-8 weeks. The best sequential management pathway of sciatica is insufficiently researched. The level of evidence of most conservative treatments is limited. Systematic reviews show short-term effects for some non-surgical treatment options (non-opioid medication, epidural injection), but most conservative treatments (bed rest, exercise therapy) do not show effectiveness. Early surgery fastens recovery as compared to prolonged conservative care with possible delayed surgery in patients who are surgical candidates, but without important differences in long-term outcome between these two approaches. More research is needed to identify subgroups of patients with different prognostic profiles, as treatment results are unsatisfactory in 15 up to even 40% of the patients. More research is also needed concerning new and potentially promising developments such as the potential effects of biological agents. For now, shared decision making between well-informed patients and their physicians should determine the individual treatment strategy.

How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review.

Many terms exist to describe radiating leg pain or symptoms associated with back pain (e.g. sciatica, radiculopathy or lumbosacral radicular syndrome) and it appears that these terms are used inconsistently. Despite attempts of the International Association for the Study of Pain (IASP) to standardize the use of terminology in this field, there are indications that confusion exists. In **chapter 3**, we systematically reviewed the terms used to define radiating leg pain and the associated eligibility criteria reported in randomised controlled trials of conservative treatments for radiating leg pain or symptoms. We also evaluated how the eligibility criteria for specific terms compared to the taxonomy of the IASP.

Eligible studies were identified from two recent systematic reviews and an updated search of their search strategy. Studies were included if they recruited adults with radiating leg pain associated with back pain. Two independent reviewers screened the studies and extracted data. Studies were grouped according to the terms used to describe radiating leg pain. 31 of the 77 included studies used multiple terms to describe radiating leg pain; the most commonly used terms were sciatica (60 studies) and disc herniation (19 studies). Most studies that used the term sciatica included pain distribution in the eligibility criteria, but studies were inconsistent in including signs (e.g. neurological deficits) and imaging findings. Similarly, studies that used other terms to describe radiating leg pain used inconsistent eligibility criteria between studies and to the IASP taxonomy, except that positive imaging findings were required for almost all studies that used disc herniation to describe radiating leg pain. In view of the varying terms to describe, and eligibility criteria to define, radiating leg pain, consensus needs to be reached for each of communication and comparison between studies.

What is the diagnostic accuracy of history taking to assess lumbosacral nerve root compression? A cross-sectional diagnostic study.

The diagnosis of sciatica is primarily based on history taking and physical examination. Most physical tests used in isolation show poor diagnostic accuracy. Little is known about the diagnostic accuracy of history items. In **chapter 4**, we therefore examined the diagnostic accuracy of history taking for the presence of lumbosacral nerve root compression or disc herniation on magnetic resonance imaging (MRI) in patients with sciatica. We included 395 adult patients with severe disabling radicular leg pain of 6 to12 weeks duration in our cross-sectional diagnostic study. Data were prospectively collected in nine hospitals. History was taken according to a standardized protocol. Lumbosacral nerve root compression and disc herniation on MRI were independently assessed by two neuroradiologists and one neurosurgeon blinded to any clinical infor-

mation. The diagnostic odds ratio of 20 history items was explored and a diagnostic model of six history items pre-selected from the literature was tested (including age, gender, pain worse in leg than in back, sensory loss, muscle weakness, and more pain on coughing/sneezing/straining).

Exploring the diagnostic odds ratio of 20 history items revealed a significant contribution in diagnosing nerve root compression for "male sex", "pain worse in leg than in back" and "a non-sudden onset". A significant contribution to the diagnosis of a herniated disc was found for "body mass index <30", "a non-sudden onset" and "sensory loss". Multivariate logistic regression analysis of six history items pre-selected from the literature revealed an area under the receiver operating characteristic curve of 0.65 (95% confidence interval, 0.58–0.71) for the model diagnosing nerve root compression, and an area under the receiver operating characteristic curve of 0.66 (95% confidence interval, 0.58–0.74) for the model diagnosing disc herniation. In conclusion, a few history items used in isolation had significant diagnostic value and the diagnostic accuracy of a model with six pre-selected items was poor.

Does localization of worsening of pain during coughing, sneezing and straining matter in the assessment of lumbosacral nerve root compression? A short report.

In the previous diagnostic study in 395 patients with severe sciatica, one of the questions asked to patients was the influence of coughing, sneezing and straining on the intensity of pain. This question could be answered on a 4-point scale: no worsening of pain, worsening of back pain, worsening of leg pain, worsening of back and leg pain. In our initial analyses we dichotomized these answer categories into "worsening of leg and/or back pain" versus "no worsening of pain". Post hoc we wondered if we used the best dichotomization option in our analysis. Therefore we tested in **chapter 5** whether variations in dichotomizing answer options (related to the localization of pain) influences the diagnostic accuracy of the question if pain worsens during coughing, sneezing or straining to assess the presence of lumbosacral nerve root compression and disc herniation on MRI.

The diagnostic odds ratio (DOR) changed into significant values when the answer option was more narrowed to worsening of leg pain. The highest DOR was observed for the answer option 'worsening of leg pain' with a DOR of 2.28 (95% CI 1.28-4.04) for the presence of nerve root compression and a DOR of 2.50 (95% CI 1.27-4.90) for the presence of a herniated disc on MRI. In conclusion, worsening of leg pain during coughing, sneezing or straining has a significant diagnostic value for the presence of nerve root

compression and disc herniation on MRI in patients with sciatica. This study highlights the importance of the formulation of answer options in history taking.

Can a single question be used to predict outcome at 1-year follow-up as accurately as validated questionnaires on kinesiophobia, disability, and quality of life in patients with sciatica in primary care? An observational study.

Validated questionnaires are used on a regular basis in research and health care, however they are time-consuming to administer. Therefore we tested in **chapter 6** whether a single question can be used to predict outcome at 1-year as accurately as validated questionnaires on kinesiophobia, disability, or health-related quality of life in patients with sciatica. 135 patients with sciatica in primary care were included in this observational study within a randomised clinical trial. Kinesiophobia was measured with the Tampa Scale for Kinesiophobia (TSK), disability with the Roland Morris Disability Questionnaire, and health-related quality of life with the EQ-5D and the 36-item Short Form (SF-36) Physical Component Summary. Participants also answered a newly devised substitute question for each questionnaire on an 11-point numerical rating scale. Global perceived effect and severity of leg pain were measured at 1-year follow-up.

The correlation coefficient between the TSK and its substitute question was r = 0.46 (which is regarded medium to large). The substitute question was better at predicting pain severity in the leg at 1-year follow-up than the TSK (addition of explained variation of 11% versus 4% in a logistic regression analysis). The TSK and its substitute question did not significantly differ in their prediction of global perceived effect at 1-year follow-up. The other substitute questions and both the Roland Morris Disability Questionnaire and EQ-5D did not contribute significantly to one or both of their prediction models. In conclusion, the present study shows that it may be feasible to replace the Tampa Scale for Kinesiophobia by its unique substitute question when predicting outcome at 1-year follow-up in patients with sciatica.

What is the effect of physical therapy on the relation of kinesiophobia and outcome in patients with sciatica in primary care? A subgroup analysis.

A higher level of kinesiophobia seems to be associated with poor recovery in patients with sciatica. In **chapter 7** we investigated the effect of physical therapy on the relation of kinesiophobia at baseline with outcome in patients with sciatica. A total of 135 patients with acute sciatica in primary care were randomized to physical therapy plus general practitioners' care or to general practitioners' care alone. Kinesiophobia at baseline was measured with the Tampa Scale for Kinesiophobia (TSK) and a single substitute question for kinesiophobia (SQK). Pain and recovery were assessed at 3 and 12-months follow-up. Regression analysis was used to test for interaction between the level of kinesiophobia

at baseline and treatment allocation. Subgroup results were calculated for patients 'suggestive of high fear of movement' and for patients 'suggestive of low fear of movement'.

Physical therapy significantly interacted with kinesiophobia at baseline in the analysis with leg pain intensity at 12-months follow-up (interaction effect for TSK and SQK: $p=0.07$ and $p<0.01$, respectively). Of the patients 'suggestive of high fear of movement', patients randomized to the physical therapy group non-significantly reported one-point lower leg pain intensity on a 0-10 scale at 12-months follow-up compared to the control group (1.8 vs 2.8). Physical therapy did not interact with kinesiophobia at baseline regarding any outcome at 3-months follow-up or recovery at 12-months follow-up. In conclusion, there is preliminary evidence that physical therapy may reduce the negative effect of kinesiophobia at baseline on reported leg pain intensity at 12-months follow-up in these patients with sciatica.

What is known about prognostic factors predicting outcome in non-surgically treated patients with sciatica? A systematic review.

Identification of prognostic factors for surgery in patients with sciatica is important to be able to predict surgery in an early stage. Identification of prognostic factors predicting persistent pain, disability and recovery are important for better understanding of the clinical course, to inform patient and physician and support decision making. Consequently, in **chapter 8** we systematically reviewed prognostic factors predicting outcome in non-surgically treated patients with sciatica. A search of Medline, Embase, Web of Science and Cinahl, up to March 2012 was performed for prospective cohort studies on prognostic factors for non-surgically treated sciatica. Two reviewers independently selected studies for inclusion and assessed the risk of bias. Outcomes were pain, disability, recovery and surgery. A best evidence synthesis was carried out in order to assess and summarize the data. The initial search yielded 4392 articles of which 23 articles reporting on 14 original cohorts met the inclusion criteria.

High clinical, methodological and statistical heterogeneity among studies was found. Reported evidence regarding prognostic factors predicting the outcome in sciatica is limited. The majority of factors that have been evaluated, e.g., age, body mass index, smoking and sensory disturbance, showed no association with outcome. The only positive association with strong evidence was found for leg pain intensity at baseline as prognostic factor for subsequent surgery.

What is the prognostic value of magnetic resonance imaging findings in patients with sciatica? An observational study.

Magnetic resonance imaging (MRI) findings may have prognostic value in patients with intense sciatica and intuitively help to identify subgroups of patients that might benefit more from either early surgery or a strategy of prolonged conservative care. Therefore we aimed to determine the prognostic value of MRI variables to predict outcome in patients with sciatica and whether MRI facilitates the decision-making between early surgery and prolonged conservative care in sciatica. **Chapter 9** reports on the results of this prospective observational evaluation of 283 sciatica patients who were randomized to surgery or prolonged conservative care with surgery if needed. Multiple MRI characteristics of the degenerated disc herniation were scored. Recovery was registered on a 7-point Likert scale. Complete/near complete recovery was considered to be a satisfactory outcome. Leg pain severity was measured on a 0-100 mm visual analogue scale. Cox models were used to study the influence of MRI variables on rate of recovery, and linear mixed models to determine the predictive value of MRI variables for leg pain severity during follow-up. Interaction of each MRI predictor with treatment allocation was tested.

Baseline MRI variables that associated with less leg pain severity during 1-year were the reader's assessment of presence of nerve root compression ($p<0.001$), and assessment of extrusion as compared to protrusion of the disc herniation ($p=0.006$). Both variables tended to associate, but not statistically significant, with satisfactory outcome during 1-year follow up (Hazard ratio [HR] 1.45; 95% Confidence Interval [CI] 0.93-2.24 and HR 1.24; 95%CI 0.96-1.61 respectively). The size of disc herniation at baseline was not associated to outcome. There was no significant change between the effects between treatment groups. In conclusion, MRI assessment of the presence of nerve root compression and extrusion of a herniated disc at baseline was associated with less leg pain during 1-year follow-up, irrespective of a surgical or conservative treatment. MRI was not demonstrated to be helpful in decision making between early surgery versus prolonged conservative care.

Chapter 10 gives an overview of the principal findings of this thesis and how to interpret these results in the context of existing literature and some important methodological issues. In addition, implications for future research and clinical implications are discussed.

Samenvatting

SAMENVATTING

Hoofdstuk 1 geeft een introductie over de klinische aspecten van het lumbosacraal radiculair syndroom (LRS), de motivatie voor ons onderzoek en een overzicht van deze dissertatie. Het LRS is een van de meest voorkomende aandoeningen van de wervelkolom met een 'life-time' incidentie van 12 tot 40%. De meest voorkomende oorzaak van het LRS is een discushernia. Andere oorzaken zijn niet mechanische irritatie van de zenuwwortel (zoals een infectie), lumbale stenose of (zeldzaam) een tumor. Het LRS geeft een aanzienlijke ziektelast. Rugproblemen zijn, zeker in de geïndustrialiseerde landen, een van de meest kostbare medische problemen. Ondanks deze hoge maatschappelijke last, is het diagnostisch en prognostisch proces bij patiënten met het LRS onvoldoende wetenschappelijk onderzocht.

Wat wordt er in de recente literatuur bediscussieerd over klinische aspecten van het LRS? Een literatuuroverzicht.

Hoofdstuk 2 bediscussieert de literatuur over nieuwe ontwikkelingen betreffende het LRS. Recente studies ondersteunen de theorie van een multifactoriële oorzaak van het LRS waarbij irritatie van de zenuwwortel kan ontstaan door mechanische en niet mechanische oorzaken. Het is niet duidelijk welke combinatie van vragen in de anamnese en lichamelijk onderzoek het beste de aanwezigheid van een discushernia op Magnetic Resonance Imaging (MRI) voorspelt. Een MRI is essentieel voor patiënten met alarmsymptomen en wanneer een chirurgische behandeling wordt overwogen, maar lijkt van weinig waarde voor andere indicaties bij het LRS.

Ruim 75% van de patiënten met een LRS verbetert binnen 3 maanden. Als er geen alarmsymptomen zijn wordt de eerste 6-8 weken een conservatief beleid aanbevolen. Het is onduidelijk wat de beste behandelstrategie voor patiënten met het LRS is. Het niveau van bewijs van de meeste conservatieve behandelingen is beperkt. Systematische reviews laten korte termijn effecten zien voor sommige conservatieve behandelingen (niet opioïden, epidurale injecties), maar andere conservatieve behandelingen (bedrust, oefentherapie) laten geen effectiviteit zien. Bij patiënten met een operatie-indicatie, versnelt operatie het herstel vergeleken met conservatieve behandeling alleen op korte termijn; na een jaar zijn evenveel mensen in beide groepen hersteld. Meer onderzoek naar subgroepen van patiënten met verschillende prognostische profielen is nodig, omdat behandelresultaten onvoldoende zijn in 15 tot zelfs 40% van de patiënten. Vooralsnog zou een gezamenlijke besluitvorming tussen goed geïnformeerde patiënten en hun artsen de individuele behandelstrategie moeten bepalen.

Hoe wordt uitstralende pijn in het been gedefinieerd in gerandomiseerde studies naar conservatieve therapieën in de eerste lijn? Een systematisch literatuuroverzicht.

Er bestaan veel termen die uitstralende pijn in het been of andere symptomen geassocieerd met rugpijn beschrijven (zoals het lumbosacraal radiculair syndroom, sciatica of radiculopathie). Het lijkt erop dat deze termen door elkaar worden gebruikt. Ondanks pogingen van de International Association for the Study of Pain (IASP) om de terminologie te standaardiseren, zijn er aanwijzingen dat er nog steeds onduidelijkheid bestaat. In **hoofdstuk 3** geven we een systematisch overzicht van de termen die gebruikt worden om uitstralende pijn in het been te definiëren en de daarbij horende selectiecriteria die worden gerapporteerd in gerandomiseerde studies naar conservatieve therapieën voor uitstralende pijn in het been of bijbehorende symptomen. We vergeleken de selectiecriteria voor de specifieke termen ook met de taxonomie van de IASP.

Studies uit twee recente systematische literatuuroverzichten (inclusief update) bestaande uit volwassen patiënten met uitstralende pijn in het been geassocieerd met rugpijn werden geïncludeerd. Twee onafhankelijke beoordelaars screenden de studies en extraheerden data uit de studies. Studies werden gegroepeerd naar de gebruikte term om uitstralende pijn in het been te beschrijven. In 31 van de 77 geïncludeerde studies gebruikte men meerdere termen om uitstralende pijn in het been te beschrijven. De meest gebruikte term was sciatica (60 studies) en discus hernia (19 studies). De meeste studies die de term sciatica gebruikten hanteerden pijn distributie als selectiecriteria, maar de studies waren inconsistent wat betreft het includeren van uitkomsten van lichamelijk onderzoek (zoals neurologische uitval) en beeldvorming. Ook voor studies die andere termen gebruikten werden inconsistenties in selectiecriteria tussen studies en de IASP taxonomie gevonden, behalve wat betreft positieve uitkomst op beeldvorming dat vereist was voor bijna alle studies die discushernia als term gebruikten. Het is wenselijk om tot consensus te komen wat betreft definities voor uitstralende pijn in het been en bijbehorende symptomen om communicatie in de klinische praktijk en in het onderzoek te faciliteren en om vergelijking van studies te vergemakkelijken.

Wat is de diagnostische waarde van de anamnese in patiënten met het LRS? Een cross-sectionele diagnostische studie.

De diagnose lumbosacraal radiculair syndroom wordt gebaseerd op de anamnese en lichamelijk onderzoek. De meeste testen die bij het lichamelijk onderzoek worden uitgevoerd blijken echter van weinig diagnostische waarde. Er is weinig bekend over de diagnostische waarde van de anamnese. Daarom onderzochten we in **hoofdstuk 4** de diagnostische waarde van de anamnese bij patiënten met een ernstig LRS om wortelcompressie of een discushernia op MRI vast te stellen. We includeerden 395 vol-

wassen patiënten met ernstige radiculaire beenklachten gedurende 6-12 weken in onze diagnostische studie. Data werden prospectief in 9 ziekenhuizen verzameld. De anamnese werd volgens een gestandaardiseerd protocol afgenomen. De aanwezigheid van lumbosacrale wortelcompressie en/of een discushernia op MRI werd onafhankelijk en geblindeerd voor klinische informatie door twee neuroradiologen en één neurochirurg beoordeeld. De diagnostische odds ratio van 20 vragen werd berekend en daarnaast werd een diagnostisch model met 6 anamnese vragen die van te voren geselecteerd waren uit de literatuur getest (leeftijd, geslacht, pijn in het been erger dan in de rug, gevoelsverlies, krachtsverlies en meer pijn bij hoesten/niezen/persen).

Van de 20 anamnese vragen gaven 'mannelijk geslacht', 'pijn in het been erger dan in de rug', en een 'niet plotseling begin' een significante bijdrage aan de diagnose wortelcompressie. Een significante bijdrage aan de diagnose discushernia werd gezien voor 'body mass index <30', 'niet plotseling begin', en 'gevoelsverlies'. De multivariabele logistische regressie van 6 geselecteerde anamnese vragen had een area under the receiver operating characteristic curve (AUC) van 0.65 (95% betrouwbaarheidsinterval (95%BI) 0.58–0.71) voor het diagnostisch model met wortelcompressie en een AUC van 0.66 (95%BI 0.58–0.74) voor het diagnostisch model voor een discushernia. Samenvattend hadden sommige anamnese vragen een significante waarde in deze tweedelijns populatie maar de discriminatie van een diagnostisch model was onvoldoende.

Is de lokalisatie van verergering van pijn bij hoesten, niezen en persen van belang bij het vaststellen van lumbosacrale wortelcompressie? Een korte uiteenzetting.

In de hierboven beschreven diagnostische studie van 395 patiënten met een ernstig LRS werd onder andere gevraagd naar het effect van hoesten, niezen en persen op de pijn. Deze vraag had 4 antwoordmogelijkheden: geen verergering van pijn, verergering van rugpijn, verergering van pijn in het been, verergering van pijn in rug en been. In eerste instantie hebben we deze antwoordmogelijkheden gedichotomiseerd in 'verergering van been en/of rugpijn' versus 'geen verergering van pijn'. Naderhand vroegen we ons af of we de beste keuze wat betreft het dichotomiseren hadden gemaakt. Daarom testten we in **hoofdstuk 5** of variaties in dichotomisatie van de antwoordmogelijkheden (gerelateerd aan de lokalisatie van pijn) de diagnostische waarde beïnvloedt van de vraag of pijn verergert bij hoesten, niezen en persen om lumbosacrale wortelcompressie en discushernia vast te stellen op MRI.

De diagnostische odds ratio (DOR) werd significant wanneer het antwoord meer werd toegespitst op verergering van pijn in het been. De hoogste DOR werd geobserveerd voor de antwoordmogelijkheid 'verergering van pijn in het been' met een DOR van 2.28

(95% BI 1.28-4.04) voor de aanwezigheid van wortelcompressie en een DOR van 2.50 (95% BI 1.27-4.90) voor de aanwezigheid van een discushernia op MRI. Concluderend heeft verergering van pijn in het been bij hoesten, niezen en persen een significante diagnostische bijdrage voor het stellen van wortelcompressie en een discushernia op MRI in patiënten met een ernstig LRS. Deze studie benadrukt het belang van de formulering van antwoordmogelijkheden bij het afnemen van de anamnese.

Kan één enkele vraag uitkomst op 1 jaar in patiënten met het LRS net zo goed voorspellen als gevalideerde vragenlijsten over bewegingsangst, invaliditeit en kwaliteit van leven? Een observationele studie.

Om bewegingsangst, invaliditeit en kwaliteit van leven te meten bij patiënten met het LRS worden in wetenschappelijk onderzoek veelal vragenlijsten afgenomen, bijvoorbeeld de Tampa Schaal voor Kinesiofobie (TSK), Roland Morris Disability Questionnaire (RDQ) en de EQ-5D en 36-item Short Form (SF-36). Voor gebruik in de dagelijkse praktijk is dit echter tijdrovend. Daarom onderzochten we in **hoofdstuk 6** of het mogelijk is om de TSK, RDQ, EQ-5D en SF-36 elk door 1 vraag te vervangen om bij patiënten met het LRS in de huisartsenpraktijk de uitkomst op 1 jaar te voorspellen. Als onderdeel van een gerandomiseerde studie bij 135 patiënten met het LRS werden bovenstaande vragenlijsten afgenomen. De patiënten beantwoordden ook voor elke vragenlijst één speciaal ontwikkelde en unieke vervangvraag op een 11-punts schaal. Uitkomstmaten waren 'global perceived effect' en ernst van de pijn in het been.

De correlatie coëfficiënt tussen de TSK en zijn vervangvraag was 0.46 (matig tot groot). De vervangvraag voorspelde pijn in het been op 1 jaar beter dan de TSK (additionele verklaarde variantie van 11% versus 4% in een logistische regressie analyse). Er werd geen verschil gevonden tussen de TSK en zijn vervangvraag in het voorspellen van de 'global perceived effect'. Voor de RDQ, EQ-5D, de physical component summary van de SF-36 en hun vervangvragen werden inconsistente of niet-significante bijdrages aan de modellen gevonden. Concluderend lijkt het mogelijk om de TSK door één unieke vraag te vervangen om de uitkomst van patiënten met LRS na 1 jaar te voorspellen.

Wat is het effect van fysiotherapie op de relatie van kinesiofobie met uitkomst in patiënten met het LRS in de eerste lijn? Een subgroep analyse.

Er wordt recent veel aandacht besteed aan de zoektocht naar subgroepen van patiënten met rugpijn op basis van prognostische kenmerken met als doel om de uitkomsten te verbeteren. Patiënten met kinesiofobie vormen mogelijk een subgroep omdat een hoger niveau van kinesiofobie geassocieerd is met slechtere uitkomsten. Daarom onderzochten we in **hoofdstuk 7** het effect van fysiotherapie op de relatie tussen kinesiofobie op baseline en pijn in het been en herstel op 3 en 12 maanden follow-up in patiënten met

het LRS. 135 patiënten met een acuut LRS werden gerandomiseerd tussen fysiotherapie en huisartsenzorg of huisartsenzorg alleen. Kinesiofobie op baseline werd gemeten met de Tampa Schaal voor Kinesiofobie (TSK) en één vervangvraag over kinesiofobie (SQK). Pijn en herstel werden gemeten op 3 en 12 maanden na randomisatie. In regressie analyses werd de interactie tussen het niveau van kinesiofobie op baseline en de gelote behandeling getest. Subgroep resultaten werden berekend voor de patiënten geclassificeerd met een hoog niveau van kinesiofobie en voor patiënten geclassificeerd met een laag niveau van kinesiofobie.

Fysiotherapie had een significante interactie met kinesiofobie op baseline in de analyse met pijn in het been op 12 maanden follow-up (interactie effect voor TSK en SQK respectievelijk $p=0.07$ en $p<0.01$). Van de 73 patiënten geclassificeerd met een hoog niveau van kinesiofobie, rapporteerden de patiënten gerandomiseerd in de fysiotherapie groep één punt lager op een 0-10 schaal over ernst van de pijn in het been op 12 maanden follow-up in vergelijking met de controle groep (1.8 vs. 2.8, niet significant). Fysiotherapie had geen interactie met kinesiofobie op baseline voor pijn in het been op 3 maanden en herstel op 3 en 12 maanden follow-up. Concluderend vermindert aanvullende fysiotherapie mogelijk het negatieve effect van kinesiofobie op pijn in het been na 12 maanden follow-up.

Wat is bekend over prognostische factoren in patiënten met het LRS die niet operatief behandeld worden? Een systematisch literatuuroverzicht.

Het identificeren van prognostische factoren voor operatieve behandeling in patiënten met het LRS is belangrijk om de kans op operatie in een vroeg stadium te kunnen voorspellen. Het identificeren van prognostische factoren die persisterende pijn, invaliditeit en herstel voorspellen is belangrijk voor een beter begrip van het beloop en om de patiënt en arts te informeren en daarmee de besluitvorming te ondersteunen. Daarom evalueerden we in **hoofdstuk 8** systematisch de literatuur over prognostische factoren die uitkomst voorspellen in niet-operatief behandelde patiënten met het LRS. We zochten tot maart 2012 in Medline, Embase, Web of Science en Cinahl naar prospectieve cohort studies naar prognostische factoren in niet-operatief behandelde LRS. Twee beoordelaars selecteerden studies voor inclusie onafhankelijk van elkaar en beoordeelden de kwaliteit van de studies. Uitkomsten waren pijn, invaliditeit, herstel en operatie. Een 'best evidence synthesis' werd gedaan om de data te analyseren en samen te vatten.

De zoektocht leverde 4392 artikelen op waarvan 23 artikelen betreffende 14 originele cohorten voldeden aan de inclusiecriteria. Grote klinische, methodologische en statistische heterogeniteit tussen studies werd gevonden. Er bleek slechts beperkt bewijs over prognostische factoren bij het LRS. Voor de meerderheid van de factoren die werd geëvalueerd,

zoals leeftijd, body mass index, roken en sensibiliteitsstoornis, werd geen associatie met de uitkomst gevonden. De enige positieve associatie (met sterk bewijs) werd gevonden voor de ernst van pijn in het been als prognostische factor voor een operatieve behandeling.

Wat is de prognostische waarde van MRI bevindingen in patiënten met het LRS? Een observationele studie.

Bevindingen op de MRI kunnen prognostische waarde hebben in patiënten met ernstige klachten van een LRS en helpt gevoelsmatig om subgroepen te identificeren van patiënten die mogelijk meer baat hebben bij een operatieve of juist conservatieve behandeling. Daarom bepaalden we in **hoofdstuk 9** de prognostische waarde van bevindingen op de MRI om uitkomst gedurende 1 jaar follow-up te voorspellen en of MRI de besluitvorming tussen vroege operatieve of conservatieve behandeling zou kunnen faciliteren in patiënten met het LRS. Verschillende bevindingen op de MRI werden gescoord van 283 patiënten met een ernstig LRS die gerandomiseerd werden tussen operatie of een verlengde conservatieve behandeling met operatie wanneer nodig. Herstel werd gedefinieerd als volledig of bijna volledig herstel op een 7-punts Likert schaal. Ernst van pijn in het been werd gemeten op een 0-100mm visuele analoge schaal. Met Cox modellen werd de invloed van MRI variabelen op snelheid van herstel bepaald en met gemixte lineaire modellen werd de prognostische waarde van MRI variabelen op ernst van pijn in het been gedurende 1 jaar bepaald. Daarnaast werd de interactie van elke MRI variabele met de gelote behandeling bepaald.

MRI variabelen die statistisch significant geassocieerd bleken met minder pijn in het been gedurende 1 jaar waren de beoordeelde aanwezigheid van wortelcompressie ($p<0.001$) en de beoordeelde aanwezigheid van een extrusie van de discushernia in vergelijking met een protrusie ($p=0.006$). Beide variabelen neigden tot een associatie met herstel gedurende 1 jaar follow-up, maar dit was niet significant (Hazard ratio [HR] 1.45; 95%BI 0.93-2.24 en HR 1.24; 95%BI 0.96-1.61). De grootte van de discushernia associeerde niet met uitkomst gedurende 1 jaar follow-up. Er werden geen significante interacties tussen MRI variabelen en de gelote behandeling gevonden. Concluderend waren de aanwezigheid van wortelcompressie en een extrusie op MRI geassocieerd met minder pijn in het been gedurende 1 jaar follow-up, ongeachte de behandeling. De MRI bevindingen hadden geen nuttig aandeel in de besluitvorming tussen vroege operatie of conservatieve behandeling.

Hoofdstuk 10 geeft een overzicht van de belangrijkste bevindingen van dit proefschrift en de interpretatie van deze bevindingen in het kader van bestaande literatuur en enkele belangrijke methodologische vraagstukken. Hierop volgend worden de implicaties voor de klinische praktijk en de implicaties voor verder onderzoek bediscussieerd.

Dankwoord

DANKWOORD

Aan het onderzoek beschreven in dit proefschrift hebben veel mensen meegewerkt. Zonder hulp van anderen was dit proefschrift er nooit gekomen. Ik wil iedereen hiervoor van harte bedanken. Een aantal mensen wil ik in het bijzonder noemen.

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Curriculum Vitae

CURRICULUM VITAE

Annemieke Verwoerd is geboren op 14 februari 1984 in Snelrewaard. Na het voltooien van het voortgezet wetenschappelijk onderwijs begon zij in 2002 met de studie geneeskunde aan de Erasmus Universiteit in Rotterdam. Zes jaar later rondde zij deze studie succesvol af. Na een korte klinische ervaring in de psychiatrie begon zij in 2009 met de huisartsopleiding.

In 2010 startte Annemieke met haar promotietraject naar de diagnose en prognose van het lumbosacraal radiculair syndroom onder leiding van prof.dr. Koes, prof.dr. Peul en dr. Verhagen. Haar opleidingstraject tot huisarts en onderzoeker bestond uit periodes 'huisartsopleiding' en periodes 'onderzoek'. In 2011 behaalde zij een Master of Science in Clinical Epidemiology aan het Netherlands Institute for Health Sciences (NIHES).

Als verdieping binnen de huisartsopleiding heeft Annemieke de differentiatie 'Bewegingsapparaat' gevolgd en behaald. Daarnaast had zij zitting als huisarts in opleiding in de selectiecommissie van de huisartsopleiding in Rotterdam en in de geschillencommissie en adviescommissie (betreffende opleidingsaangelegenheden) van de Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst (KNMG). Haar werkzaamheden voor de geschillencommissie en adviescommissie heeft zij na het afronden van de huisartsopleiding voortgezet als huisarts-lid. Ook geeft zij sinds 2012, in wisselende frequentie, onderwijs aan geneeskunde studenten. Begin februari 2014 heeft zij de huisartsopleiding afgerond (met een oorkonde van Huisartsopleiding Nederland vanwege blijk van een hoog kennisniveau van de huisartsgeneeskunde op basis van de uitkomsten van de landelijke huisartsgeneeskundige kennistoetsen). Sindsdien werkt zij als waarnemend huisarts.

Annemieke is getrouwd met Marcel Roest en samen hebben ze een zoon Milan (geboren 7 mei 2013).

PhD Portfolio

PHD PORTFOLIO

Name PhD student:	Annemieke Verwoerd	Promotors:	Prof.dr. B.W. Koes and
Erasmus MC Department:	General Practice		Prof.dr. W.C. Peul
PhD period:	2010 – 2015	Supervisor:	Dr. A.P. Verhagen

	Year	ECTS
1. PhD training		
Courses / training		
Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2010-2011	70
Biomedical English Writing and Communication	2011	4
BROK ('Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers')	2012	1
BKO ('Basis Kwalificatie Onderwijs')	2012-present	1
Professional education		
Vocational training for general practitioner, Erasmus MC Rotterdam	2009-2014	
Oral presentations		
NAPCRG Annual Meeting, New Orleans	2012	1
World congress on Low Back and Pelvic Girdle Pain (9th), Dubai	2013	1
Poster presentations		
Back Pain Forum (12th), Odense	2012	1
NAPCRG Annual Meeting, New Orleans	2012	1
World congress on Low Back and Pelvic Girdle Pain (9th), Dubai	2013	1
Back Pain Forum (13th), Campos do Jordão	2014	1
2. Teaching		
Supervising student session 'How to judge a paper'	2011	1
Teaching 5th year medical students, Clinical Reasoning, Erasmus MC	2012-2013	3
Teaching 6th year medical students during internship General Practice, Erasmus MC	2012-present	3

List of publications

LIST OF PUBLICATIONS

This thesis

Lin CW, Verwoerd AJ, Maher CG, Verhagen AP, Pinto RZ, Luijsterburg PA, Hancock MJ. *How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review.* Eur J Pain 2014;18:455-64.

Verwoerd AJ, Peul WC, Willemsen SP, Koes BW, Vleggeert-Lankamp CL, El Barzouhi A, Luijsterburg PA, Verhagen AP. *Diagnostic accuracy of history taking to assess lumbosacral nerve root compression.* Spine J 2014;14:2028-37

Verwoerd AJ, Luijsterburg PA, Lin CW, Jacobs WC, Koes BW, Verhagen AP. *Systematic review of prognostic factors predicting outcome in non-surgically treated patients with sciatica.* Eur J Pain 2013;17:1126-37.

Verwoerd AJ, Luijsterburg PA, Timman R, Koes BW, Verhagen AP. *A single question was as predictive of outcome as the Tampa Scale for Kinesiophobia in people with sciatica: an observational study.* Journal of physiotherapy 2012;58:249-54.

Verwoerd AJ, Luijsterburg PA, Koes BW, El Barzouhi A, Verhagen AP. *Effect of Physical Therapy on the Relation of Kinesiophobia and Outcome in Patients with Sciatica in Primary Care: A Subgroup Analysis from a Randomized Controlled Trial.* Under review.

Verwoerd AJ, Verhagen AP, Peul WC, Vleggeert-Lankamp CL, Koes BW, El Barzouhi A. *Sciatica: a clinical review.* Submitted for publication.

Verwoerd AJ, Mens J, El Barzouhi A, Peul WC, Koes BW, Verhagen AP. *Does localization of worsening of pain during coughing, sneezing and straining matter in the assessment of lumbosacral nerve root compression? A short report.* Under review.

El Barzouhi A*, Verwoerd AJ*, Peul WC, Verhagen AP, Lycklama à Nijeholt GJ, Van der Kallen BF, Koes BW, Vleggeert-Lankamp CL. *Prognostic value of Magnetic Resonance Imaging in patients with sciatica.* Submitted for publication.

* Both authors contributed equally

Other publications

El Barzouhi A, Vleggeert-Lankamp CL, Lycklama à Nijeholt GJ, Van der Kallen BF, Van den Hout WB, Verwoerd AJ, Koes BW, Peul WC. *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery.* PloS One 2013;8:e68411.

Verwoerd JH, Mattace-Raso FU. *Mild Cognitive Impairment.* Huisarts Wet 2012;55:464-7.

Verwoerd JH, Boute FJ. *Erythema ab igne.* Medisch Contact 2012;13:575.

Meijer M, Verwoerd AJ. *Acupuncture for 'frequent attenders' with medically unexplained symptoms.* Br J Gen Pract 2011;61:495; author reply -6.

Verwoerd JH, Duinkerken A, Van der Wouden JC. *Jeugd-ggz: problemen rond verwijzen en communicatie. Een kwalitatief onderzoek onder Rotterdamse huisartsen.* Huisarts Wet 2009;52:236-40.