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Comparative effectiveness and prognostic factors for outcome of surgical and non-surgical management of lumbar spinal stenosis in an elderly population: Protocol for an observational study

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Comparative effectiveness and prognostic factors for outcome of surgical and non-surgical management of lumbar spinal stenosis in an elderly population: Protocol for an observational study

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ABSTRACT

Introduction: Lumbar spinal stenosis is a common cause of low back and leg pain in the elderly impacting physical activity and quality of life. Initial treatments are non-surgical options. If unsuccessful, surgery is advocated. The literature is not clear as to the outcome of surgery when compared to non-surgical treatment, and the optimal time for surgery is not explicit.

Materials and analysis: This observational study is designed to investigate the course of treatment, compare effectiveness of surgical and non-surgical management in patients with lumbar spinal stenosis, and identify prognostic factors for outcome in the context of current clinical practice. Prospectively registered data on treatment, outcome and patient characteristics are collected from nationwide registers on health and social issues, a clinical registry of people with chronic back pain and hospital medical records. Primary outcome is change in physical function measured by the Zurich Claudication Questionnaire. Secondary outcomes are changes in symptom severity, pain-related function, health-related quality of life, general self-efficacy. All outcomes will be assessed at baseline, 6 and 12 months. These variables will be compared between those who undergo surgery for lumbar spinal stenosis and those managing non-surgically at 12 months follow up according to different analysis populations. Prespecified prognostic factors of interest at baseline include: treatment allocation, back and leg pain intensity, comorbidity, duration of symptoms, pre-treatment function, self-rated health, income, general self-efficacy and MRI graded compression of central stenosis.

Ethics and dissemination: The study has been evaluated by The Regional Committees on Health Research for Southern Denmark (S-20172000-200) and notified to the Danish Data Protection Agency (18/22336). All participants provide consent. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following the guidance from the STROBE and PROGRESS statement. Potential sources of bias will be addressed using ROBINS-I.

Trial registration number: Clinicaltrials.gov (NCT03548441)
KEYWORDS

- Lumbar spinal stenosis
- Surgery
- Non-surgical management
- Comparative effectiveness
- Prognostics factors

STRENGTHS AND LIMITATIONS

- The main limitation of this study is that analyses are not based on randomised treatment assignments.
- Another potential weakness may be loss to follow up of data from the clinical registry of up to 65%.
- The results are strengthened by results are strengthened by a guesstimated large sample size from linking patient reported outcome measures to data from national registers, and by data being collected prospectively and systematically as part of current clinical practice.
INTRODUCTION

Lumbar spinal stenosis is a degenerative condition among elderly people, which can have a substantial impact on mobility, functioning and health-related quality of life [1]. The cardinal symptom of lumbar spinal stenosis is neurogenic claudication, consisting of lower limb pain and neurological symptoms exacerbated with walking and standing [2]. Some degree of stenosis may be present in up to 80% of patients over the age of 70 years [3], but symptomatic stenosis seems relatively uncommon [4]. It is estimated that 13-14% of patients with low back pain who see a specialist and 3-4% who see a general physician may have lumbar spinal stenosis [2]. The natural course of lumbar spinal stenosis is largely unknown, but over the course of 10 years, symptoms have been found to worsen in 31% of patients, improve in 38% and remain unchanged in 31% despite progressive anatomic changes [5], and peer-reviewed literature related to non-surgical management of patients with lumbar spinal stenosis does not seem to support the concern that these patients may be at risk of a decline in health status over time [6]. As the ageing population continues to grow, the number of individuals having lumbar spinal stenosis, the public health related issues and the economic ramifications associated with treatment must be expected to increase [6]. Thus, identifying effective treatment options for this population is of paramount importance [6].

Initial treatment are non-surgical options including a combination of drugs, exercise, manual therapy [7], lifestyle modification and multidisciplinary rehabilitation [2]. If unsuccessful, surgery is advocated. Lumbar spinal stenosis is the most frequent indication for spinal surgery in patients 65 years or older with 3 to 11.5 cases per 100.000 inhabitants per year [3]. Nonetheless, the literature is not clear as to the outcome of surgery when compared to non-surgical treatment [1], and the optimal timing for surgical decompression has not yet been established [8]. Due to the fluctuating natural history of lumbar spinal stenosis, surgery may be offered to patients soon after the onset of symptoms or several months or even years later [8]. Surgery has been reported as the most effective treatment for lumbar spinal stenosis, when outcome is defined as reduced pain and disability, as well as improved quality of life [9]. However, this was not the case for walking distance, the most essential functional limitation associated with lumbar spinal stenosis [9], and a recent systematic literature review has reported no differences in pain-related disability between surgery and non-surgical treatment at 3, 6 and 12 months, with only one of five studies reporting a difference in favour of surgery [1]. Even so, the undeniable patho-anatomical aetiology of lumbar spinal stenosis makes it understandable that some patients prefer the surgical solution. As surgery carries some risks, particularly in the elderly population [10], it is relevant to investigate the outcome of non-surgical treatment and identify factors prognosticating which patients are more likely to manage without surgical treatment, and which ones are better off with surgery.
Multiple factors may be of prognostic importance to the outcome in lumbar spinal stenosis surgery including duration of symptoms, greater back pain relative to leg pain [11], preoperative function, self-rated health, income, comorbidity and psychosocial factors [12]. Self-efficacy is assumed to be an underlying factor explaining positive effects on health behaviour, health status, self-management behaviour and health care utilization in older people with chronic disease [13]. Grading of compression on preoperative magnetic resonance imaging (MRI) does not correlate to the severity of clinical condition nor predict surgical outcome after 1 year [14]. Symptomatic improvement is also seen in non-surgical treatment, but evidence for prognostic factors of outcome in non-surgical management [15], and what guides allocation of treatment [16] is sparse.

Rationale for this study
Evidence-based recommendations to guide clinical practice are lacking [1] and decision-making related to management of symptomatic lumbar spinal stenosis in daily clinical practice remains a challenge [17]. Randomised controlled trials comparing surgical with non-surgical treatment have been done, but the overall evidence is of low quality [1]. Hence, they provide little confidence to conclude whether surgical treatment or a non-surgical approach is better for lumbar spinal stenosis and no new recommendations to guide clinical practice [1]. Comparative effectiveness research attempts to compare the effects of a number of prespecified treatments in current use on clinical outcomes in order to guide decision-making [18]. The emphasis on clinical goals and decisions distinguishes comparative effectiveness research from trials that are designed to compare an experimental intervention or exposure to a control comparator (unexposed), to establish proof-of-concept, or to elucidate a mechanism of action. For that reason, we have decided to perform an observational study in the context of clinical practice focusing on the comparative effectiveness of surgical and non-surgical management of lumbar spinal stenosis and prognostic factors for outcome.

Aim and objectives
The aim of this study is to investigate the course of treatment for elderly patients with lumbar spinal stenosis with the objectives to 1) compare the effectiveness of spinal surgery to non-surgical management and 2) identify prognostic factors at baseline for outcome at 12 months follow up.

METHODS AND ANALYSIS
Design and setting
Prospectively registered data on treatment, outcome and patient characteristics are obtained from nationwide registers on health and social issues [19], a clinical registry of people with chronic back
pain (SpineData) located at the Spine Centre of Southern Denmark, Lillebaelt Hospital, Middelfart, Denmark [20] and hospital medical records. Baseline data are captured at point of first clinical contact, follow up data at 6 and 12 months (see figure 1).

Participants
All patients older than 60 years, diagnosed with lumbar spinal stenosis and having first clinical contact at the Spine Centre of Southern Denmark, Lillebaelt Hospital, Middelfart from January 1st – December 31st 2017 eligible for this study, will be identified in the National Patient Register [21]. Follow-up time from the date of first clinical contact (baseline) is 6 and 12 months.

Inclusion criteria
1) Included in the SpineData registry.
2) >60 years
4) Give consent to use patient-reported data for research purposes.

Outcome measures
Primary outcome measure
The primary outcome is change in physical function score between baseline and 12 months follow up measured with Zurich Claudication Questionnaire (ZCQ). It has good psychometric properties, is widely used and recommended in outcome assessment of patients with lumbar spinal stenosis [22,23]. The questionnaire has three domains (symptom severity, physical function, and patients’ satisfaction). The satisfaction subscale which assesses satisfaction with surgery is omitted in this study as we include a non-surgical group. Maximum score is 5 for symptom severity and 4 for physical function, lower scores indicate less disability. The ZCQ score is considered to represent a ‘successful improvement’ when the subscales are judged as ‘success’ [24] that is, a decrease of at least 0.48 in symptom severity and 0.52 in physical function [22].

Secondary outcome measures
Secondary outcome measures are change in score between baseline and 12-months follow-up in:
1) Symptom severity score obtained by the ZCQ [22].
2) Pain related physical function obtained by Oswestry disability index (ODI) [25].
3) Health related quality of life (HRQL) obtained by EQ-5D-3L [26].
4) General self-efficacy obtained by General Self Efficacy Scale (GSE) [27].
The ODI assesses pain-related physical functioning in spinal disorders [28,29]. It has been tested extensively, has shown good psychometric properties and is applicable in a wide variety of settings [28,30]. The ODI contains 10 questions designed to realise how the back or leg pain is affecting the ability to manage everyday life. These are summarised to a score, ranging from 0-100. Higher scores express higher pain and disability.

EQ-5D-3L is a widely used measure of generic HRQL and considered valid and responsive in patients with chronic low back pain [31]. It evaluates 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These health states are converted into a single summary index with a total score ranging from –0.6 to 1, where 1 corresponds to perfect health. Furthermore, EQ-5D-3L encloses the EQ visual analogue scale (EQ VAS), scoring the respondents self-rated health [32]. Higher scores express higher HRQL.

The GSE estimates perceived self-efficacy [27] and is used in patients with chronic pain [33]. Higher scores express higher self-efficacy.

All questionnaires will either have been validated in Danish or validated in its original language and translated into Danish following scientific standards [34]. All outcomes are measured at baseline, 6 and 12 months.

Potential prognostic and extrinsic factors
The study focuses on exploring prognostic factors for outcome related to apparent treatment allocation, back pain intensity, leg pain intensity, duration of symptoms, comorbidity, pre-treatment function, self-rated health, income, general self-efficacy and MRI graded compression. Pain intensity is obtained using the 11-point Numerical Pain Rating Scale (NPRS) [29]. Comorbidity is estimated using the Charlson comorbidity index [35]. MRI graded compression is estimated using the classification described by Ishimoto et al [4].

Data on age, sex, height, weight, cohabitation status, work status, level of education, socio-economic classification, use of primary health care services, number of prior hospital admissions, daily dosage of prescriptive analgesic medicine will be collected to control for potential confounding, mediating or moderating effects related to these variables.

Data collection
Data relating to age, sex, cohabitation, ICD-10 diagnosis code, treatment, prior hospital admissions, hospital department, work status, daily dosage of prescriptive analgesic medicine, income, socio-economic classification, level of education and number of consultations in primary health care centres will be collected from nationwide registers [19].
At point of first clinical contact, patients and clinicians complete the baseline questionnaire of the SpineData clinical registry which include questions covering all health components of WHO’s International Classification of Functioning, Disability and Health (ICF) [36]. In addition to the outcome measures, information about body mass index (BMI), back and leg pain intensity, duration of symptoms, smoking, alcohol, level of physical activity and psychosocial construct is available in the SpineData registry [20]. Wherever possible, the questions and questionnaires have been based on evidence of their role in the diagnosis, prognosis or treatment of spinal pain [20]. Patients complete all questionnaires without any assistance from clinicians or administrative personnel.

For patients with available diagnostic MRIs performed at Lillebaelt Hospital, radiologists use a standardised protocol classifying the degree of central stenosis into mild, moderate or severe as described by Ishimoto et al 2013 [4]. MRI descriptions are accessible in hospital medical records.

All data collected are depicted in table 1.

Table 1 Data collected including primary endpoint

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
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<th>12 months</th>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td>X</td>
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<td>Height</td>
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<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohabitation status</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td><strong>Socio-economic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Socio-economic classification</td>
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<td></td>
<td></td>
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<tr>
<td>Work status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Highest level of education completed</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Health care factors</strong></td>
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<tr>
<td>Number of consultations in primary health care centres</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Daily dosage of prescriptive analgesic medicine</td>
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<td>X</td>
</tr>
<tr>
<td>Hospital department</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Symptom and pain related factors</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Duration of symptoms</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back pain intensity, NPRS</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leg pain intensity, NPRS</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Symptom Severity, ZCQ</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Charlson Comorbidity Index</td>
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<tr>
<td><strong>Activity limitation factors</strong></td>
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<tr>
<td>Physical function, ZCQ*</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pain related physical function, ODI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Personal factors</strong></td>
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<tr>
<td>General self-efficacy, GSE</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health related quality of life, EQ VAS (0-100)</td>
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<tr>
<td>Health related quality of life, EQ-5D-3L</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
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Clinical findings
ICD-10 diagnosis code (DM480, DM996) X
MRI findings (degree of central stenosis) X

1) Primary endpoint; NRS, Numerical Rating Scale; ZCQ, Zurich Claudication Questionnaire; ODI, Oswestry Disability Index; HRQL, Health Related Quality of Life; EQ-5D-3L, EurQoL self-perceived health related quality of life; EQ VAS, EurQoL Visual Analogue Scale; GSE, General Self-Efficacy Scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; MRI, Magnetic Resonance Imaging

Interventions
Surgical management (exposed)
Patients receiving surgical treatment undergo various types of posterior decompressive surgery with or without spinal fusion. The method used for decompressive surgery or fusions is determined solely by the surgeon. Procedure codes are available in the National Patient Register [21].

Non-surgical management (unexposed)
Patients managing lumbar spinal stenosis non-surgically are either referred to rehabilitation primary health care centre or referred back to their general practitioner for treatment. Treatment may include physiotherapy, chiropractic treatment, lifestyle changes and/or pain management. Post-surgically patients may also be referred to rehabilitation at a primary health care centre. Use of health care services in primary care and daily dosage of analgesic medicine is available in the National Health Service Register [37] and the National Prescription Registry [38] respectively.

Patient and public involvement
This study follows the European League Against Rheumatism (EULAR) recommendations for the inclusion of patient research partners in scientific projects [39]. The study is designed with assistance from three Danish patient representatives, Anna Karen Guldager Rüsz (AKGR), Tove Theilmann Petersen (TTP) and Peter Christian Christensen (PCC). They are all diagnosed with lumbar spinal stenosis and were selected in connection with routine care and their participation in a multidisciplinary rehabilitation programme for patients with lumbar spinal stenosis. The patient research partners have participated in discussion of the idea, relevance and purpose of the study and will contribute with comments on patient information regarding the findings of the study.

Choice of outcome measures were discussed with the patients after they were selected in collaboration with health care professionals who have extensive clinical experience in diagnosing, goalsetting, decision-making and treating patients with lumbar spinal stenosis and including patient preferences into this process.

A lay summary of the study results will be written for patients and disseminated through patient groups (i.e. The Danish Rheumatism Association) and online fora (i.e. the Lillebaelt Hospital website) to raise awareness of the study and future research areas.
**Statistical analyses**

We anticipate that in the course of a 12 months period, the SpineData registry collects information on 2500 - 3000 consenting baseline episodes of patient care on patients older than 60 years with low back pain, of which 300 patients may be expected to undergo surgery for lumbar spinal stenosis [40]. Assuming equal distribution of patients treated surgically and non-surgically after 1 year, we guesstimate to enrol 600 patients to the lumbar spinal stenosis cohort.

To determine if this guesstimated cohort size will be sufficient to achieve ≥80% probability of detecting a statistically significant difference in primary outcome between groups, an *a priori* power analysis has been performed.

The minimal clinically important difference in mean change on the physical function scale of the Zurich Claudication Questionnaire is considered to be 0.52 points (22). Thus, an enrolment flow and distribution of 600 patients in a balanced design (figure 2) will have a power of 0.956 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (*p* ≤ 0.05), assuming a common standard deviation of 1 point to detect a mean difference of 0.3 points on the physical function scale.

In addition, we will have a power of 0.849 for at two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (*p* ≤ 0.05), assuming a common standard deviation of 1 point, in a total sample size of 400 with a balanced design to detect a mean difference of 0.3 points on the physical function scale.

Even if we are to test for equivalence between surgical and non-surgical treatment, a total sample size of 400 in a balanced design will yield a power of 0.999 for two one-sided tests (TOST) analysis for additive equivalence of two-sample normal means with bounds -0.25 and 0.25 for the mean difference and a significance level of 0.05 (*p* ≤ 0.05), assuming a mean difference of 0 points and a common standard deviation of 0.5 points on the physical function scale.

For an overview of the expected distribution of patients enrolled, please refer to figure 2.

Following recommendations for the development of a multivariable prognostic model of 50 events for the first covariate and adding 10-20 events required for each prognostic variable [41], we would be able to perform a multivariable analysis for potential prognostic factors for outcome with approximately 30 variables in a cohort of 600 patients.

Patient characteristics will be summarised using descriptive statistics. Descriptive results will be given as means with standard deviations (or medians with interquartile range) and as percentages. Comparisons will be made on these variables and outcome measures between patients who undergo surgery for lumbar spinal stenosis (exposed) and those who manage non-surgically (unexposed). Data will be analysed in analogy to a randomised trial [42], realising however, that
this comparative effectiveness study with repeated measures, is not randomly assigning individuals to treatment groups.

In the basic (i.e. crude) statistical model, there will be two fixed effect factors: group and time and the interaction between them. This model will aim to describe the longitudinal progress (trajectories) for the two groups and subsequently adjust for potentially confounding variables as a consequence of patients not being randomly assigned to the two groups (i.e. adjusted model). Random effects result from variation between and within participants; anticipating that measures on the same participant at the different times are correlated, and that measures taken close together in time being more highly correlated than measures taken far apart in time. Observations on different participants will be assumed independent. In the statistical analyses the following potential ‘candidate confounding variables’ will be considered for statistical adjustment: age, level of education, socioeconomic classification, BMI, comorbidity, use of primary health care services, prior hospital admissions and consumption of prescriptive analgesic medicine.

One of the primary distinguishing features of analysis of repeated measures data is the need to accommodate the covariation of the measures on the same sampling unit. For the choice of covariance structure, we will utilise graphical techniques, numerical comparisons of covariance estimates, and indices of goodness-of-fit. After the covariance is satisfactorily modelled, the estimated covariance matrix is used to compute generalised least squares estimates of fixed effects of treatments and time.

The statistical model will also compare the study population with those withdrawing or crossing over to surgery. Multivariable analyses will be applied to derive models adjusting for multiple factors. For the purpose of pre-specified analyses, we will consider the ‘data as available’ to constitute the primary analysis population; as indicated below this cohort of observed patients will then rightfully allow for patients ‘changing group’ between baseline and the 12 months assessment, thereby violating the intention-to-treat principle.

Missing data
Missing data always threaten the validity of longitudinal clinical studies. As there is no analytic approach that can assuredly produce unbiased estimates of treatment effects when relevant data are missing we will emphasise the importance to minimise missing data.

We will distinguish treatment discontinuation (i.e. switching between groups) from missing outcome data [43]. Data collection is often stopped after treatment discontinuation, but we will attempt to continue recording outcome data on individuals after they potentially discontinue/switch from the initial treatment group or missed clinic visits. Conversely, outcome data may be missing for individuals who do not discontinue treatment, as when there is loss to follow up. The latter
missing outcome data scenario is a standard missing data problem [43], but group switching is
better viewed as a form of non-compliance and will be treated using ideas from the causal literature
on non-compliance [44]. We consider methods of analysis that are model-based superior to
available-, complete-case analysis or single-imputation methods such as the last observation carried
forward. As the degree of ‘missingness’ in the data will likely raise questions about the validity of
preferred methods such as model based imputation, protocolised sensitivity analyses will be
performed to determine whether the conclusions are sensitive to assumptions about the missing-data
mechanism.

Analysis populations
The full analysis set represents the population as close as possible to the ideal implied by the
intention-to-treat principle. However missing data within participants can present serious problems
depending on the amount, cause and pattern of missing data in a non-randomised study design. The
‘as observed population’, allowing for switch between groups, will be compared with two
alternative populations (i) the intention to treat population in which collected data for the individual
patient stay in the initial group and (ii) the per protocol population in which only those without
‘protocol violations’ will be included; see below for definitions.

*Intention-to-treat population:* The principle which asserts that the effect of a treatment policy
such as non-surgical management can be best assessed by evaluating on the basis of the intention to
treat an individual, hence the planned treatment regimen, rather than the actual treatment given. In
this study it has the consequence that patients initially allocated to a specific treatment group should
be followed up, assessed and analysed as members of that group irrespective of their compliance to
the planned course of treatment. Thus, (initially) non-surgical patients remain in that group even if
they subsequently accept surgery, and (initially) surgical patients remain in that group even if they
start using post-surgical rehabilitation.

*As-Observed population (available case analysis):* Based on the ‘Full Analysis Set’ being all
the data available at baseline, with no replacement for missing data, with group legitimately
changing according what is observed, hence which treatments patients ended up accepting [i] only
surgery, [ii] only non-surgical management, or [iii] a secondary switch to accept surgery.

*Per-Protocol population:* The set of data generated by the subset of patients who complied
with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of
treatment, according to the underlying scientific model. The following definition will be used to
cover a per protocol patient from each group: The per protocol population includes all patients in
the intention to treat population but excluding those crossing over from non-surgical management to
surgery. In the surgical group patients undergoing surgery less than 3 months prior to completing
the 12 months follow up questionnaires will also be excluded. The reason being that pain intensity and physical impairment is expected to increase immediately after surgery and patients undergoing surgery for lumbar spinal stenosis at the Spine Centre of Southern Denmark are subject to post-surgical restrictions in a post-surgical recovery period of up to 12 weeks. Thus, patient reported outcome measures recorded during this period are assumed non-comparable to those in the non-surgical group.

All analyses will be performed using STATA (version 15.1, StataCorp LLC, College Station, Texas, USA). The analyses will be made in collaboration with a statistical expert.

ETHICS AND DISSEMINATION
The study will be performed according to the ‘Declaration of Helsinki’ [45], ‘The European Code of Conduct for Research Integrity’ [46] and ‘The Danish Code of Conduct for Research Integrity’ [47]. Following review from The Regional Committees on Health Research Ethics for Southern Denmark, ethical approval is not required for this study according to ‘The Danish Act on Research Ethics Review of Health Research Projects’ (S-20172000-200) [48]. The study has been notified to the Danish Data Protection Agency [49] (17/30636), and permission to extract data from hospital records will be obtained from the Danish Patient Safety Authority [50]. Consent to use patient-reported information from the SpineData registry for research purposes are obtained electronically prior to patients completing the questionnaires. Patients, who do not consent, will not be included. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following the guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [51] and Prognosis Research Strategy (PROGRESS) [52] statement. Potential sources of bias will be addressed using Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) [42].

DISCUSSION
This article presents a protocol for an observational study designed to investigate the course of treatment by comparing the effectiveness of surgical and non-surgical management in patients with lumbar spinal stenosis and identify prognostic factors for outcome in the context of current clinical practice. Prospectively registered data and patient reported outcome measures are collected from the national registers, the SpineData clinical registry of people with chronic back pain and hospital medical records.

The main limitation of this study is that analyses are not based on randomised treatment assignments. However, data are collected prospectively, and results are strengthened by a potentially large sample size from linking patient reported outcome measures to data from national
registers. Another potential weakness may be loss to follow up as data from the clinical SpineData registry may only be 50% at 6 months and 35% at 12 months, and the percentages of clinician reported findings in SpineData and medical journals as well as MRI descriptions available are unknown. To minimise missing data, an independent administrative assistant will send out a reminder including a paper version of the questionnaires to patients, who do not respond to the 12 months follow-up. A third possible limitation is that we may not have equal number of patients in the surgical and non-surgical group, due to the fact that we do not know how many patients will be diagnosed with lumbar spinal stenosis and receive surgery.

Nonetheless, the strengths of this study are, that it will estimate outcome of non-surgical management and provide knowledge of factors prognosticating outcome in both surgical and non-surgical management of lumbar spinal stenosis. Hence, the knowledge obtained in this study is expected to help clinicians guide patients in choosing surgical or non-surgical treatment for lumbar spinal stenosis, and researchers in selecting variables of interest in future randomised controlled trials comparing the effect of the two management options.
LEGENDS

Figure 1 Study flow diagram with enrolment and follow up
Figure 2 Expected distribution of patients enrolled
Table 1 Data collected including primary outcome

ACKNOWLEDGEMENTS
The authors wish to thank patient research partners Anna Karen Guldager Rüsz, Peter Christian Christensen and Tove Theilmann Petersen for their help in this study.

AUTHOR CONTRIBUTIONS
HAB and BSC conceived the study. All authors participated in the study design and the preliminary analysis plan. HAB constructed the first draft of the manuscript. All authors contributed to writing the manuscript. TM contributed substantially to writing the section on outcome measures. RC contributed substantially to the power analysis calculations and in writing the statistical analyses section. BSC contributed substantially to writing the introduction and the section on data collection. All authors participated in critical scrutinising and revision of the manuscript and approved the final version.

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Thomas Maribo and Berit Schiøttz-Christensen have nothing to disclose.

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Figure 1 Study flow diagram with enrolment and follow up
Figure 2 Expected distribution of patients enrolled
# STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item #</th>
<th>Recommendation</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1 (a)</td>
<td>Indicate the study’s design with a commonly used term in the title or the abstract</td>
<td>1</td>
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<tr>
<td></td>
<td>1 (b)</td>
<td>Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>2</td>
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<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>4</td>
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<tr>
<td><strong>Objectives</strong></td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>Study design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>4</td>
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<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>4</td>
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<tr>
<td>Participants</td>
<td>6 (a)</td>
<td>Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
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<td>6 (b)</td>
<td>For matched studies, give matching criteria and number of exposed and unexposed</td>
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<tr>
<td>Variables</td>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
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<tr>
<td>Data sources/</td>
<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
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<td>Bias</td>
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<td>Describe any efforts to address potential sources of bias</td>
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<td>Study size</td>
<td>10</td>
<td>Explain how the study size was arrived at</td>
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<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>10-12</td>
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<tr>
<td>Statistical methods</td>
<td>12 (a)</td>
<td>Describe all statistical methods, including those used to control for confounding</td>
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<td>12 (b)</td>
<td>Describe any methods used to examine subgroups and interactions</td>
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<td>12 (c)</td>
<td>Explain how missing data were addressed</td>
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<td>12 (d)</td>
<td>If applicable, explain how loss to follow-up was addressed</td>
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<td><strong>Results</strong></td>
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| Participants             | 13*  | (a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
                        |      | (b) Give reasons for non-participation at each stage                                                                                                                                                         | No results  |
|                          |      | (c) Consider use of a flow diagram                                                                                                                                                                          | yet          |
| Descriptive data         | 14*  | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders                                                                       | No results  |
|                          |      | (b) Indicate number of participants with missing data for each variable of interest                                                                                                                          | yet          |
|                          |      | (c) Summarise follow-up time (e.g., average and total amount)                                                                                                                                                | yet          |
| Outcome data             | 15*  | Report numbers of outcome events or summary measures over time                                                                                                                                                | No results   |
| Main results             | 16   | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | No results   |
|                          |      | (b) Report category boundaries when continuous variables were categorized                                                                                                                                   | yet          |
|                          |      | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period                                                                                           | yet          |
| Other analyses           | 17   | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses                                                                                                             | No results   |
| Discussion               |      |                                                                                                                                                                                                              |              |
| Key results              | 18   | Summarise key results with reference to study objectives                                                                                                                                                    | No results   |
| Limitations              |      |                                                                                                                                                                                                              |              |
| Interpretation           | 20   | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence                                             | 13           |
| Generalisability         | 21   | Discuss the generalisability (external validity) of the study results                                                                                                                                       | No results   |
| Other information        |      |                                                                                                                                                                                                              |              |
| Funding                  | 22   | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based                                                                 | 14           |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
Comparative effectiveness and prognostic factors for outcome of surgical and non-surgical management of lumbar spinal stenosis in an elderly population: Protocol for an observational study

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Comparative effectiveness and prognostic factors for outcome of surgical and non-surgical management of lumbar spinal stenosis in an elderly population: Protocol for an observational study

Helle Algren Brøgger¹⁻⁴, Thomas Maribo⁵⁻⁶, Robin Christensen³⁻⁷, Berit Schiøttz-Christensen¹⁻²

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Word count: 3854 (excl. title page, abstract, references, figures and tables etc.)
ABSTRACT

Introduction: Lumbar spinal stenosis is a common cause of low back and leg pain in the elderly and affects both physical activity and quality of life. First-line treatments are non-surgical options but if unsuccessful, surgery is advocated. The literature is not clear as to the outcome of surgery compared to non-surgical treatment, and the optimal time for surgery is not explicit. This observational study is designed to investigate the course of treatment, compare effectiveness of surgical and non-surgical management in patients with lumbar spinal stenosis, and identify prognostic factors for outcome in the context of current clinical practice.

Materials and analysis: Prospectively registered data on treatment, outcome, and patient characteristics are collected from nationwide registers on health and social issues, a clinical registry of people with chronic back pain, and hospital medical records. Primary outcome is change in physical function measured by the Zurich Claudication Questionnaire. Secondary outcomes are changes in symptom severity, pain-related function, health-related quality of life, and general self-efficacy. Outcomes are assessed at baseline and 6 and 12 months. Outcomes at 12 months will be compared for patients who undergo surgery for lumbar spinal stenosis and patients managed non-surgically, using different analytical approaches. Prespecified prognostic factors of interest at baseline include treatment allocation, back and leg pain intensity, comorbidity, duration of symptoms, pre-treatment function, self-rated health, income, general self-efficacy, and MRI-graded severity of central stenosis.

Ethics and dissemination: The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20172000-200) and notified to the Danish Data Protection Agency (18/22336). All participants provide consent. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences according to the STROBE and PROGRESS statements. Potential sources of bias will be addressed using ROBINS-I.

Trial registration number: Clinicaltrials.gov (NCT03548441)
KEYWORDS

- Lumbar spinal stenosis
- Surgery
- Non-surgical management
- Comparative effectiveness
- Prognostic factors

STRENGTHS AND LIMITATIONS

- The main limitation of this study is that analyses are not based on randomised treatment assignments
- Another potential weakness may be up to 65% loss of follow-up data in the clinical registry
- The results are strengthened by a large sample size that is ‘guesstimated’ from assumptions of expected patient numbers and their distribution across treatment groups
- Data are collected prospectively and systematically as part of current clinical practice
- Data on patient-reported outcomes are linked to data from hospital medical records and national registers on health and social issues
INTRODUCTION
Lumbar spinal stenosis is a degenerative condition among elderly people that can substantially affect mobility, functioning, and health-related quality of life [1]. The cardinal symptom of lumbar spinal stenosis is neurogenic claudication, consisting of lower limb pain and neurological symptoms exacerbated with walking and standing [2]. Some degree of stenosis may be present in up to 80% of patients over 70 years old [3], but symptomatic stenosis seems relatively uncommon [4]. Lumbar spinal stenosis has been reported in 13–14% of patients with low back pain who see a specialist and 3–4% who see a general physician [2]. The natural course of lumbar spinal stenosis is largely unknown, but over the course of 10 years, symptoms have been found to worsen in 31% of patients, improve in 38%, and remain unchanged in 31% despite progressive anatomic changes [5]. Peer-reviewed literature does not seem to support the concern that patients managed non-surgically may be at risk of worsening health status over time [6]. As the ageing population continues to grow, the number of individuals with lumbar spinal stenosis and the associated public health and economic consequences must be expected to increase [6]. Identifying effective treatment options for this population is thus important [6].

First-line treatment is non-surgical and may include a combination of drugs, exercise, manual therapy [7], lifestyle modification, and multidisciplinary rehabilitation [2]. If unsuccessful, surgery is advocated. Lumbar spinal stenosis is the most frequent indication for spinal surgery in patients 65 years or older, with 3–11.5 cases per 100,000 inhabitants per year [3]. The literature is not clear as to the outcome of surgery compared to non-surgical treatment [1], however, and the optimal timing for surgical decompression has not yet been established [8]. Due to the fluctuating natural history of lumbar spinal stenosis, surgery may be offered to patients soon after the onset of symptoms or several months or even years later [8]. Surgery has been reported as the most effective treatment for lumbar spinal stenosis when outcome is defined as reduced pain and disability and improved quality of life [9]. This was not the case for walking distance, however, which is the key functional limitation associated with lumbar spinal stenosis [9]. A recent systematic literature review reported no differences in pain-related disability between surgery and non-surgical treatment at 3, 6, and 12 months, with only one of five studies reporting a difference in favour of surgery [1]. The undeniable patho-anatomical aetiology of lumbar spinal stenosis makes it understandable that some patients prefer a surgical solution, but important concerns have been raised about surgical risks, particularly for elderly patients having complex fusions [10,11]. Studies have shown similar outcomes in elderly individuals undergoing minimally invasive spine surgery (without fusion) with little additional risk [11,12]. Hence, it is relevant to investigate the outcome of non-surgical treatment and to identify prognostic factors that could help determine which patients are more likely to manage without surgical treatment, and which patients would benefit more from surgery.
Multiple factors may be related to the outcome from lumbar spinal stenosis surgery including duration of symptoms, greater back pain relative to leg pain [13], smoking [14], previous spinal surgery [15], preoperative function, self-rated health, income, comorbidity, and psychosocial factors [16]. Self-efficacy is assumed to be an underlying factor explaining positive effects on health behaviour, health status, self-management behaviour, and health care utilisation in older people with chronic disease [17]. Radiological severity on preoperative magnetic resonance imaging (MRI) is not associated with clinical severity nor surgical outcome after 1 year [18,19]. Symptomatic improvement is also seen in non-surgical treatment, but evidence is sparse for prognostic factors of outcome in non-surgical management [20] and the aspects that guide allocation of treatment [21].

**Rationale for this study**

Evidence-based guidelines for clinical practice are lacking [1], and decision-making related to management of symptomatic lumbar spinal stenosis in daily clinical practice remains a challenge [22]. The overall evidence from randomised controlled trials comparing surgical and non-surgical treatment is of low quality [1] and provides little confidence to conclude whether a surgical or non-surgical approach is better for lumbar spinal stenosis [1]. Comparative effectiveness research aims to guide decision-making by comparing the effects on clinical outcomes of a number of prespecified treatments in current use [23]. The emphasis on clinical goals and decisions distinguishes comparative effectiveness research from trials that are designed to compare an experimental intervention or exposure to a control comparator (unexposed), to establish proof-of-concept, or to elucidate a mechanism of action. For that reason, we have decided to perform an observational study in the context of clinical practice, focusing on the comparative effectiveness of surgical and non-surgical management of lumbar spinal stenosis and prognostic factors for outcome.

**Aim and objectives**

The aim of this study is to investigate the course of treatment for elderly patients with lumbar spinal stenosis with the objectives to 1) compare the effectiveness of spinal surgery to non-surgical management and 2) identify prognostic factors at baseline for outcome at 12 months follow-up.

**METHODS AND ANALYSIS**

**Design and setting**

Prospectively registered data on treatment, outcome, and patient characteristics are obtained from nationwide registers on health and social issues [24], a clinical registry of people with chronic back pain (SpineData) located at the Spine Centre of Southern Denmark, Lillebaelt Hospital, Middelfart,
Denmark [25], and hospital medical records. Baseline data are captured at point of first clinical contact and at 6-month and 12-month follow-ups (see Figure 1).

**Participants**

All patients older than 60 years, diagnosed with lumbar spinal stenosis, and having first clinical contact at the Spine Centre of Southern Denmark, Lillebaelt Hospital, Middelfart from January 1st – December 31st 2017 will be identified in the National Patient Register [26].

Criteria for patient inclusion

1) Included in the SpineData registry
2) >60 years
3) ICD-10 diagnosis of degenerative lumbar spinal stenosis registered in the nationwide patient registry between January 1st – December 31st 2017, i.e. including central stenosis, foraminal stenosis as well as stenosis and spondylolisthesis or spondylodesis combined (DM480, DM996, DM431, DM472)
4) Gives consent to use patient-reported data for research purposes

**Outcome measures**

Primary outcome

Primary outcome is change in physical function score between baseline and 12-month follow-up measured with Zurich Claudication Questionnaire (ZCQ). The questionnaire has good psychometric properties, is widely used, and is recommended in outcome assessment of patients with lumbar spinal stenosis [27,28]. It has three domains (scales): physical function, symptom severity, and patient satisfaction with surgery. The satisfaction subscale is omitted in this study, as we include a non-surgical group. The physical function scale contains 5 items (questions) designed to specifically assess walking capacity in patients with lumbar spinal stenosis [29], and the symptom severity scale has 7 items. Scores are calculated as the unweighted mean of all answered items and range from 1 to 4 (physical function) or 1 to 5 (symptom severity). Lower scores indicate less disability. The ZCQ score is considered to represent a ‘successful improvement’ when the subscales are judged as ‘success’ [30]. Minimal clinically important difference (MCID) in mean change is 0.52 on the physical function scale and 0.48 on the symptom severity scale [27].

Secondary outcomes

Secondary outcomes are change in score between baseline and 12-month follow-up in:

1) Symptom severity score on the ZCQ [27]
2) Pain-related physical function on the Oswestry disability index (ODI) [31]
3) Health-related quality of life (HRQL) on the EQ-5D-3L [32]
4) General self-efficacy on the General Self Efficacy Scale (GSE) [33].

The ODI assesses pain-related physical functioning in spinal disorders [34,35]. It has been tested extensively, has good psychometric properties, and is applicable in a wide variety of settings [34,36]. The ODI contains 10 questions about how back or leg pain affects the ability to manage everyday life. These are summarised to a score ranging from 0-100. Higher scores reflect worse pain and disability.

EQ-5D-3L is a widely used generic measure of HRQL that is considered valid and responsive for patients with chronic low back pain [37]. It evaluates 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three levels of severity. The resulting health states can be converted into a single summary index with a total score ranging from –0.6 to 1, where 1 corresponds to perfect health. The EQ-5D-3L includes a EuroQol visual analogue scale (EQ VAS) from 0-100 for respondents’ self-rated health [38]. Higher scores reflect better HRQL.

The GSE measures perceived self-efficacy [33] and is used in patients with chronic pain [39]. Higher scores reflect higher self-efficacy.

All questionnaires will either have been validated in Danish or validated in its original language and translated into Danish following scientific standards [40].

Potential prognostic and extrinsic factors
The study explores prognostic factors for outcome related to treatment allocation, back and leg pain intensity, duration of symptoms, smoking, comorbidity, anxiety/depression, previous spinal surgery, pre-treatment function, self-rated health, income, general self-efficacy, and MRI-graded severity. Pain intensity is measured using the 11-point Numerical Pain Rating Scale (NPRS) [35]. Comorbidity is assessed using the Charlson comorbidity index (i.e. including diabetes, cardiovascular and pulmonary comorbidity) [41]. MRI-graded severity is estimated using the classification described by Ishimoto et al. [4].

Data on age, sex, height, weight, cohabitation status, work status, level of education, socio-economic classification, use of primary health care services, prior hospital admissions, and use of prescriptive analgesic medicine will be collected to control for potential confounding, mediating, or moderating effects.
Data collection

Data on age, sex, cohabitation, ICD-10 diagnosis, treatment, previous spinal surgery, prior hospital admissions, hospital department, work status, use of prescriptive analgesic medicine, income, socio-economic classification, level of education, and number of consultations in primary health care centres will be collected from nationwide registers [24].

At the first clinical contact, patients complete the baseline questionnaire of the SpineData clinical registry which includes questions covering all the health components of WHO’s International Classification of Functioning, Disability and Health (ICF) [42]. In addition to the outcome measures, information about body mass index (BMI), back and leg pain intensity, duration of symptoms, and smoking is available in the SpineData registry [25]. Wherever possible, questions and questionnaires have been based on evidence of their role in the diagnosis, prognosis, or treatment of spinal pain [25]. Patients complete the questionnaires without assistance from clinicians or administrative personnel.

For patients with diagnostic MRIs performed at Lillebaelt Hospital, radiologists use a standardised protocol classifying mild, moderate, or severe central stenosis as described by Ishimoto et al. 2013 [4]. MRI descriptions are available in hospital medical records.

The data collected are depicted in Table 1.

Table 1 Data collected, including primary endpoint

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<td></td>
</tr>
<tr>
<td>Number of consultations in primary health care centres</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Daily dosage of prescriptive analgesic medicine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hospital department</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Symptom and pain related factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back pain intensity, NPRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leg pain intensity, NPRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Symptom severity, ZCQ</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Charlson comorbidity Index  X  X  X

**Activity limitation factors**
- Physical function, ZCQ*  X  X  X
- Pain-related physical function, ODI  X  X  X

**Personal factors**
- General self-efficacy, GSE  X  X  X
- Self-described health status, EQ-5D-3L  X  X  X
- Self-rated health-related quality of life, EQ VAS (0-100)  X  X  X
- Anxiety/depression, item 5, EQ-5D-3L  X  X  X

**Clinical findings**
- ICD-10 diagnosis code (DM480, DM996, DM431, DM472)  X
- MRI findings (severity of central stenosis)  X

*Primary endpoint; NRS, Numerical Rating Scale; ZCQ, Zurich Claudication Questionnaire; ODI, Oswestry Disability Index; EQ VAS, EuroQoL visual analogue scale; GSE, General Self-Efficacy Scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; MRI, magnetic resonance imaging

**Interventions**

**Surgical management (exposed)**

Patients receiving surgical treatment undergo various types of posterior decompressive surgery. Most common are decompression only (i.e. laminectomy or microdecompression) and decompression plus arthrodesis [43]. Surgical procedure is determined solely by the surgeon and is recorded in the National Patient Register [26].

**Non-surgical management (unexposed)**

Patients managing lumbar spinal stenosis non-surgically are either referred to rehabilitation at a primary health care centre or referred back to their general practitioner for treatment. Treatment may include physiotherapy, chiropractic treatment, lifestyle changes, and/or pain management. Post-surgical patients may also be referred to rehabilitation at a primary health care centre. Use of health care services in primary care is recorded in the National Health Service Register [44], while analgesic medicine is available through the National Prescription Registry [45].

**Patient and public involvement**

This study follows the European League Against Rheumatism (EULAR) recommendations for the inclusion of patient research partners in scientific projects [46]. It is designed with assistance from three Danish patient representatives, Anna Karen Guldager Rüsz, Tove Theilmann Petersen and Peter Christian Christensen. All are diagnosed with lumbar spinal stenosis and were selected in connection with routine care and participation in a multidisciplinary rehabilitation programme for patients with lumbar spinal stenosis. They have participated in discussions about the relevance and purpose of the study and will contribute with comments on the patient information about the study findings.
Choice of outcome measures was discussed with the patients after selection in collaboration with health care professionals with extensive clinical experience in diagnosing, goal setting, decision-making, and treating patients with lumbar spinal stenosis and including patient preferences into this process.

A lay summary of the study results will be disseminated through patient groups and online fora to raise awareness of the study and future research areas.

**Statistical analyses**

We anticipate that over 12 months, the SpineData registry will collect information on 2500–3000 baseline episodes for consenting patients over 60 years with low back pain, of which 300 patients are expected to undergo surgery for lumbar spinal stenosis [47]. Assuming equal distribution of patients treated surgically and non-surgically after 1 year, we guesstimate to enrol 600 patients to the lumbar spinal stenosis cohort.

To determine if this cohort size will be sufficient to achieve $\geq80\%$ probability of detecting a statistically significant difference in primary outcome between groups, an *a priori* power analysis was performed.

An enrolment flow and distribution of 600 patients in a balanced design (Figure 2) will have a power of 0.956 for a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 ($p \leq 0.05$), assuming a common standard deviation of 1 point, to detect a mean difference of 0.3 points on the physical function scale.

With the same assumptions, in case of missing data, a balanced design with total sample size of 400 will have a power of 0.849 to detect a mean difference of 0.3 points on the physical function scale.

Even if we are to test for equivalence between surgical and non-surgical treatment, a total sample size of 400 in a balanced design would yield a power of 0.999 for two one-sided tests (TOST) for additive equivalence of two-sample normal means with bounds -0.25 and 0.25 for the mean difference and a significance level of 0.05 ($p \leq 0.05$), assuming a mean difference of 0 points and a common standard deviation of 0.5 points on the physical function scale.

Following recommendations for the development of a multivariable prognostic model of 50 events for the first covariate and adding 10–20 events required for each prognostic variable [48], we would be able to perform a multivariable analysis for potential prognostic factors for outcome with approximately 30 variables in a cohort of 600 patients.

Patient characteristics will be summarised using descriptive statistics, i.e. as means with standard deviations (or medians with interquartile range) and percentages. Variables and outcome data will be compared between patients who undergo surgery for lumbar spinal stenosis (exposed)
and patients who have non-surgical management (unexposed). Data will be analysed in analogy to a 
randomised trial [49] while realising, however, that this comparative effectiveness study with 
repeated measures is not randomly assigning individuals to treatment groups.

The crude statistical model will include two fixed effect factors of group and time and the 
interaction between them. This model will aim to describe the longitudinal progress (trajectories) 
for the two groups and subsequently adjust for potentially confounding variables as a consequence 
of patients not being randomly assigned to the two groups (adjusted model). Random effects result 
from variation between and within participants; anticipating that measures on the same participant 
at different times are correlated, and that measures taken close together in time are more highly 
correlated than measures taken far apart. Observations on different participants are assumed to be 
independent. In the statistical analyses, the following ‘candidate confounding variables’ will be 
considered for statistical adjustment: age, level of education, socioeconomic classification, BMI, 
comorbidity, use of primary health care services, prior hospital admissions, and use of prescriptive 
analgesic medicine.

One of the primary distinguishing features of analysis of repeated measures data is the need to 
accommodate the covariation of the measures on the same sampling unit. For the choice of 
covariance structure, we will utilise graphical techniques, numerical comparisons of covariance 
estimates, and indices of goodness-of-fit. After the covariance is satisfactorily modelled, the 
estimated covariance matrix is used to compute generalised least squares estimates of fixed effects 
of treatments and time.

The statistical model will also compare the study population with those withdrawing or 
crossing over to surgery. Multivariable analyses will be applied to derive models adjusting for 
multiple factors. For the purpose of the prespecified analyses, we will consider the ‘data as 
available’ to constitute the primary analysis population. As indicated below, this cohort of observed 
patients will allow patients to ‘change group’ between baseline and the 12-month assessment and 
thus violate the intention-to-treat principle.

Missing data

Missing data can threaten the validity of longitudinal clinical studies. In the absence of an analytic 
approach that can ensure unbiased estimates of treatment effects with missing data, we will aim to 
minimise the amount of missing data.

We will distinguish between treatment discontinuation (i.e. switching between groups) and 
missing outcome data [50]. Data collection is often stopped after treatment discontinuation, but we 
will attempt to continue recording outcome data on individuals who discontinue/switch from the 
initial treatment group or who miss clinic visits. While missing outcome data from individuals who
continue treatment but are lost to follow-up is a common cause of missing data [50], group switching is better viewed as a form of non-compliance and will be treated using ideas from the causal literature on non-compliance [51].

We consider methods of analysis that are model-based to be superior to available-case, complete-case analysis, or single-imputation methods (e.g. the last observation carried forward). As the proportion of missing data may raise questions about the validity of preferred methods such as model-based imputation, we will perform protocolised sensitivity analyses to determine whether the conclusions are sensitive to assumptions about the reasons for missing data.

Analysis populations
The full analysis set is as close as possible to the ideal population implied by the intention-to-treat principle. However missing data within participants can present serious problems depending on the amount, cause, and pattern of missing data, particularly in a non-randomised study design. The ‘as observed population’, allowing for switch between groups, will be compared with two alternative populations, (i) the intention-to-treat population in which data collected for the individual patient stay in the initial group and (ii) the per-protocol population in which only those without ‘protocol violations’ will be included; see below for definitions.

*As-observed population (available-case analysis)*: This is based on the ‘full analysis set’, being all the data available at baseline and no replacement for missing data, where patients can legitimately change group according to what is observed, i.e. patients can end up with [i] only surgery, [ii] only non-surgical management, or [iii] a secondary switch to accept surgery.

*Intention-to-treat population*: The underlying principle is that the effect of a treatment policy, such as non-surgical management, can be best assessed by basing the analysis on the intention to treat an individual, hence the planned treatment regimen rather than the actual treatment given. Patients initially allocated to a specific treatment group should thus be followed up, assessed, and analysed as members of that group irrespective of their compliance to the planned course of treatment. Initial non-surgical patients thus remain in that group even if they subsequently have surgery, while initial surgical patients remain in that group even if they use post-surgical rehabilitation.

*Per-protocol population*: Here, the analysis is restricted to the subset of patients who sufficiently comply with the protocol that their data are likely to exhibit the effects of treatment. The per-protocol non-surgical population will thus include all patients in the intention-to-treat population but will exclude those crossing over from non-surgical management to surgery. The per-protocol surgical population will include all patients in the intention-to-treat population but will exclude patients having surgery less than 3 months prior to completing the 12-month follow-up.
Pain and physical impairment are expected to increase immediately after surgery, and patients undergoing surgery for lumbar spinal stenosis at the Spine Centre of Southern Denmark are advised to restrict their activities in a post-surgical recovery period of up to 12 weeks. Patient-reported outcome recorded during this period is thus assumed to be less relevant for comparison to non-surgical patients.

The analyses will be performed using STATA (version 15.1, StataCorp LLC, College Station, Texas, USA) and in collaboration with a statistical expert.

ETHICS AND DISSEMINATION

The study will be performed according to the Declaration of Helsinki [52], the European Code of Conduct for Research Integrity [53], and the Danish Code of Conduct for Research Integrity [54]. A review by the Regional Committees on Health Research Ethics for Southern Denmark concluded that ethical approval was not required for this study according to the Danish Act on Research Ethics Review of Health Research Projects (S-20172000-200) [55]. The study has been notified to the Danish Data Protection Agency [56] (17/30636), and permission to extract data from hospital records will be obtained from the Danish Patient Safety Authority [57]. Consent to use patient-reported information from the SpineData registry is obtained electronically prior to patients completing the questionnaires. Patients who do not consent will not be included.

Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [58] and Prognosis Research Strategy (PROGRESS) [59] statements. Potential sources of bias will be addressed using Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) [49].

DISCUSSION

This article presents a protocol for an observational study designed to investigate the course of treatment by comparing the effectiveness of surgical and non-surgical management in patients with lumbar spinal stenosis and identifying prognostic factors for outcome. Prospectively registered data on health and social variables and patient-reported outcome are collected from national registers, the SpineData clinical registry of people with chronic back pain, and hospital medical records.

The main limitation of this study is that analyses are not based on randomised treatment assignments, meaning that selection bias is a concern. Patient characteristics not accounted for in this study are likely to influence the decision whether to choose surgery or not. The study would thus benefit from patient groups being more similar with only the intervention differing between the groups.
We aim to strengthen the study results by collecting data prospectively, by having a large sample size (that is ‘guesstimated’ from assumptions of expected patient numbers and their distribution across treatment groups), and by linking patient-reported outcome to data from national registers. We are aware that loss to follow-up could be a problem. Data from the clinical SpineData registry may only be 50% at 6 months and 35% at 12 months, and the proportion of MRI descriptions available in hospital medical records is unknown. To minimise missing data, an independent administrative assistant will send out a reminder, including a paper version of the questionnaires, to patients who do not respond to the 12-month follow-up.

While we do not know the exact treatment modalities in the non-surgical group, we are not comparing outcome of surgery to any specific non-surgical treatment.

This study will assess outcome from non-surgical management and will provide knowledge about factors that can predict outcome in surgical and non-surgical management of lumbar spinal stenosis. This should help clinicians in guiding patients when choosing surgical or non-surgical treatment for lumbar spinal stenosis, and researchers in selecting variables of interest in future randomised controlled trials comparing the effect of the two management options.
LEGENDS

Figure 1 Study flow diagram with enrolment and follow-up
Figure 2 Expected distribution of enrolled patients
Table 1 Data collected, including primary outcome

ACKNOWLEDGEMENTS

The authors wish to thank patient research partners Anna Karen Guldager Rüsz, Peter Christian Christensen, and Tove Theilmann Petersen for their help in this study. The authors thank Claire Gudex, assistant professor at the Department of Clinical Research, University of Southern Denmark for proofreading of the final draft.

AUTHOR CONTRIBUTIONS

HAB and BSC conceived the study. All authors participated in the study design and the preliminary analysis plan. HAB constructed the first draft of the manuscript. All authors contributed to writing the manuscript. TM contributed substantially to writing the section on outcome measures. RC contributed substantially to the power analysis calculations and in writing the statistical analyses section. BSC contributed substantially to writing the introduction and the section on data collection. All authors participated in critical scrutinising and revision of the manuscript and approved the final version.

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COMPETING INTERESTS

Thomas Maribo and Berit Schiøttz-Christensen have nothing to disclose.

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Sports Science and Clinical Biomechanics, University of Southern Denmark), non-financial support from Expert testimony, grants from Grants/grants pending (Axellus A/S, AbbVie, Cambridge Weight Plan, Janssen, MSD, Mundipharma, Novartis, and Roche), grants from Payment for lectures including service on speakers bureaus (Abbott, Amgen, Axellus, Bayer HealthCare Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Cambridge Weight Plan, Ipsen, Janssen, Laboratoires Expanscience, MSD, Mundipharma, Norpharma, Novartis, Pfizer, Roche, Rottapharm-Madaus, Sobi, and Wyeth), grants from Payment for manuscript preparation (Axellus, Bristol-Myers Squibb, and Cambridge Weight Plan, Aleris-Hamlet (via Norpharma)), non-financial support from Patents (planned, pending or issued), non-financial support from Royalties, grants from Payment for development of educational presentations (Bristol-Myers Squibb, MSD, Pfizer), non-financial support from Stock/stock options, grants from Travel/accommodations/meeting expenses unrelated to activities listed (Abbott, AbbVie, Axellus, Biogen, Bristol-Myers Squibb, Cambridge Weight Plan, Celgene, Laboratoires Expanscience, Norpharma, Novartis, Pfizer, Roche, Rottapharm-Madaus, and Wyeth), non-financial support from Other (err on the side of full disclosure), outside the submitted work; and is involved in many health-care initiatives and research that could benefit from wide uptake of this publication (including Cochrane, OMERACT, IDEOM, RADS, and the GRADE Working Group). Musculoskeletal Statistics Unit, The Parker Institute is grateful for the financial support received from public and private foundations, companies and private individuals over the years. The Parker Institute is supported by a core grant from the Oak Foundation; The Oak Foundation is a group of philanthropic organisations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world.


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doi:10.1097/01.brs.0000231727.88477.da


doi:10.1097/BRS.0b013e3182541955


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28 Tomkins-Lane CC, Battié MC. Validity and reproducibility of self-report measures of walking capacity in lumbar spinal stenosis. Spine 2010;35:2097–102. doi:10.1097/BRS.0b013e3181f5e13b


30 Tuli SK, Yerby SA, Katz JN. Methodological approaches to developing criteria for improvement in lumbar spinal stenosis surgery. Spine 2006;31:1276–80. doi:10.1097/01.brs.0000217615.20018.6c


52 WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-


Figure 1 Study flow diagram with enrolment and follow-up
Figure 2 Expected distribution of enrolled patients
STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item #</th>
<th>Recommendation</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>2</td>
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<tr>
<td>Introduction</td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>4</td>
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<tr>
<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td>4</td>
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<tr>
<td>Methods</td>
<td></td>
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<tr>
<td>Study design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>4</td>
</tr>
<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>4</td>
</tr>
<tr>
<td>Participants</td>
<td>6</td>
<td>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
<td>5</td>
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<td>(b) For matched studies, give matching criteria and number of exposed and unexposed</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Variables</td>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td>6</td>
</tr>
<tr>
<td>Data sources/</td>
<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td>7</td>
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<tr>
<td>measurement</td>
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<tr>
<td>Bias</td>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
<td>13</td>
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<tr>
<td>Study size</td>
<td>10</td>
<td>Explain how the study size was arrived at</td>
<td>9</td>
</tr>
<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>10 - 12</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
<td>10 - 12</td>
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<td>(b) Describe any methods used to examine subgroups and interactions</td>
<td>10 - 12</td>
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<td>(c) Explain how missing data were addressed</td>
<td>11, 13</td>
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<td>(d) If applicable, explain how loss to follow-up was addressed</td>
<td>11</td>
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<td>(e) Describe any sensitivity analyses</td>
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</table>

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<table>
<thead>
<tr>
<th><strong>Participants</strong></th>
<th>13*</th>
<th>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</th>
<th>No results yet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>(b) Give reasons for non-participation at each stage</td>
<td>No results yet</td>
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<td>(c) Consider use of a flow diagram</td>
<td>No results yet</td>
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<tr>
<td><strong>Descriptive data</strong></td>
<td>14*</td>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
<td>No results yet</td>
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<td>(b) Indicate number of participants with missing data for each variable of interest</td>
<td>No results yet</td>
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<td></td>
<td>(c) Summarise follow-up time (eg, average and total amount)</td>
<td>No results yet</td>
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<tr>
<td><strong>Outcome data</strong></td>
<td>15*</td>
<td>Report numbers of outcome events or summary measures over time</td>
<td>No results yet</td>
</tr>
<tr>
<td><strong>Main results</strong></td>
<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</td>
<td>No results yet</td>
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<td>(b) Report category boundaries when continuous variables were categorized</td>
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<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
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<tr>
<td><strong>Other analyses</strong></td>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</td>
<td>No results yet</td>
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<tr>
<td><strong>Discussion</strong></td>
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<td>No results yet</td>
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<tr>
<td><strong>Key results</strong></td>
<td>18</td>
<td>Summarise key results with reference to study objectives</td>
<td>No results yet</td>
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<tr>
<td><strong>Limitations</strong></td>
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<td>No results yet</td>
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<tr>
<td><strong>Interpretation</strong></td>
<td>20</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
<td>13</td>
</tr>
<tr>
<td><strong>Generalisability</strong></td>
<td>21</td>
<td>Discuss the generalisability (external validity) of the study results</td>
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<tr>
<td><strong>Other information</strong></td>
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<td>No results yet</td>
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<tr>
<td><strong>Funding</strong></td>
<td>22</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
<td>14</td>
</tr>
</tbody>
</table>

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.