BMJ Open

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024752
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2018
Complete List of Authors:	Chen, Lingxiao; University of Sydney, Health Sciences Ferreira, Paulo; University of Sydney, Faculty of Health Science Beckenkamp, Paula; University of Sydney, Health Sciences Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research,
Keywords:	meta-analysis, SURGERY, degenerative lumbar spinal stenosis

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Lingxiao Chen[1], Paulo H Ferreira[1], Paula R Beckenkamp[1], Manuela L Ferreira[2]

[1]Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141.
[2]Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

Corresponding author:
Lingxiao Chen
Address: Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141.
Telephone: +61 466 965 326
Email: lche4036@uni.sydney.edu.au

ABSTRACT

Introduction

Surgical and invasive procedures are widely used in adults with degenerative lumbar spinal stenosis when conservative treatments fail. However, little is known about the comparative efficacy and safety of these interventions. To address this, we will perform a network meta-analysis (NMA) and systematic review to compare the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

Methods and analysis

We will include randomised controlled trials (for efficacy and safety outcomes) and non-randomised controlled studies (for safety outcomes) assessing surgical and invasive treatments for adults with degenerative lumbar spinal stenosis. For efficacy, our primary outcome will be physical function. Secondary outcomes will include pain intensity, health related quality of life, global impression of recovery, work absenteeism and mobility. For safety, our primary outcome will be all-cause mortality. Secondary outcomes will include adverse events (number of events or number of people with an event) and treatment withdrawal due to adverse effect. Two reviewers will independently select studies, extract data and assess the risk of bias of included studies. Random-effects NMA will be performed to combine all the evidence under the frequentist framework and the ranking results will be presented through the surface under the cumulative ranking curve and mean rank. All analyses will be performed in Stata and R.

Ethics and dissemination

No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number

CRD42018094180

Strengths and limitations of this study

- This is the first network meta-analysis to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.
- The main strengths are that only randomised controlled trials (RCT) will be included for the efficacy outcomes (physical function, pain intensity, health-related quality of life, global impression of recovery, work absenteeism and mobility), and RCT and non-randomised studies with a control group will be included for safety outcomes (all-cause mortality, adverse effect and treatment withdrawal due to adverse effect).
- Additional strength is that informative missingness difference of means (IMDoM) for continuous outcomes and informative missing odds ratios (IMOR) for dichotomous outcomes will be used to deal with the missing data.
- The main limitation will be the limited data from lower socioeconomic countries considering the high cost of the surgical and invasive treatments.

INTRODUCTION

Degenerative lumbar spinal canal stenosis is characterized by decreased spinal canal diameter due to structural changes of the spine (e.g. facet joints, ligaments) due to ageing. Typically, patients will present with neurogenic claudication, defined as pain, numbness and/or fatigue in the lower limbs that is worsened during walking and standing, and alleviated with forward bending or sitting (1, 2). In the United States, the prevalence of degenerative lumbar spinal stenosis in the general population can be as high as 22.5% for relative stenosis (i.e. ≤12 mm canal diameter), and 7.3% for absolute stenosis (i.e. ≤10 mm canal diameter) (3). These figures increase drastically with age, reaching 47.2% and 19.4%, respectively, for those 60 years of age or older (3).

Most guidelines will recommend a course of conservative care, including the North American Spine Society guidelines, for patients with degenerative lumbar spinal stenosis (2). However, when conservative treatments fail, surgical and invasive options are indicated (2, 4, 5). Surgical decompression (including laminectomies or laminotomies), with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections are commonly used in the management of spinal stenosis (6-11). However, the evidence supporting the superiority of one option over the other is still unclear for most (7, 12, 13). For instance, past meta-analyses have shown that interspinous spacers is superior to X-STOP interspinous spacer in improving axial pain severity and Zurich Claudication Questionnaire patient satisfaction score; whereas the addition of spinal fusion to surgical decompression does not add any benefit to surgical decompression alone (14, 15). Moreover, existing meta-analyses use pairwise analytical approaches, and therefore can only provide results for the comparison of two interventions at any one time (4, 11, 14-28). A network meta-analysis (NMA) is the best design and analytical approach to compare and rank multiple interventions simultaneously, based on their relative estimate effects in each outcome (29). NMA have been used in similar fields, including sciatica, lumbar disc herniation and osteoarthritis, but, to date, no NMA has been conducted to establish the comparative effectiveness and safety of invasive approaches for degenerative lumbar spinal canal stenosis (30-32). As such, our aim is to perform a NMA and systematic review to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

METHODS AND ANALYSIS

Criteria for considering studies for this review

The protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (33). Any changes made to this protocol will be updated in the PROSPERO registration.

Types of participants

We will include studies that recruited participants who are 40 years of age or older, with a diagnosis of degenerative lumbar spinal stenosis. We will exclude studies on patients with malignancy, trauma, vertebral fracture, infection, and inflammatory disorders. For studies including degenerative lumbar spinal stenosis and associated spondylolisthesis, only those of participants with Meyerding grade I spondylolisthesis will be included. Studies including mixed populations will only be included if the data for patients with degenerative lumbar spinal stenosis can be extracted separately or if at least 80% of the patients are diagnosed with degenerative lumbar spinal stenosis.

Types of interventions

Studies comparing any surgical or invasive intervention for adults with degenerative lumbar spinal stenosis will be included. For example, surgical decompression, including laminectomies or laminotomies, with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections. The comparison group could be no treatment, usual care, sham operation, another active option or a combination of approaches.

Outcome measures

The outcome data will grouped into short-term (<=6 months), mid-term (6 to 12 months), and long-term (>=12 months) follow-up assessment (34). For studies which report outcomes in multiple time points, data closest to the 6 and 12-month follow-up time will be included in the main analyses. For outcomes in other time points, subgroup analyses will be performed.

Primary outcomes

1. Physical function, commonly measured by Oswestry disability index (ODI), Roland Morris disability questionnaire (RMDQ), Patient Specific Function Scale (PSFS), and core outcome measures index (COMI) (34). Other rating scales will be included if they have been proposed in peer-reviewed journals.

2. All-cause mortality, measured by the percentage of patients who died following randomisation.

Secondary outcomes

1. Pain intensity, commonly measured by numeric rating scale (NRS) and the visual analogue scale (VAS) (35, 36). Other rating scales will also be included if they have been proposed in peer-reviewed journals. Pain intensity will be categorised and analysed according to the following three groups: back pain, leg pain and overall pain.
2. Health related quality of life (HRQOL), commonly measured by 36-Item Short Form Survey (SF-36), EQ-5D, Nottingham health profile (NHP) and 12-Item Short Form Survey (SF-12) (34). SF-36, NHP and SF-12 could be mapped into EQ-5D (37). As above, other tools will also be included if they have been proposed in peer-reviewed journals.
3. Global impression of recovery, measured by the percentage of the patients satisfied with their recovery.
4. Work absenteeism, measured by the number of days of sick leave.
5. Mobility, measured by walking distance.
6. Adverse event, measured by the number of participants with an adverse event, or number of adverse events per group. Adverse events could include nerve injury, dural tear, vascular injury, deep infection, and pulmonary embolus.
7. Treatment withdrawal due to adverse effect, measured by the percentage of patients who drop out due to adverse effect.

Types of studies

For the efficacy outcomes (physical function, pain intensity, HRQOL, global impression of recovery, work absenteeism and mobility), only randomised controlled trials (RCT) will be included. For safety outcomes (all-cause mortality, adverse effect and treatment withdrawal due to adverse effect), RCT and non-randomised studies with a control group will be included. For cross-over studies, only data before wash-out period will be used. For cluster randomized trials, we will extracted data which is adjusted for clustering. If these data are unavailable, we will extract original data and adjust them for clustering (38, 39).

Search strategy

Electronic searches

The following databases will be searched for published studies: AMED, CINAHL, EMBASE, the Cochrane Library and MEDLINE (including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE). Ongoing studies and grey literatures will be searched from WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and the US National Institutes of Health (https://clinicaltrials.gov/). The search strategy for MEDLINE is provided as a supplemental material.

Reference lists and other sources

Reference lists of all included studies, relevant systematic reviews and meta-analyses, and guidelines will be screened for eligible additional studies to be included.

Identification and selection of studies

Two reviewers will independently screen titles and abstracts of the articles from the search. Before formal screening of titles, we will perform an intra-tester agreement test (kappa test) by randomly selecting 50 citations (through random number table) to be reviewed by two independent reviewers (38). An agreement of 80% or more will be considered acceptable. If we do not achieve the percentage of the agreement, we will randomly select another 50 citations subsequently until 80% percentage of agreement is reached. Any disagreement will be solved by discussion and if necessary, a third reviewer will arbitrate the decision. When studies fail to provide the necessary data, the authors will be contacted and further information requested.

Data extraction

Two reviewers will independently extract data from the included studies using a standardised data extraction form. Similarly, a pilot test will be performed before the formal extraction. We will randomly select 5 articles using a random number table to confirm we have enough inter-rater agreement (at least 80%). Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. The following data will be extracted from each included study based on recommendations from previous studies (34, 40).

1. Study characteristics, such as year of study publication, first author, journal, sample size, study funding and location.
2. Patient characteristics, such as age, gender, including and excluding criteria, diagnostic

criteria, type of lumbar spinal stenosis, comorbidities, duration of symptoms and previous treatment.

3. Intervention characteristics.
4. Primary and secondary outcomes.

Measurement of treatment effect

Relative treatment effects

1. Continuous outcomes: If the studies use the same rating scale, we will use mean difference (MD) with its 95% confidence interval (CI). If different rating scales are used, standardised mean difference (SMD) with its 95% CI will be used.
2. Dichotomous outcomes: odds ratio (OR) with its 95% CI will be used.
3. For all-cause mortality, the number needed to harm (NNM) will be calculated (38).

Relative treatment ranking

The surface under the cumulative ranking curve (SUCRA) and mean ranks will be used to rank each intervention for each outcome (41). Rank-heat plot will be used to show the ranking results of each outcome for each intervention (42).

Dealing with missing outcome data and missing statistics

For continuous outcomes, if the study only reports standard error (SE), P value or CI, we will convert them into standard deviation (SD) (38). If the study reports median and interquartile range (IQR), we will calculate SD by dividing the IQR by 1.35 and considering the median equivalent to the mean (38). If relevant information is provided in figures, we will extract the data from the graphs. If data cannot be obtained, we will contact the authors. If we do not obtain relevant data, informative missingness difference of means (IMDoM) will be used as one kind of sensitivity analysis to explore the uncertainty of our results under the missing at random assumption (43).

For dichotomous outcomes, firstly, we will try to contact the authors to obtain data. In the absence of a response or of relevant data, informative missing odds ratios (IMOR) for dichotomous outcomes will be used to explore the uncertainty of our results under the missing at random assumption (43).

Risk of bias assessment

Two reviewers will independently assess the risk of bias of the included studies. Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. We will contact the authors to obtain further information if the third reviewer think it is necessary.

For RCT, the risk of bias tool based on Cochrane Handbook for systematic reviews for interventions and the recommendation from Cochrane Back and Neck Group will be used (38, 40). The tool has 13 items, which is: 1. Random sequence generation; 2. Allocation concealment; 3. Blinding of participants; 4. Blinding of personnel/ care providers; 5. Blinding of outcome assessor; 6. Incomplete outcome data; 7. Selective Reporting; 8. Group similarity at baseline; 9. Co-interventions 10. Compliance; 11. Intention-to-treat-analysis; 12. Timing of outcome assessments; 13. Other Bias. For the item 13, we will mainly focus on whether the study received commercial funding. For efficacy outcomes, only studies with a low risk of bias in the item "Random sequence generation" will be included. For each item, we will rate it as low risk of bias, unclear risk of bias or high risk of bias. If 7 or more items are rated as low risk of bias and the study has no serious flaws, we will rate the study as low risk of bias (44, 45).

For non-randomised trials, the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool will be used (46). The tool has seven domains: 1. Bias due to confounding; 2. Bias in selection of participants into the study; 3. Bias in classification of interventions; 4. Bias due to deviations from intended interventions; 5. Bias due to missing data; 6. Bias in measurement of outcomes; 7. Bias in selection of the reported result. For each domain, we could rate it as one of the following: Low risk of bias, Moderate risk of bias, Serious risk of bias, Critical risk of bias and No information, as well as the overall risk of bias.

Data analysis

The characteristics of study, patient and intervention will be summarized descriptively. We will make a narrative review for some comparisons if insufficient data is provided. Network plot will be drawn to descript the available interventions. The size of the node reflects the number of patients in each intervention. The breadth of the edge shows the number of comparisons. For efficacy outcomes, pair-wise and network meta-analysis will be performed for data from RCT. For safety outcomes, pair-wise and network meta-analysis will be performed for data from RCT and NRS, separately.

Pairwise meta-analyses

We will perform traditional pair-wise meta-analyses through random-effect model for every direct comparison. In some subgroups, we will also perform pair-wise meta-analyses if network meta-analyses could not be performed. The heterogeneity will be assessed by I-square and tau-square (38).

Assessment of the transitivity assumption

The potential baseline effect modifiers will be assessed to confirm they are similar among different comparisons before we perform network meta-analyses (29). If any difference is found, we will perform meta-regression to explore the influence on the results.

Network meta-analyses

Random-effect network meta-analyses under the frequentist framework will be performed to combine both direct and indirect comparisons (47, 48). The heterogeneity parameter is assumed the same for each network (49). Prediction interval plot will be drawn to reflect the uncertainly of the results in a future study (50).

Assessment of inconsistency

Bucher method as a local method and design-by-treatment interaction model as a global method will be used (51, 52). If any inconsistency is found, node-splitting method will be used to explore the original of the inconsistency (53).

Exploring sources of heterogeneity or inconsistency with subgroup analyses and meta-regression

For two primary outcomes (physical function and all-cause mortality), subgroup analyses and meta-regressions will be performed to assess the influence of the potential effect modifiers. Subgroup analyses will be performed as follows: 1. Single level spinal stenosis versus multiple levels; 2. Duration of follow-up (e.g., 6 months, 1 year, 2 years and 5 years); 3. Patients with versus patients without degenerative spondylolisthesis; 4. Type of disease: central, foraminal or lateral. Meta-regression will be performed as follows: 1. Age; 2. Percentage of the male; 3. Sample size; 4. Baseline pain intensity; 5. Baseline physical function.; 6. Percentage of the smoker; 7. Body mass index (BMI).

Sensitivity analyses

For two primary outcomes (physical function and all-cause mortality), sensitivity analyses will be performed as follows: 1. only studies with low risk of bias; 2. studies with imputed data through either IMDoM or IMOR; 3. Studies without a non-active comparison group; 4. Studies without receiving commercial funding; 5. Studies without data from grey literatures.

Publication bias

Comparison-adjusted funnel plot will be used to test the publication bias if the number of included studies is larger than 10 (41). As described above, meta-regression procedures using sample size and effect estimates will be performed to detect the small-study effect (54).

Grading the evidence

The Grading of Recommendations, Assessment, Development and Evaluations framework will be used to evaluate the quality of evidence (55).

Statistical software

All analyses will be performed in Stata (StataCrop. 2017. Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LP) and R (Version 3.4.3. R Core Team. 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Patient and Public Involvement

Patients will not be involved.

ETHICS AND DISSEMINATION

This research does not require ethics approval because it uses data form literatures. We will publish the research in a peer-reviewed journal after completing it.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. The Lancet. 2018 Mar 20.

2. Kreiner DS, Shaffer WO, Baisden JL, Gilbert TJ, Summers JT, Toton JF, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). The spine journal : official journal of the North American Spine

Society. 2013;13(7):734-43.

3. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, et al. Spinal stenosis prevalence and association with symptoms: the Framingham Study. The spine journal : official journal of the North American Spine Society. 2009;9(7):545-50.

4. Machado GC, Ferreira PH, Yoo RI, Harris IA, Pinheiro MB, Koes BW, et al. Surgical options for lumbar spinal stenosis. The Cochrane database of systematic reviews. 2016;11:Cd012421.

5. May S, Comer C. Is surgery more effective than non-surgical treatment for spinal stenosis, and which non-surgical treatment is more effective? A systematic review. Physiotherapy. 2013;99(1):12-20.

6. Benyamin RM, Staats PS, Mi DASEI. MILD(R) Is an Effective Treatment for Lumbar Spinal Stenosis with Neurogenic Claudication: MiDAS ENCORE Randomized Controlled Trial. Pain physician. 2016;19(4):229-42.

7. Deyo RA, Martin BI, Ching A, Tosteson AN, Jarvik JG, Kreuter W, et al. Interspinous spacers compared with decompression or fusion for lumbar stenosis: complications and repeat operations in the Medicare population. Spine. 2013;38(10):865-72.

8. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. Jama. 2010;303(13):1259-65.

9. Elsheikh NA, Amr YM. Effect of Adding Calcitonin to Translaminar Epidural Steroid in Degenerative Lumbar Spinal Canal Stenosis. Pain physician. 2016;19(3):139-46.

10. Jansson KA, Blomqvist P, Granath F, Nemeth G. Spinal stenosis surgery in Sweden 1987-1999. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2003;12(5):535-41.

11. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural Injections for Lumbar Radiculopathy and Spinal Stenosis: A Comparative Systematic Review and Meta-Analysis. Pain physician. 2016;19(3):E365-410.

12. Forsth P, Olafsson G, Carlsson T, Frost A, Borgstrom F, Fritzell P, et al. A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. The New England journal of medicine. 2016;374(15):1413-23.

13. Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, et al. Laminectomy plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. The New England journal of medicine. 2016;374(15):1424-34.

14. Shen J, Xu S, Xu S, Ye S, Hao J. Fusion or Not for Degenerative Lumbar Spinal Stenosis: A Meta-Analysis and Systematic Review. Pain physician. 2018;21(1):1-8.

15. Zhao H, Duan LJ, Gao YS, Yang YD, Zhao DY, Tang XS, et al. Comparison of two FDA-approved interspinous spacers for treatment of lumbar spinal stenosis: Superion versus X-STOP-a meta-analysis from five randomized controlled trial studies. Journal of orthopaedic surgery and research. 2018;13(1):42.

16. Zhao XW, Ma JX, Ma XL, Li F, He WW, Jiang X, et al. Interspinous process devices(IPD) alone versus decompression surgery for lumbar spinal stenosis(LSS): A systematic review and meta-analysis of randomized controlled trials. International journal of surgery (London, England). 2017;39:57-64.

17. Yavin D, Casha S, Wiebe S, Feasby TE, Clark C, Isaacs A, et al. Lumbar Fusion for Degenerative Disease: A Systematic Review and Meta-Analysis. Neurosurgery. 2017;80(5):701-15.

18. Li AM, Li X, Yang Z. Decompression and coflex interlaminar stabilisation compared with conventional surgical procedures for lumbar spinal stenosis: A systematic review and meta-analysis. International journal of surgery (London, England). 2017;40:60-7.

19. Lee CH, Chung CK, Sohn MJ, Kim CH. Short Limited Fusion Versus Long Fusion With Deformity Correction for Spinal Stenosis With Balanced De Novo Degenerative Lumbar Scoliosis: A Meta-analysis of Direct Comparative Studies. Spine. 2017;42(19):E1126-e32.

20. Chang W, Yuwen P, Zhu Y, Wei N, Feng C, Zhang Y, et al. Effectiveness of decompression alone versus decompression plus fusion for lumbar spinal stenosis: a systematic review and meta-analysis. Archives of orthopaedic and trauma surgery. 2017;137(5):637-50.

21. Phan K, Rao PJ, Ball JR, Mobbs RJ. Interspinous process spacers versus traditional decompression for lumbar spinal stenosis: systematic review and meta-analysis. Journal of spine surgery (Hong Kong). 2016;2(1):31-40.

22. Phan K, Mobbs RJ. Minimally Invasive Versus Open Laminectomy for Lumbar Stenosis: A Systematic Review and Meta-Analysis. Spine. 2016;41(2):E91-e100.

23. Overdevest GM, Jacobs W, Vleggeert-Lankamp C, Thome C, Gunzburg R, Peul W. Effectiveness of posterior decompression techniques compared with conventional laminectomy for lumbar stenosis. The Cochrane database of systematic reviews. 2015(3):Cd010036.

24. Machado GC, Ferreira PH, Harris IA, Pinheiro MB, Koes BW, van Tulder M, et al.

Effectiveness of surgery for lumbar spinal stenosis: a systematic review and meta-analysis. PloS one. 2015;10(3):e0122800.

25. Liu K, Liu P, Liu R, Wu X, Cai M. Steroid for epidural injection in spinal stenosis: a systematic review and meta-analysis. Drug design, development and therapy. 2015;9:707-16.

26. Liang L, Jiang WM, Li XF, Wang H. Effect of fusion following decompression for lumbar spinal stenosis: a meta-analysis and systematic review. International journal of clinical and experimental medicine. 2015;8(9):14615-24.

27. Lauryssen C, Jackson RJ, Baron JM, Tallarico RA, Lavelle WF, Deutsch H, et al. Stand-alone interspinous spacer versus decompressive laminectomy for treatment of lumbar spinal stenosis. Expert review of medical devices. 2015;12(6):763-9.

28. Hong P, Liu Y, Li H. Comparison of the efficacy and safety between interspinous process distraction device and open decompression surgery in treating lumbar spinal stenosis: a meta analysis. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2015;28(1):40-9.

29. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606.

30. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet (London, England). 2017;390(10090):e21-e33.

31. Feng F, Xu Q, Yan F, Xie Y, Deng Z, Hu C, et al. Comparison of 7 Surgical Interventions for Lumbar Disc Herniation: A Network Meta-analysis. Pain physician. 2017;20(6):E863-e71.

32. Guo JR, Jin XJ, Shen HC, Wang H, Zhou X, Liu XQ, et al. A Comparison of the Efficacy and Tolerability of the Treatments for Sciatica: A Network Meta-Analysis. The Annals of pharmacotherapy. 2017;51(12):1041-52.

33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1.

34. Clement RC, Welander A, Stowell C, Cha TD, Chen JL, Davies M, et al. A proposed set of metrics for standardized outcome reporting in the management of low back pain. Acta orthopaedica. 2015;86(5):523-33.

35. Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, et al.

Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine. 2011;36(21 Suppl):S54-68.

36. Jensen MP, Mardekian J, Lakshminarayanan M, Boye ME. Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. Pain. 2008;137(2):422-7.

37. Dakin H, Abel, L, Burns, R, Yang, Y. 2018. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. Health and Quality of Life Outcomes. 16:31 HERC database of mapping studies, Version 6.0 (Last updated: 17th Jan 2017). Available at: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. .

38. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane collaboration; 2011. Available from: www.handbook.cochrane.org.

39. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. The Cochrane database of systematic reviews. 2015(9):Cd011612.

40. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine. 2015;40(21):1660-73.

41. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

42. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. Journal of clinical epidemiology. 2016;76:193-9.

43. Mavridis D, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Statistics in medicine. 2015;34(5):721-41.

44. van Tulder MW, Suttorp M, Morton S, Bouter LM, Shekelle P. Empirical evidence of an association between internal validity and effect size in randomized controlled trials of low-back pain. Spine. 2009;34(16):1685-92.

45. van Tulder MW BG, Chou R, Corbin T, Deyo RA, Furlan AD, Malmivaara A, Marin T, Peul W, Schoene ML, Maher CG, Weiner BK. Cochrane Back and Neck Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2014, Issue 2. Art. No.: BACK.

46. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ

(Clinical research ed). 2016;355:i4919.

47. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):607-17.

48. White IR. Multivariate random-effects meta-analysis. Stata Journal. 2009;9(1):40-56.

49. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):618-40.

50. Bighelli I, Salanti G, Reitmeir C, Wallis S, Barbui C, Furukawa TA. Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomised controlled trials. 2018;8(3):e019280.

51. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91.

52. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research synthesis methods. 2012;3(2):98-110.

53. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):641-56.

54. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Research synthesis methods. 2012;3(2):161-76.

55. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the Quality of Evidence from a Network Meta-Analysis. PLOS ONE. 2014;9(7): e99682.

Authors' contributions

All authors conceived the study. LC drafted the manuscript. LC and PB participated in the search strategy development. PF, PB and MF assisted in protocol design and revision. All authors read and approved the final manuscript as submitted.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp spinal stenosis/
2 canal stenosis.mp.
3 (spin* adj3 stenosis).mp.
4 (lumbar adj3 stenosis).mp.
5 (lateral adj3 stenosis).mp.
6 (central adj3 stenosis).mp.
7 (foramin* adj3 stenosis).mp.
8 neurogenic claudication.mp.
9 exp radiculopathy/
10 Radiculopathy.mp.
11 radicular pain.mp.
12 lumbar radicular pain.mp.
13 exp spondylolisthesis/
14 Spondylolisthesis.mp.
15 (lumb* adj5 spondyl*).mp.
16 exp spondylosis/
17 Spondylosis.mp.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 exp general surgery/
20 Surgery.mp.
21 exp decompression, surgical/
22 decompres* surgery.mp.
23 Decompression.mp.
24 (spin* adj3 decompress*).mp.
25 exp laminectomy/
26 Laminectom*.mp.
27 Laminotom*.mp.

28 Laminoplasty.mp.
29 exp spinal fusion/
30 (spin* adj3 fusion).mp.
31 (pedicle adj3 screw).mp.
32 lumbar fusion.mp.
33 vertebrae fusion.mp.
34 vertebral fixation.mp.
35 spinal fixation.mp.
36 Spondylodesis.mp.
37 Spondylosyndesis.mp.
38 Arthrodesis.mp. or exp arthrodesis/
39 (posterolateral adj3 fusion).mp.
40 (interbody adj3 fusion).mp.
41 (anterior adj3 fusion).mp.
42 (posterior adj3 fusion).mp.
43 (transforaminal adj3 fusion).mp.
44 (transpsoas adj3 fusion).mp.
45 (facet adj3 fusion).mp.
46 (bone adj3 graft).mp.
47 (fixation adj3 spin*).mp.
48 (pedicle adj3 fusion).mp.
49 Graft.mp.
50 (cage adj3 fusion).mp.
51 (screw adj3 fusion).mp.
52 Foraminotomy.mp. or exp foraminotomy/
53 Foraminectomy.mp.
54 exp surgical procedures, minimally invasive/
55 minim* invasive.mp.
56 epidural.mp.
57 intra-articular.mp.
58 exp Anesthesia, Epidural/

59 Analgesia, Epidural/

60 exp Injections, Epidural/

61 exp Injections, Intra-Articular/

62 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63 randomized controlled trial.pt.

64 controlled clinical trial.pt.

65 randomized.ab,ti.

66 placebo.ab,ti.

67 drug therapy.fs.

68 randomly.ab,ti.

69 trial.ab,ti.

70 groups.ab,ti.

71 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70

72 (animals not (humans and animals)).sh.

73 71 not 72

74 Non-Randomized Controlled Trials as Topic/

75 ((nonrandom* or non-random* or quasi-random* or quasi-experiment*) adj (stud* or trial*)).tw.

76 (non-RCT or non-RCTs or nRCT or nRCTs).tw.

77 exp cohort studies/

78 (cohort stud* or Follow-Up Stud* or Longitudinal Stud* or Prospective Stud* or Retrospective Stud*).tw.

79 exp case-control studies/

80 case-control* stud*.tw.

81 74 or 75 or 76 or 77 or 78 or 79 or 80

82 73 or 81

83 18 and 62 and 82

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	5
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	16
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	Not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5-6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Supplementary Material
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	8-9
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	9-10
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	9

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	11

BMJ Open

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024752.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Nov-2018
Complete List of Authors:	Chen, Lingxiao; University of Sydney, Health Sciences Ferreira, Paulo; University of Sydney, Faculty of Health Science Beckenkamp, Paula; University of Sydney, Health Sciences Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research,
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice
Keywords:	meta-analysis, SURGERY, degenerative lumbar spinal stenosis

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Lingxiao Chen[1], Paulo H Ferreira[1], Paula R Beckenkamp[1], Manuela L Ferreira[2]

[1]Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141.

[2]Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

Corresponding author:

Lingxiao Chen

Address: Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141.

Telephone: +61 466 965 326

Email: lche4036@uni.sydney.edu.au

ABSTRACT

Introduction

Surgical and invasive procedures are widely used in adults with degenerative lumbar spinal stenosis when conservative treatments fail. However, little is known about the comparative efficacy and safety of these interventions. To address this, we will perform a network meta-analysis (NMA) and systematic review to compare the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

Methods and analysis

We will include randomised controlled trials assessing surgical and invasive treatments for adults with degenerative lumbar spinal stenosis. We will search AMED, CINAHL, EMBASE, the Cochrane Library and MEDLINE. Only English studies will be included and no restriction will be set for publication status. For efficacy, our primary outcome will be physical function. Secondary outcomes will include pain intensity, health related quality of life, global impression of recovery, work absenteeism and mobility. For safety, our primary outcome will be all-cause mortality. Secondary outcomes will include adverse events (number of events or number of people with an event) and treatment withdrawal due to adverse effect. Two reviewers will independently select studies, extract data and assess the risk of bias (Revised Cochrane risk-of-bias tool for randomized trials) of included studies. The quality of the evidence will be evaluated through the Grading of Recommendations Assessment, Development and Evaluation framework. Random-effects NMA will be performed to combine all the evidence under the frequentist framework and the ranking results will be presented through the surface under the cumulative ranking curve and mean rank. All analyses will be performed in Stata and R.

Ethics and dissemination

No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number

CRD42018094180

Strengths and limitations of this study

- This is the first network meta-analysis to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.
- The main strengths are that only randomised controlled trials (RCT) will be included for both efficacy outcomes (physical function, pain intensity, health-related quality of life, global impression of recovery, work absenteeism and mobility) and safety outcomes (all-cause mortality, adverse effect and treatment withdrawal due to adverse effect).
- Additional strength is that informative missingness difference of means (IMDoM) for continuous outcomes and informative missing odds ratios (IMOR) for dichotomous outcomes will be used to deal with the missing data.
- The main limitation will be the limited data from lower socioeconomic countries considering the high cost of the surgical and invasive treatments.

INTRODUCTION

Degenerative lumbar spinal canal stenosis is characterized by decreased spinal canal diameter due to structural changes of the spine (e.g. facet joints, ligaments) due to ageing. Typically, patients will present with neurogenic claudication, defined as pain, numbness and/or fatigue in the lower limbs that is worsened during walking and standing, and alleviated with forward bending or sitting (1, 2). In the United States, the prevalence of degenerative lumbar spinal stenosis in the general population can be as high as 22.5% for relative stenosis (i.e. ≤12 mm canal diameter), and 7.3% for absolute stenosis (i.e. ≤10 mm canal diameter) (3). These figures increase drastically with age, reaching 47.2% and 19.4%, respectively, for those 60 years of age or older (3).

Most guidelines will recommend a course of conservative care, including the North American Spine Society guidelines, for patients with degenerative lumbar spinal stenosis (2). However, when conservative treatments fail, surgical and invasive options are indicated (2, 4, 5). Surgical decompression (including laminectomies or laminotomies), with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections are commonly used in the management of spinal stenosis (6-11). However, the evidence supporting the superiority of one option over the other is still unclear for most (7, 12, 13). For instance, past meta-analyses have shown that Superion interspinous spacers is superior to X-STOP interspinous spacer in improving axial pain severity and ZCQ patient satisfaction score; whereas the addition of spinal fusion to surgical decompression does not add any benefit to surgical decompression alone (14, 15). Moreover, existing meta-analyses use pairwise analytical approaches, and therefore can only provide results for the comparison of two interventions at any one time (4, 11, 14-28). A network meta-analysis (NMA) is the best design and analytical approach to compare and rank multiple interventions simultaneously, based on their relative estimate effects in each outcome (29). NMA have been used in similar fields, including sciatica, lumbar disc herniation and osteoarthritis, but, to date, no NMA has been conducted to establish the comparative effectiveness and safety of invasive approaches for degenerative lumbar

spinal canal stenosis (30-32). As such, our aim is to perform a NMA and systematic review to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

METHODS AND ANALYSIS

Criteria for considering studies for this review

The protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (33). Any changes made to this protocol will be updated in the PROSPERO registration.

Types of participants

We will include studies that recruited participants who are 40 years of age or older, with a diagnosis of degenerative lumbar spinal stenosis. We will exclude studies on patients with malignancy, trauma, vertebral fracture, infection, and inflammatory disorders. For studies including degenerative lumbar spinal stenosis and associated spondylolisthesis, only those of participants with Meyerding grade I spondylolisthesis will be included. Studies including mixed populations will only be included if the data for patients with degenerative lumbar spinal stenosis can be extracted separately or if at least 80% of the patients are diagnosed with degenerative lumbar spinal stenosis.

Types of interventions

Studies comparing any surgical or invasive intervention for adults with degenerative lumbar spinal stenosis will be included. For example, surgical decompression, including laminectomies or laminotomies, with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections. The comparison group could be no treatment, usual care, sham operation, another active option or a combination of approaches. The interventions in comparison groups will be treated as different nodes. However, if we have insufficient studies to connect different interventions, we will combine no treatment and usual care into one node to make full use of the data.

Outcome measures

The outcome data will grouped into short-term (<=6 months), mid-term (6 to 12 months), and long-term (>=12 months) follow-up assessment (34). We will perform network meta-analysis in the three time points separately. For studies which report outcomes in multiple time points, data closest to the 6 and 12-month follow-up time will be included in the main analyses. For different time points in long-term follow-up assessment (e.g., 1 year, 2 years, 5 years), subgroup analyses will be performed.

Primary outcomes

1. Physical function, commonly measured by Oswestry disability index (ODI), Roland Morris disability questionnaire (RMDQ), Patient Specific Function Scale (PSFS), and core outcome measures index (COMI) (34). Other rating scales will be included if they have been proposed in peer-reviewed journals. If the study provides more than one instruments, ODI will be used as the first choice, RMDQ as the second choose and COMI as the third choice (34).
2. All-cause mortality, measured by the percentage of patients who died following randomisation.

Secondary outcomes

1. Pain intensity, commonly measured by numeric rating scale (NRS) and the visual analogue scale (VAS) (35, 36). Other rating scales will also be included if they have been proposed in peer-reviewed journals. Pain intensity will be categorised and analysed according to the following three groups: back pain, leg pain and overall pain. If the study provides more than one instruments, VAS will be used as the first choice and NRS as the second choice (34).
2. Health related quality of life (HRQOL), commonly measured by 36-Item Short Form Survey (SF-36), EQ-5D, Nottingham health profile (NHP) and 12-Item Short Form Survey (SF-12) (34). SF-36, NHP and SF-12 could be mapped into EQ-5D (37). As above, other tools will also be included if they have been proposed in peer-

reviewed journals. If the study provides more than one instruments, EQ-5D will be used as the first choice, following by SF-36, SF-12, and NHP (34).

3. Global impression of recovery, measured by the percentage of the patients satisfied with their recovery.
4. Work absenteeism, measured by the number of days of sick leave.
5. Mobility, measured by walking distance.
6. Adverse event, measured by the number of participants with an adverse event, or number of adverse events per group. Adverse events could include nerve injury, dural tear, vascular injury, deep infection, and pulmonary embolus.
7. Treatment withdrawal due to adverse effect, measured by the percentage of patients who drop out due to adverse effect.

Types of studies

Only randomised controlled trials (RCT), which includes parallel, cross-over and cluster trials, will be included. For cross-over studies, only data before wash-out period will be used. For cluster randomized trials, we will extracted data which is adjusted for clustering. If these data are unavailable, we will extract original data and adjust them for clustering (38, 39). To decrease bias, we excluded studies with a high risk of bias in the domain risk of bias arising from the randomization process (40).

Search strategy

Electronic searches

The following databases will be searched for published studies: AMED, CINAHL, EMBASE, the Cochrane Library and MEDLINE (including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE). Unpublished and ongoing studies will be searched from WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and the US National Institutes of Health (https://clinicaltrials.gov/). Only English studies will be included and no restriction will be set for publication status. The search strategy for MEDLINE is provided as a supplemental material.

Reference lists and other sources

Reference lists of all included studies, relevant systematic reviews and meta-analyses, and guidelines will be screened for eligible additional studies to be included.

Identification and selection of studies

Two reviewers will independently screen titles and abstracts of the articles from the search. Before formal screening of titles, we will perform an intra-tester agreement test (kappa test) by randomly selecting 50 citations (through random number table) to be reviewed by two independent reviewers (38). An agreement of 80% or more will be considered acceptable. If we do not achieve the percentage of the agreement, we will randomly select another 50 citations subsequently until 80% percentage of agreement is reached. Any disagreement will be solved by discussion and if necessary, a third reviewer will arbitrate the decision. When studies fail to provide the necessary data, the authors will be contacted and further information requested.

Data extraction

Two reviewers will independently extract data from the included studies using a standardised data extraction form. Similarly, a pilot test will be performed before the formal extraction. We will randomly select 5 articles using a random number table to confirm we have enough inter-rater agreement (at least 80%). Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. The following data will be extracted from each included study based on recommendations from previous studies (34, 41).

1. Study characteristics, such as year of study publication, first author, journal, sample size, study funding and location.
2. Patient characteristics, such as age, gender, including and excluding criteria, diagnostic criteria, type of lumbar spinal stenosis, comorbidities, duration of symptoms and previous treatment.
3. Intervention characteristics.

4. Primary and secondary outcomes.

Measurement of treatment effect

Relative treatment effects

1. Continuous outcomes: If the studies use the same rating scale, we will use mean difference (MD) with its 95% confidence interval (CI). If different rating scales are used, standardised mean difference (SMD) with its 95% CI will be used.
2. Dichotomous outcomes: odds ratio (OR) with its 95% CI will be used.
3. For all-cause mortality, the number needed to harm (NNM) will be calculated (38).

Relative treatment ranking

The surface under the cumulative ranking curve (SUCRA) and mean ranks will be used to rank each intervention for each outcome (42). Rank-heat plot will be used to show the ranking results of each outcome for each intervention (43).

Dealing with missing outcome data and missing statistics

For continuous outcomes, if the study only reports standard error (SE), P value or CI, we will convert them into standard deviation (SD) (38). If the study reports median and interquartile range (IQR), we will calculate SD by dividing the IQR by 1.35 and considering the median equivalent to the mean (38). If relevant information is provided in figures, we will extract the data from the graphs. If data cannot be obtained, we will contact the authors. If we do not obtain relevant data, informative missingness difference of means (IMDoM) will be used as one kind of sensitivity analysis to explore the uncertainty of our results under the missing at random assumption (44).

For dichotomous outcomes, firstly, we will try to contact the authors to obtain data. In the absence of a response or of relevant data, informative missing odds ratios (IMOR) for dichotomous outcomes will be used to explore the uncertainty of our results under the missing at random assumption (44).

Risk of bias assessment

Two reviewers will independently assess the risk of bias of the included studies. Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. We will contact the authors to obtain further information if the third reviewer think it is necessary.

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to evaluate the risk of bias of included randomized parallel-group trials (40). The tool is comprised of five domains: 1. bias arising from the randomization process; 2. bias due to deviations from intended interventions; 3. bias due to missing outcome data; 4. bias due to missing outcome data; 5. bias in selection of the reported result. Each domain includes several signaling questions which elicit information relevant to an assessment of risk of bias. The answer option for each signaling question is: Yes, probably yes, probably no, no and no information. Based on the answers of all signaling questions in one domain, we rated the domain as low risk of bias, some concerns or high risk of bias. Finally, we got the overall risk-of-bias judgement as low risk of bias, some concerns or high risk of bias considering the risk-of-bias judgement in five domains.

For cluster-randomized trials, one more domain should be considered: bias arising from identification or recruitment of individual participants within clusters. For cross-over trials, analysis issues in cross-over trials should be additionally considered.

Data analysis

The characteristics of study, patient and intervention will be summarized descriptively. We will make a narrative review for some comparisons if insufficient data is provided. Network plot will be drawn to descript the available interventions. The size of the node reflects the number of patients in each intervention. The breadth of the edge shows the number of comparisons. For efficacy and safety outcomes, pair-wise and network meta-analysis will be performed.

Pairwise meta-analyses

We will perform traditional pair-wise meta-analyses through random-effect model with DerSimonian and Laird inverse-variance method for every direct comparison (38). In some subgroups, we will also perform pair-wise meta-analyses if network meta-analyses could not be performed. The heterogeneity will be assessed by I-square and tau-square (38).

Assessment of the transitivity assumption

The potential baseline effect modifiers (age, gender, education level, baseline physical function, smoking habit, BMI, comorbidities and previous treatment) will be assessed to confirm they are similar among different comparisons before we perform network meta-analyses (34). If any difference is found, we will perform meta-regression to explore the influence on the results.

Network meta-analyses

Random-effect network meta-analyses under the frequentist framework will be performed to combine both direct and indirect comparisons (45). The heterogeneity parameter is assumed the same for each intervention (45). Prediction interval plot will be drawn to reflect the uncertainly of the results in a future study (46, 47).

Assessment of inconsistency

Bucher method as a local method and design-by-treatment interaction model as a global method will be used (48, 49). If any inconsistency is found, node-splitting method will be used to explore the original of the inconsistency (45).

Exploring sources of heterogeneity or inconsistency with subgroup analyses and meta-regression

For two primary outcomes (physical function and all-cause mortality), subgroup analyses and meta-regressions will be performed under the three time categories (short-term, mid-term, and long-term) except for the analysis on duration of follow-up for

long-term assessment. Subgroup analyses will be performed as follows: 1. Single level spinal stenosis versus multiple levels, the assumption is that patients with multiple levels spinal stenosis might have poorer physical function and higher all-cause mortality than patients with single level; 2. Duration of follow-up for long-term assessment (e.g., 1 year, 2 years and 5 years), the assumption is that patients who received injection therapies might have poorer physical function and higher all-cause mortality in longer duration of follow than patients who received surgical therapies; 3. Patients with versus patients without degenerative spondylolisthesis, the assumption is that patients with degenerative spondylolisthesis might have poorer physical function and higher all-cause mortality than patients without; 4. Type of disease: central, foraminal or lateral, the assumption is that patients with central lumbar spinal stenosis might have poorer physical function and higher all-cause mortality than patients with foraminal or lateral. Meta-regression will be performed as follows: 1. Age; 2. Percentage of the male; 3. Sample size; 4. Baseline physical function; 5. Percentage of the smoker; 6. Body mass index (BMI).

Sensitivity analyses

For two primary outcomes (physical function and all-cause mortality), sensitivity analyses will be performed as follows: 1. only studies with low risk of bias; 2. studies with imputed data through either IMDoM or IMOR; 3. Studies without a non-active comparison group; 4. Studies without receiving commercial funding; 5. Studies without unpublished data.

Publication bias

Comparison-adjusted funnel plot will be used to test the publication bias if the number of included studies is larger than 10 (42). As described above, meta-regression procedures using sample size and effect estimates will be performed to detect the small-study effect (50).

Grading the evidence

The Grading of Recommendations, Assessment, Development and Evaluations framework will be used to evaluate the quality of evidence (51). The tool includes five domains, which are study limitations, indirectness, inconsistency, imprecision and publication bias.

Statistical software

All analyses (pair-wise meta-analysis will be only performed in Stata and network meta-analysis will be performed in both Stata and R) will be performed in Stata (StataCrop. 2017. Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LP) and R (Version 3.4.3. R Core Team. 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Patient and Public Involvement

Patients will not be involved.

ETHICS AND DISSEMINATION

This research does not require ethics approval because it uses data form literatures. We will publish the research in a peer-reviewed journal after completing it.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. The Lancet.
2. Kreiner DS, Shaffer WO, Baisden JL, Gilbert TJ, Summers JT, Toton JF, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). The spine journal : official journal of the North American Spine Society. 2013;13(7):734-43.
3. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, et al. Spinal stenosis prevalence and association with symptoms: the Framingham Study. The spine journal : official journal of the North American Spine Society. 2009;9(7):545-50.
4. Machado GC, Ferreira PH, Yoo RI, Harris IA, Pinheiro MB, Koes BW, et al. Surgical options for lumbar spinal stenosis. The Cochrane database of systematic reviews. 2016;11:Cd012421.
5. May S, Comer C. Is surgery more effective than non-surgical treatment for spinal stenosis, and which non-surgical treatment is more effective? A systematic review. Physiotherapy. 2013;99(1):12-20.
6. Benyamin RM, Staats PS, Mi DASEI. MILD(R) Is an Effective Treatment for Lumbar Spinal

Stenosis with Neurogenic Claudication: MiDAS ENCORE Randomized Controlled Trial. Pain physician. 2016;19(4):229-42.

7. Deyo RA, Martin BI, Ching A, Tosteson AN, Jarvik JG, Kreuter W, et al. Interspinous spacers compared with decompression or fusion for lumbar stenosis: complications and repeat operations in the Medicare population. Spine. 2013;38(10):865-72.

8. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. Jama. 2010;303(13):1259-65.

9. Elsheikh NA, Amr YM. Effect of Adding Calcitonin to Translaminar Epidural Steroid in Degenerative Lumbar Spinal Canal Stenosis. Pain physician. 2016;19(3):139-46.

10. Jansson KA, Blomqvist P, Granath F, Nemeth G. Spinal stenosis surgery in Sweden 1987-1999. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2003;12(5):535-41.

11. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural Injections for Lumbar Radiculopathy and Spinal Stenosis: A Comparative Systematic Review and Meta-Analysis. Pain physician. 2016;19(3):E365-410.

12. Forsth P, Olafsson G, Carlsson T, Frost A, Borgstrom F, Fritzell P, et al. A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. The New England journal of medicine. 2016;374(15):1413-23.

13. Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, et al. Laminectomy plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. The New England journal of medicine. 2016;374(15):1424-34.

14. Shen J, Xu S, Xu S, Ye S, Hao J. Fusion or Not for Degenerative Lumbar Spinal Stenosis: A Meta-Analysis and Systematic Review. Pain physician. 2018;21(1):1-8.

15. Zhao H, Duan LJ, Gao YS, Yang YD, Zhao DY, Tang XS, et al. Comparison of two FDA-approved interspinous spacers for treatment of lumbar spinal stenosis: Superion versus X-STOP-a meta-analysis from five randomized controlled trial studies. Journal of orthopaedic surgery and research. 2018;13(1):42.

16. Zhao XW, Ma JX, Ma XL, Li F, He WW, Jiang X, et al. Interspinous process devices(IPD) alone versus decompression surgery for lumbar spinal stenosis(LSS): A systematic review and meta-analysis of randomized controlled trials. International journal of surgery (London, England). 2017;39:57-64.

17. Yavin D, Casha S, Wiebe S, Feasby TE, Clark C, Isaacs A, et al. Lumbar Fusion for Degenerative Disease: A Systematic Review and Meta-Analysis. Neurosurgery. 2017;80(5):701-15.

18. Li AM, Li X, Yang Z. Decompression and coflex interlaminar stabilisation compared with conventional surgical procedures for lumbar spinal stenosis: A systematic review and meta-analysis. International journal of surgery (London, England). 2017;40:60-7.

19. Lee CH, Chung CK, Sohn MJ, Kim CH. Short Limited Fusion Versus Long Fusion With Deformity Correction for Spinal Stenosis With Balanced De Novo Degenerative Lumbar Scoliosis: A Meta-analysis of Direct Comparative Studies. Spine. 2017;42(19):E1126-e32.

20. Chang W, Yuwen P, Zhu Y, Wei N, Feng C, Zhang Y, et al. Effectiveness of decompression alone versus decompression plus fusion for lumbar spinal stenosis: a systematic review and meta-analysis. Archives of orthopaedic and trauma surgery. 2017;137(5):637-50.

21. Phan K, Rao PJ, Ball JR, Mobbs RJ. Interspinous process spacers versus traditional

decompression for lumbar spinal stenosis: systematic review and meta-analysis. Journal of spine surgery (Hong Kong). 2016;2(1):31-40.

22. Phan K, Mobbs RJ. Minimally Invasive Versus Open Laminectomy for Lumbar Stenosis: A Systematic Review and Meta-Analysis. Spine. 2016;41(2):E91-e100.

23. Overdevest GM, Jacobs W, Vleggeert-Lankamp C, Thome C, Gunzburg R, Peul W. Effectiveness of posterior decompression techniques compared with conventional laminectomy for lumbar stenosis. The Cochrane database of systematic reviews. 2015(3):Cd010036.

24. Machado GC, Ferreira PH, Harris IA, Pinheiro MB, Koes BW, van Tulder M, et al. Effectiveness of surgery for lumbar spinal stenosis: a systematic review and meta-analysis. PloS one. 2015;10(3):e0122800.

25. Liu K, Liu P, Liu R, Wu X, Cai M. Steroid for epidural injection in spinal stenosis: a systematic review and meta-analysis. Drug design, development and therapy. 2015;9:707-16.

26. Liang L, Jiang WM, Li XF, Wang H. Effect of fusion following decompression for lumbar spinal stenosis: a meta-analysis and systematic review. International journal of clinical and experimental medicine. 2015;8(9):14615-24.

27. Lauryssen C, Jackson RJ, Baron JM, Tallarico RA, Lavelle WF, Deutsch H, et al. Stand-alone interspinous spacer versus decompressive laminectomy for treatment of lumbar spinal stenosis. Expert review of medical devices. 2015;12(6):763-9.

28. Hong P, Liu Y, Li H. Comparison of the efficacy and safety between interspinous process distraction device and open decompression surgery in treating lumbar spinal stenosis: a meta analysis. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2015;28(1):40-9.

29. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606.

30. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet (London, England). 2017;390(10090):e21-e33.

31. Feng F, Xu Q, Yan F, Xie Y, Deng Z, Hu C, et al. Comparison of 7 Surgical Interventions for Lumbar Disc Herniation: A Network Meta-analysis. Pain physician. 2017;20(6):E863-e71.

32. Guo JR, Jin XJ, Shen HC, Wang H, Zhou X, Liu XQ, et al. A Comparison of the Efficacy and Tolerability of the Treatments for Sciatica: A Network Meta-Analysis. The Annals of pharmacotherapy. 2017;51(12):1041-52.

33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1.

34. Clement RC, Welander A, Stowell C, Cha TD, Chen JL, Davies M, et al. A proposed set of metrics for standardized outcome reporting in the management of low back pain. Acta orthopaedica. 2015;86(5):523-33.

35. Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, et al. Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine. 2011;36(21 Suppl):S54-68.

36. Jensen MP, Mardekian J, Lakshminarayanan M, Boye ME. Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. Pain. 2008;137(2):422-7.

37. Dakin H, Abel, L, Burns, R, Yang, Y. 2018. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. Health and Quality of Life Outcomes. 16:31 HERC database of mapping studies, Version 6.0 (Last updated: 17th Jan 2017). Available at: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. .

38. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane collaboration; 2011. Available from: www.handbook.cochrane.org.

39. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. The Cochrane database of systematic reviews. 2015(9):Cd011612.

40. Higgins JPT SJ, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews. 2016(10 (Suppl 1)).

41. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine. 2015;40(21):1660-73.

42. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

43. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. Journal of clinical epidemiology. 2016;76:193-9.

44. Mavridis D, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Statistics in medicine. 2015;34(5):721-41.

45. White IR. Network meta-analysis. Stata Journal. 2015;15(4):951-85.

46. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ (Clinical research ed). 2011;342:d549.

47. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009;172(1):137-59.

48. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91.

49. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research synthesis methods. 2012;3(2):98-110.

50. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Research synthesis methods. 2012;3(2):161-76.

51. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the Quality of Evidence from a Network Meta-Analysis. PloS one. 2014;9(7):e99682.

Authors' contributions

All authors conceived the study. LC drafted the manuscript. LC and PB participated in

the search strategy development. PF, PB and MF assisted in protocol design and revision. All authors read and approved the final manuscript as submitted.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp spinal stenosis/
2 canal stenosis.mp.
3 (spin* adj3 stenosis).mp.
4 (lumbar adj3 stenosis).mp.
5 (lateral adj3 stenosis).mp.
6 (central adj3 stenosis).mp.
7 (foramin* adj3 stenosis).mp.
8 neurogenic claudication.mp.
9 exp radiculopathy/
10 Radiculopathy.mp.
11 radicular pain.mp.
12 lumbar radicular pain.mp.
13 exp spondylolisthesis/
14 Spondylolisthesis.mp.
15 (lumb* adj5 spondyl*).mp.
16 exp spondylosis/
17 Spondylosis.mp.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 exp general surgery/
20 Surgery.mp.
21 exp decompression, surgical/
22 decompres* surgery.mp.
23 Decompression.mp.
24 (spin* adj3 decompress*).mp.
25 exp laminectomy/
26 Laminectom*.mp.
27 Laminotom*.mp.

28 Laminoplasty.mp.
29 exp spinal fusion/
30 (spin* adj3 fusion).mp.
31 (pedicle adj3 screw).mp.
32 lumbar fusion.mp.
33 vertebrae fusion.mp.
34 vertebral fixation.mp.
35 spinal fixation.mp.
36 Spondylodesis.mp.
37 Spondylosyndesis.mp.
38 Arthrodesis.mp. or exp arthrodesis/
39 (posterolateral adj3 fusion).mp.
40 (interbody adj3 fusion).mp.
41 (anterior adj3 fusion).mp.
42 (posterior adj3 fusion).mp.
43 (transforaminal adj3 fusion).mp.
44 (transpsoas adj3 fusion).mp.
45 (facet adj3 fusion).mp.
46 (bone adj3 graft).mp.
47 (fixation adj3 spin*).mp.
48 (pedicle adj3 fusion).mp.
49 Graft.mp.
50 (cage adj3 fusion).mp.
51 (screw adj3 fusion).mp.
52 Foraminotomy.mp. or exp foraminotomy/
53 Foraminectomy.mp.
54 exp surgical procedures, minimally invasive/
55 minim* invasive.mp.
56 epidural.mp.
57 intra-articular.mp.
58 exp Anesthesia, Epidural/

59 Analgesia, Epidural/

60 exp Injections, Epidural/

61 exp Injections, Intra-Articular/

62 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63 randomized controlled trial.pt.

64 controlled clinical trial.pt.

65 randomized.ab,ti.

66 placebo.ab,ti.

67 drug therapy.fs.

68 randomly.ab,ti.

69 trial.ab,ti.

70 groups.ab,ti.

71 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70

72 (animals not (humans and animals)).sh.

73 71 not 72

74 18 and 62 and 73

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	5
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	17
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	Not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4-5
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5, 7
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Supplementary Material
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	8
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	8-9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	10
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	9, 11
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	11-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	13

BMJ Open

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024752.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Feb-2019
Complete List of Authors:	Chen, Lingxiao; University of Sydney, Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School Ferreira, Paulo; University of Sydney, Discipline of Physiotherapy, Faculty of Health Sciences Beckenkamp, Paula; University of Sydney, Discipline of Physiotherapy, Faculty of Health Sciences Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice
Keywords:	meta-analysis, SURGERY, degenerative lumbar spinal stenosis

Comparative efficacy and safety of surgical and invasive treatments for adults with degenerative lumbar spinal stenosis: protocol for a network meta-analysis and systematic review

Lingxiao Chen[1], Paulo H Ferreira[2], Paula R Beckenkamp[2], Manuela L Ferreira[1]

[1]Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

[2]Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141.

Corresponding author:

Lingxiao Chen

Address: Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

Telephone: +61 466 965 326

Email: lche4036@uni.sydney.edu.au

ABSTRACT

Introduction

Surgical and invasive procedures are widely used in adults with degenerative lumbar spinal stenosis when conservative treatments fail. However, little is known about the comparative efficacy and safety of these interventions. To address this, we will perform a network meta-analysis (NMA) and systematic review to compare the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

Methods and analysis

We will include randomised controlled trials assessing surgical and invasive treatments for adults with degenerative lumbar spinal stenosis. We will search AMED, CINAHL, EMBASE, the Cochrane Library and MEDLINE. Only English studies will be included and no restriction will be set for publication status. For efficacy, our primary outcome will be physical function. Secondary outcomes will include pain intensity, health related quality of life, global impression of recovery, work absenteeism and mobility. For safety, our primary outcome will be all-cause mortality. Secondary outcomes will include adverse events (number of events or number of people with an event) and treatment withdrawal due to adverse effect. Two reviewers will independently select studies, extract data and assess the risk of bias (Revised Cochrane risk-of-bias tool for randomized trials) of included studies. The quality of the evidence will be evaluated through the Grading of Recommendations Assessment, Development and Evaluation framework. Random-effects NMA will be performed to combine all the evidence under the frequentist framework and the ranking results will be presented through the surface under the cumulative ranking curve and mean rank. All analyses will be performed in Stata and R.

Ethics and dissemination

No ethical approval is required. The research will be published in a peer-reviewed journal.

PROSPERO registration number

CRD42018094180

Strengths and limitations of this study

- This is the first network meta-analysis to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.
- The main strengths are that only randomised controlled trials (RCT) will be included for both efficacy outcomes (physical function, pain intensity, health-related quality of life, global impression of recovery, work absenteeism and mobility) and safety outcomes (all-cause mortality, adverse effect and treatment withdrawal due to adverse effect).
- Additional strength is that informative missingness difference of means (IMDoM) for continuous outcomes and informative missing odds ratios (IMOR) for dichotomous outcomes will be used to deal with the missing data.
- The main limitation will be the limited data from lower socioeconomic countries considering the high cost of the surgical and invasive treatments.

INTRODUCTION

Degenerative lumbar spinal canal stenosis is characterized by decreased spinal canal diameter due to structural changes of the spine (e.g. facet joints, ligaments) due to ageing. Typically, patients will present with neurogenic claudication, defined as pain, numbness and/or fatigue in the lower limbs that is worsened during walking and standing, and alleviated with forward bending or sitting (1, 2). In the United States, the prevalence of degenerative lumbar spinal stenosis in the general population can be as high as 22.5% for relative stenosis (i.e. ≤12 mm canal diameter), and 7.3% for absolute stenosis (i.e. ≤10 mm canal diameter) (3). These figures increase drastically with age, reaching 47.2% and 19.4%, respectively, for those 60 years of age or older (3).

Most guidelines recommend a course of conservative care, including the North American Spine Society guidelines, for patients with degenerative lumbar spinal stenosis (2). However, when conservative treatments fail, surgical and invasive options are indicated (2, 4, 5). Surgical decompression (including laminectomies or laminotomies), with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections are commonly used in the management of spinal stenosis (6-11). However, the evidence supporting the superiority of one option over the other is still unclear for most (7, 12, 13). For instance, past meta-analyses have shown that Superion interspinous spacer is superior to X-STOP interspinous spacer in improving axial pain severity and ZCQ patient satisfaction score; whereas the addition of spinal fusion to surgical decompression does not add any benefit to surgical decompression alone (14, 15). Moreover, existing meta-analyses use pairwise analytical approaches, and therefore can only provide results for the comparison of two interventions at any one time (4, 11, 14-28). A network meta-analysis (NMA) is the best design and analytical approach to compare and rank multiple interventions simultaneously, based on their relative estimate effects in each outcome (29). NMA have been used in similar fields, including sciatica, lumbar disc herniation and osteoarthritis, but, to date, no NMA has been conducted to establish the comparative effectiveness and safety of invasive approaches for degenerative lumbar

spinal canal stenosis (30-32). As such, our aim is to perform a NMA and systematic review to assess the efficacy and safety of surgical and invasive procedures for adults with degenerative lumbar spinal stenosis.

METHODS AND ANALYSIS

Criteria for considering studies for this review

The protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (33). Any changes made to this protocol will be updated in the PROSPERO registration.

Types of participants

We will include studies that recruited participants who are 40 years of age or older, with a diagnosis of degenerative lumbar spinal stenosis. We will exclude studies on patients with malignancy, trauma, vertebral fracture, infection, and inflammatory disorders. For studies including degenerative lumbar spinal stenosis and associated spondylolisthesis, only those of participants with Meyerding grade I spondylolisthesis will be included. Studies including mixed populations will only be included if the data for patients with degenerative lumbar spinal stenosis can be extracted separately or if at least 80% of the patients are diagnosed with degenerative lumbar spinal stenosis.

Types of interventions

Studies comparing any surgical or invasive intervention for adults with degenerative lumbar spinal stenosis will be included. For example, surgical decompression, including laminectomies or laminotomies, with or without fusion, interspinous process spacer devices, minimally invasive surgical decompression, and corticosteroidal epidural injections. The comparison group could be no treatment, usual care, sham operation, another active option or a combination of approaches. The interventions in comparison groups will be treated as different nodes. However, if we have insufficient studies to connect different interventions, we will combine no treatment and usual care into one node to make full use of the data.

Outcome measures

The outcome data will grouped into short-term (<=6 months), mid-term (6 to 12 months), and long-term (>=12 months) follow-up assessment (34). We will perform network meta-analysis in the three time points separately. For studies which report outcomes in multiple time points, data closest to the 6 and 12-month follow-up time will be included in the main analyses. For different time points in long-term follow-up assessment (e.g., 1 year, 2 years, 5 years), subgroup analyses will be performed.

Primary outcomes

1. Physical function, commonly measured by Oswestry disability index (ODI), Roland Morris disability questionnaire (RMDQ), Patient Specific Function Scale (PSFS), and core outcome measures index (COMI) (34). Other rating scales will be included if they have been proposed in peer-reviewed journals. If the study provides more than one instruments, ODI will be used as the first choice, RMDQ as the second choose and COMI as the third choice (34).
2. All-cause mortality, measured by the percentage of patients who died following randomisation.

Secondary outcomes

1. Pain intensity, commonly measured by numeric rating scale (NRS) and the visual analogue scale (VAS) (35, 36). Other rating scales will also be included if they have been proposed in peer-reviewed journals. Pain intensity will be categorised and analysed according to the following three groups: back pain, leg pain and overall pain. If the study provides more than one instruments, VAS will be used as the first choice and NRS as the second choice (34).
2. Health related quality of life (HRQOL), commonly measured by 36-Item Short Form Survey (SF-36), EQ-5D, Nottingham health profile (NHP) and 12-Item Short Form Survey (SF-12) (34). SF-36, NHP and SF-12 could be mapped into EQ-5D (37). As above, other tools will also be included if they have been proposed in peer-

reviewed journals. If the study provides more than one instruments, EQ-5D will be used as the first choice, following by SF-36, SF-12, and NHP (34).

3. Global impression of recovery, measured by the percentage of the patients satisfied with their recovery.
4. Work absenteeism, measured by the number of days of sick leave.
5. Mobility, measured by walking distance.
6. Adverse event, measured by the number of participants with an adverse event, or number of adverse events per group. Adverse events could include nerve injury, dural tear, vascular injury, deep infection, and pulmonary embolus.
7. Treatment withdrawal due to adverse effect, measured by the percentage of patients who drop out due to adverse effect.

Types of studies

Only randomised controlled trials (RCT), which includes parallel, cross-over and cluster trials, will be included. For cross-over studies, only data before wash-out period will be used. For cluster randomized trials, we will extracted data which is adjusted for clustering. If these data are unavailable, we will extract original data and adjust them for clustering (38, 39). To decrease bias, we excluded studies with a high risk of bias in the domain risk of bias arising from the randomization process (40).

Search strategy

Electronic searches

The following databases will be searched for published studies: AMED, CINAHL, EMBASE, the Cochrane Library and MEDLINE (including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE). Unpublished and ongoing studies will be searched from WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and the US National Institutes of Health (https://clinicaltrials.gov/). Only English studies will be included and no restriction will be set for publication status. The search strategy for MEDLINE is provided as a supplemental material.

Reference lists and other sources

Reference lists of all included studies, relevant systematic reviews and meta-analyses, and guidelines will be screened for eligible additional studies to be included.

Identification and selection of studies

Two reviewers will independently screen titles and abstracts of the articles from the search. Before formal screening of titles, we will perform an intra-tester agreement test (kappa test) by randomly selecting 50 citations (through random number table) to be reviewed by two independent reviewers (38). An agreement of 80% or more will be considered acceptable. If we do not achieve the percentage of the agreement, we will randomly select another 50 citations subsequently until 80% percentage of agreement is reached. Any disagreement will be solved by discussion and if necessary, a third reviewer will arbitrate the decision. When studies fail to provide the necessary data, the authors will be contacted and further information requested.

Data extraction

Two reviewers will independently extract data from the included studies using a standardised data extraction form. Similarly, a pilot test will be performed before the formal extraction. We will randomly select 5 articles using a random number table to confirm we have enough inter-rater agreement (at least 80%). Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. The following data will be extracted from each included study based on recommendations from previous studies (34, 41).

1. Study characteristics, such as year of study publication, first author, journal, sample size, study funding and location.
2. Patient characteristics, such as age, gender, including and excluding criteria, diagnostic criteria, type of lumbar spinal stenosis, comorbidities, duration of symptoms and previous treatment.
3. Intervention characteristics.

4. Primary and secondary outcomes.

Measurement of treatment effect

Relative treatment effects

1. Continuous outcomes: If the studies use the same rating scale, we will use mean difference (MD) with its 95% confidence interval (CI). If different rating scales are used, standardised mean difference (SMD) with its 95% CI will be used.
2. Dichotomous outcomes: odds ratio (OR) with its 95% CI will be used.
3. For all-cause mortality, the number needed to harm (NNM) will be calculated (38).

Relative treatment ranking

The surface under the cumulative ranking curve (SUCRA) and mean ranks will be used to rank each intervention for each outcome (42). Rank-heat plot will be used to show the ranking results of each outcome for each intervention (43).

Dealing with missing outcome data and missing statistics

For continuous outcomes, if the study only reports standard error (SE), P value or CI, we will convert them into standard deviation (SD) (38). If the study reports median and interquartile range (IQR), we will calculate SD by dividing the IQR by 1.35 and considering the median equivalent to the mean (38). If relevant information is provided in figures, we will extract the data from the graphs. If data cannot be obtained, we will contact the authors. If we do not obtain relevant data, informative missingness difference of means (IMDoM) will be used as one kind of sensitivity analysis to explore the uncertainty of our results under the missing at random assumption (44).

For dichotomous outcomes, firstly, we will try to contact the authors to obtain data. In the absence of a response or of relevant data, informative missing odds ratios (IMOR) for dichotomous outcomes will be used to explore the uncertainty of our results under the missing at random assumption (44).

Risk of bias assessment

Two reviewers will independently assess the risk of bias of the included studies. Any disagreement will be solved by discussion. Otherwise, a third reviewer will make a decision. We will contact the authors to obtain further information if the third reviewer think it is necessary.

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to evaluate the risk of bias of included randomized parallel-group trials (40). The tool is comprised of five domains: 1. bias arising from the randomization process; 2. bias due to deviations from intended interventions; 3. bias due to missing outcome data; 4. bias due to missing outcome data; 5. bias in selection of the reported result. Each domain includes several signaling questions which elicit information relevant to an assessment of risk of bias. The answer option for each signaling question is: Yes, probably yes, probably no, no and no information. Based on the answers of all signaling questions in one domain, we rated the domain as low risk of bias, some concerns or high risk of bias. Finally, we got the overall risk-of-bias judgement as low risk of bias, some concerns or high risk of bias considering the risk-of-bias judgement in five domains.

For cluster-randomized trials, one more domain should be considered: bias arising from identification or recruitment of individual participants within clusters. For cross-over trials, analysis issues in cross-over trials should be additionally considered.

Data analysis

The characteristics of study, patient and intervention will be summarized descriptively. We will make a narrative review for some comparisons if insufficient data is provided. Network plot will be drawn to descript the available interventions. The size of the node reflects the number of patients in each intervention. The breadth of the edge shows the number of comparisons. For efficacy and safety outcomes, pair-wise and network meta-analysis will be performed.

Pairwise meta-analyses

We will perform traditional pair-wise meta-analyses through random-effect model with DerSimonian and Laird inverse-variance method for every direct comparison (38). In some subgroups, we will also perform pair-wise meta-analyses if network meta-analyses could not be performed. The heterogeneity will be assessed by I-square and tau-square (38).

Assessment of the transitivity assumption

The potential baseline effect modifiers (age, gender, education level, baseline physical function, smoking habit, BMI, comorbidities and previous treatment) will be assessed to confirm they are similar among different comparisons before we perform network meta-analyses (34). If any difference is found, we will perform meta-regression to explore the influence on the results.

Network meta-analyses

Random-effect network meta-analyses under the frequentist framework will be performed to combine both direct and indirect comparisons (45). The heterogeneity parameter is assumed the same for each intervention (45). Prediction interval plot will be drawn to reflect the uncertainly of the results in a future study (46, 47).

Assessment of inconsistency

Bucher method as a local method and design-by-treatment interaction model as a global method will be used (48, 49). If any inconsistency is found, node-splitting method will be used to explore the original of the inconsistency (45).

Exploring sources of heterogeneity or inconsistency with subgroup analyses and meta-regression

For two primary outcomes (physical function and all-cause mortality), subgroup analyses and meta-regressions will be performed under the three time categories (short-term, mid-term, and long-term) except for the analysis on duration of follow-up for

long-term assessment. Subgroup analyses will be performed as follows: 1. Single level spinal stenosis versus multiple levels, the hypothesis is that patients with multiple levels spinal stenosis might have poorer physical function and higher all-cause mortality than patients with single level; 2. Duration of follow-up for long-term assessment (e.g., 1 year, 2 years and 5 years), the hypothesis is that patients who received injection therapies might have poorer physical function and higher all-cause mortality in longer duration of follow than patients who received surgical therapies; 3. Patients with versus patients without degenerative spondylolisthesis, the hypothesis is that patients with degenerative spondylolisthesis might have poorer physical function and higher all-cause mortality than patients without; 4. Type of disease: central, foraminal or lateral, the hypothesis is that patients with central lumbar spinal stenosis might have poorer physical function and higher all-cause mortality than patients with foraminal or lateral. Meta-regression will be performed as follows: 1. Age; 2. Percentage of the male; 3. Sample size; 4. Baseline physical function; 5. Percentage of the smoker; 6. Body mass index (BMI).

Sensitivity analyses

For two primary outcomes (physical function and all-cause mortality), sensitivity analyses will be performed as follows: 1. only studies with low risk of bias; 2. studies with imputed data through either IMDoM or IMOR; 3. Studies without a non-active comparison group; 4. Studies without receiving commercial funding; 5. Studies without unpublished data.

Publication bias

Comparison-adjusted funnel plot will be used to test the publication bias if the number of included studies is larger than 10 (42). As described above, meta-regression procedures using sample size and effect estimates will be performed to detect the small-study effect (50).

Grading the evidence

The Grading of Recommendations, Assessment, Development and Evaluations framework will be used to evaluate the quality of evidence (51). The tool includes five domains, which are study limitations, indirectness, inconsistency, imprecision and publication bias.

Statistical software

All analyses (pair-wise meta-analysis will be only performed in Stata and network meta-analysis will be performed in both Stata and R) will be performed in Stata (StataCrop. 2017. Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LP) and R (Version 3.4.3. R Core Team. 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Patient and Public Involvement

Patients will not be involved.

ETHICS AND DISSEMINATION

This research does not require ethics approval because it uses data form literatures. We will publish the research in a peer-reviewed journal after completing it.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. The Lancet.
2. Kreiner DS, Shaffer WO, Baisden JL, Gilbert TJ, Summers JT, Toton JF, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). The spine journal : official journal of the North American Spine Society. 2013;13(7):734-43.
3. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, et al. Spinal stenosis prevalence and association with symptoms: the Framingham Study. The spine journal : official journal of the North American Spine Society. 2009;9(7):545-50.
4. Machado GC, Ferreira PH, Yoo RI, Harris IA, Pinheiro MB, Koes BW, et al. Surgical options for lumbar spinal stenosis. The Cochrane database of systematic reviews. 2016;11:Cd012421.
5. May S, Comer C. Is surgery more effective than non-surgical treatment for spinal stenosis, and which non-surgical treatment is more effective? A systematic review. Physiotherapy. 2013;99(1):12-20.
6. Benyamin RM, Staats PS, Mi DASEI. MILD(R) Is an Effective Treatment for Lumbar Spinal

Stenosis with Neurogenic Claudication: MiDAS ENCORE Randomized Controlled Trial. Pain physician. 2016;19(4):229-42.

7. Deyo RA, Martin BI, Ching A, Tosteson AN, Jarvik JG, Kreuter W, et al. Interspinous spacers compared with decompression or fusion for lumbar stenosis: complications and repeat operations in the Medicare population. Spine. 2013;38(10):865-72.

8. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. Jama. 2010;303(13):1259-65.

9. Elsheikh NA, Amr YM. Effect of Adding Calcitonin to Translaminar Epidural Steroid in Degenerative Lumbar Spinal Canal Stenosis. Pain physician. 2016;19(3):139-46.

10. Jansson KA, Blomqvist P, Granath F, Nemeth G. Spinal stenosis surgery in Sweden 1987-1999. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2003;12(5):535-41.

11. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural Injections for Lumbar Radiculopathy and Spinal Stenosis: A Comparative Systematic Review and Meta-Analysis. Pain physician. 2016;19(3):E365-410.

12. Forsth P, Olafsson G, Carlsson T, Frost A, Borgstrom F, Fritzell P, et al. A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. The New England journal of medicine. 2016;374(15):1413-23.

13. Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, et al. Laminectomy plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. The New England journal of medicine. 2016;374(15):1424-34.

14. Shen J, Xu S, Xu S, Ye S, Hao J. Fusion or Not for Degenerative Lumbar Spinal Stenosis: A Meta-Analysis and Systematic Review. Pain physician. 2018;21(1):1-8.

15. Zhao H, Duan LJ, Gao YS, Yang YD, Zhao DY, Tang XS, et al. Comparison of two FDA-approved interspinous spacers for treatment of lumbar spinal stenosis: Superion versus X-STOP-a meta-analysis from five randomized controlled trial studies. Journal of orthopaedic surgery and research. 2018;13(1):42.

16. Zhao XW, Ma JX, Ma XL, Li F, He WW, Jiang X, et al. Interspinous process devices(IPD) alone versus decompression surgery for lumbar spinal stenosis(LSS): A systematic review and meta-analysis of randomized controlled trials. International journal of surgery (London, England). 2017;39:57-64.

17. Yavin D, Casha S, Wiebe S, Feasby TE, Clark C, Isaacs A, et al. Lumbar Fusion for Degenerative Disease: A Systematic Review and Meta-Analysis. Neurosurgery. 2017;80(5):701-15.

18. Li AM, Li X, Yang Z. Decompression and coflex interlaminar stabilisation compared with conventional surgical procedures for lumbar spinal stenosis: A systematic review and meta-analysis. International journal of surgery (London, England). 2017;40:60-7.

19. Lee CH, Chung CK, Sohn MJ, Kim CH. Short Limited Fusion Versus Long Fusion With Deformity Correction for Spinal Stenosis With Balanced De Novo Degenerative Lumbar Scoliosis: A Meta-analysis of Direct Comparative Studies. Spine. 2017;42(19):E1126-e32.

20. Chang W, Yuwen P, Zhu Y, Wei N, Feng C, Zhang Y, et al. Effectiveness of decompression alone versus decompression plus fusion for lumbar spinal stenosis: a systematic review and meta-analysis. Archives of orthopaedic and trauma surgery. 2017;137(5):637-50.

21. Phan K, Rao PJ, Ball JR, Mobbs RJ. Interspinous process spacers versus traditional

decompression for lumbar spinal stenosis: systematic review and meta-analysis. Journal of spine surgery (Hong Kong). 2016;2(1):31-40.

22. Phan K, Mobbs RJ. Minimally Invasive Versus Open Laminectomy for Lumbar Stenosis: A Systematic Review and Meta-Analysis. Spine. 2016;41(2):E91-e100.

23. Overdevest GM, Jacobs W, Vleggeert-Lankamp C, Thome C, Gunzburg R, Peul W. Effectiveness of posterior decompression techniques compared with conventional laminectomy for lumbar stenosis. The Cochrane database of systematic reviews. 2015(3):Cd010036.

24. Machado GC, Ferreira PH, Harris IA, Pinheiro MB, Koes BW, van Tulder M, et al. Effectiveness of surgery for lumbar spinal stenosis: a systematic review and meta-analysis. PloS one. 2015;10(3):e0122800.

25. Liu K, Liu P, Liu R, Wu X, Cai M. Steroid for epidural injection in spinal stenosis: a systematic review and meta-analysis. Drug design, development and therapy. 2015;9:707-16.

26. Liang L, Jiang WM, Li XF, Wang H. Effect of fusion following decompression for lumbar spinal stenosis: a meta-analysis and systematic review. International journal of clinical and experimental medicine. 2015;8(9):14615-24.

27. Lauryssen C, Jackson RJ, Baron JM, Tallarico RA, Lavelle WF, Deutsch H, et al. Stand-alone interspinous spacer versus decompressive laminectomy for treatment of lumbar spinal stenosis. Expert review of medical devices. 2015;12(6):763-9.

28. Hong P, Liu Y, Li H. Comparison of the efficacy and safety between interspinous process distraction device and open decompression surgery in treating lumbar spinal stenosis: a meta analysis. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2015;28(1):40-9.

29. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606.

30. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet (London, England). 2017;390(10090):e21-e33.

31. Feng F, Xu Q, Yan F, Xie Y, Deng Z, Hu C, et al. Comparison of 7 Surgical Interventions for Lumbar Disc Herniation: A Network Meta-analysis. Pain physician. 2017;20(6):E863-e71.

32. Guo JR, Jin XJ, Shen HC, Wang H, Zhou X, Liu XQ, et al. A Comparison of the Efficacy and Tolerability of the Treatments for Sciatica: A Network Meta-Analysis. The Annals of pharmacotherapy. 2017;51(12):1041-52.

33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1.

34. Clement RC, Welander A, Stowell C, Cha TD, Chen JL, Davies M, et al. A proposed set of metrics for standardized outcome reporting in the management of low back pain. Acta orthopaedica. 2015;86(5):523-33.

35. Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, et al. Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine. 2011;36(21 Suppl):S54-68.

36. Jensen MP, Mardekian J, Lakshminarayanan M, Boye ME. Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. Pain. 2008;137(2):422-7.

37. Dakin H, Abel, L, Burns, R, Yang, Y. 2018. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. Health and Quality of Life Outcomes. 16:31 HERC database of mapping studies, Version 6.0 (Last updated: 17th Jan 2017). Available at: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. .

38. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane collaboration; 2011. Available from: www.handbook.cochrane.org.

39. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. The Cochrane database of systematic reviews. 2015(9):Cd011612.

40. Higgins JPT SJ, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews. 2016(10 (Suppl 1)).

41. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine. 2015;40(21):1660-73.

42. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.

43. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. Journal of clinical epidemiology. 2016;76:193-9.

44. Mavridis D, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Statistics in medicine. 2015;34(5):721-41.

45. White IR. Network meta-analysis. Stata Journal. 2015;15(4):951-85.

46. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ (Clinical research ed). 2011;342:d549.

47. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009;172(1):137-59.

48. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91.

49. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research synthesis methods. 2012;3(2):98-110.

50. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Research synthesis methods. 2012;3(2):161-76.

51. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the Quality of Evidence from a Network Meta-Analysis. PloS one. 2014;9(7):e99682.

Authors' contributions

All authors conceived the study. LC drafted the manuscript. LC and PB participated in

the search strategy development. PF, PB and MF assisted in protocol design and revision. All authors read and approved the final manuscript as submitted.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp spinal stenosis/
2 canal stenosis.mp.
3 (spin* adj3 stenosis).mp.
4 (lumbar adj3 stenosis).mp.
5 (lateral adj3 stenosis).mp.
6 (central adj3 stenosis).mp.
7 (foramin* adj3 stenosis).mp.
8 neurogenic claudication.mp.
9 exp radiculopathy/
10 Radiculopathy.mp.
11 radicular pain.mp.
12 lumbar radicular pain.mp.
13 exp spondylolisthesis/
14 Spondylolisthesis.mp.
15 (lumb* adj5 spondyl*).mp.
16 exp spondylosis/
17 Spondylosis.mp.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 exp general surgery/
20 Surgery.mp.
21 exp decompression, surgical/
22 decompres* surgery.mp.
23 Decompression.mp.
24 (spin* adj3 decompress*).mp.
25 exp laminectomy/
26 Laminectom*.mp.
27 Laminotom*.mp.

28 Laminoplasty.mp.
29 exp spinal fusion/
30 (spin* adj3 fusion).mp.
31 (pedicle adj3 screw).mp.
32 lumbar fusion.mp.
33 vertebrae fusion.mp.
34 vertebral fixation.mp.
35 spinal fixation.mp.
36 Spondylodesis.mp.
37 Spondylosyndesis.mp.
38 Arthrodesis.mp. or exp arthrodesis/
39 (posterolateral adj3 fusion).mp.
40 (interbody adj3 fusion).mp.
41 (anterior adj3 fusion).mp.
42 (posterior adj3 fusion).mp.
43 (transforaminal adj3 fusion).mp.
44 (transpsoas adj3 fusion).mp.
45 (facet adj3 fusion).mp.
46 (bone adj3 graft).mp.
47 (fixation adj3 spin*).mp.
48 (pedicle adj3 fusion).mp.
49 Graft.mp.
50 (cage adj3 fusion).mp.
51 (screw adj3 fusion).mp.
52 Foraminotomy.mp. or exp foraminotomy/
53 Foraminectomy.mp.
54 exp surgical procedures, minimally invasive/
55 minim* invasive.mp.
56 epidural.mp.
57 intra-articular.mp.
58 exp Anesthesia, Epidural/

59 Analgesia, Epidural/

60 exp Injections, Epidural/

61 exp Injections, Intra-Articular/

62 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63 randomized controlled trial.pt.

64 controlled clinical trial.pt.

65 randomized.ab,ti.

66 placebo.ab,ti.

67 drug therapy.fs.

68 randomly.ab,ti.

69 trial.ab,ti.

70 groups.ab,ti.

71 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70

72 (animals not (humans and animals)).sh.

73 71 not 72

74 18 and 62 and 73

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	5
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	17
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	Not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4-5
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5, 7
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Supplementary Material
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	8
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	8-9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	10
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	9, 11
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	11-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	13