ABSTRACT

Introduction Low back pain and neck pain are leading causes of disability. Although several studies have examined the effect of exercise on fear of movement in people with spine-related pain, the overall evidence supporting the beneficial effect of different forms of exercise on fear of movement remains unknown. This systematic review will determine the strength of evidence for the effect of exercise/physical activity on fear of movement in people with non-specific spine-related pain.

Methods/analysis This review protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. The review will include randomised controlled trials and non-randomised studies that recruited adults (≥18 years) with chronic non-specific spine-related pain and where a validated measure of fear of movement/kinesiophobia such as the Tampa Scale of Kinesiophobia (TSK) and the Fear Avoidance Behaviour Questionnaire (FABQ) or any other validated measures to ascertain fear of movement/kinesiophobia was employed. Bibliographic databases include MEDLINE, PsycINFO, EMBASE, CINAHL, ZETOC, Web of Science, PubMed and Google Scholar as well as key journals/grey literature will be searched from inception to 31 January 2022. Only articles published in English will be considered eligible. Two independent reviewers will search, screen studies, extract data and assess risk of bias. Preintervention and postintervention mean and SD will be considered. The risk of bias will be assessed using the Grading of Recommendations Assessment, Development and Evaluation and Risk Of Bias in Non-randomised Studies of Interventions guidelines. The results will be pooled into a meta-analysis. A narrative synthesis of the results will be presented if heterogeneity is high. The overall quality of evidence and risk of bias will be assessed using the Grading of Recommendations Assessment, Development and Evaluation and Risk Of Bias in Non-randomised Studies of Interventions guidelines.

INTRODUCTION

Low back pain (LBP) is the leading cause of disability and adjusted life-years lived with disability worldwide and will continue to increase as the population ages. Approximately 80% of all adults will have LBP at some point in their lifetime and of those, 20% will likely develop chronic LBP. In the UK, estimates for the adult population with LBP accounts for approximately 11% of all disability burden from all disease. The second biggest cause of sickness absence in 2017 was attributed to musculoskeletal conditions accounting for more than 28 million days lost in work (absenteeism), costing the UK an estimated £7 billion annually.

Most people will experience an episode of neck pain at some point during their life. Neck pain is among the most common medical condition requiring medical care with up to 70% of the global population experiencing neck pain at least once in their lifetime. Of those between 50% and 85% will continue to report neck pain 1–5 years later. Neck pain is ranked as the second most common musculoskeletal condition after LBP, and fourth highest in terms of years lived with disability.
Fear avoidance refers to the belief that any movement or activity should be avoided to reduce pain or reinjury. Fear of movement develops as a result of avoidant behaviour to any new exposure of pain, leading to the avoidance of perceived painful activities, like physical activity and exercise, which may be perceived to be painful. The likelihood of those people with spinal pain developing physical disabilities becomes greater, as their increased fear of movement restricts their daily activities. There is evidence that fear avoidance beliefs can be predictive for negative or worse outcomes for patients with LBP, hence the need for early interventions to decrease these beliefs in the hope for a more successful outcome.

A study by Balci et al. found that both land and aquatic exercises have a positive influence on kinesiophobia in patients with chronic LBP. Additionally, another study provided evidence that a 12-week Pilates intervention group had a more beneficial impact on kinesiophobia (alongside other factors) when compared with a control group. A recent systematic review that investigated the effectiveness of exercise in reducing fear avoidance beliefs compared with non-exercise comparator concluded that there was moderate evidence for exercise interventions in reducing fear avoidance belief in people with pain including those with chronic LBP. However, this review examined pooled data of several exercise types, which reduces the ability to determine which exercise type was most effective in reducing fear avoidance beliefs.

Another review examined the effectiveness of conservative treatment compared with surgical intervention in reducing kinesiophobia and fear avoidance belief, found limited evidence that exercise reduces fear avoidance beliefs in people with chronic LBP. However, this review only included studies which compared exercise to other intervention modalities, reducing the ability to determine whether exercise alone was effective in reducing fear avoidance belief. Furthermore, Leonhardt et al. investigated whether physical activity was associated with fear avoidance measured by the Tampa Scale of Kinesiophobia (TSK) in people with acute and chronic LBP and concluded that fear of movement might be a dysfunctional cognitive impairment which is not related to increased physical activity or specific movement but a fear of movement in general. On the other hand, a study by Elfving et al. revealed that patients with chronic, non-specific LBP with higher levels of fear avoidance beliefs, and pain catastrophising were more likely to report low levels of physical activity. Results of these studies show that the effect of exercise/physical activity on reducing fear of movement/kinesiophobia in people with non-specific spine-related pain is currently not clear.

The aim of this systematic review is to examine whether exercise/physical activity interventions are effective in reducing fear of movement/kinesiophobia in people with non-specific spine-related pain. The findings of this review may provide some insight into the merit of physical activity/exercise in relation to fear avoidance behaviour in people with non-specific spine-related pain enabling more targeted treatment option.

METHODS

This review protocol follows the reporting guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (online supplemental file 1) and the methodological recommendations for conducting systematic reviews according to the Cochrane Handbook for diagnostic test accuracy.

Search strategy

The following citation databases MEDLINE, PsycINFO, EMBASE, CINAHL, ZETOC, Web of Science and PubMed in combination with database-specific filters for randomised controlled trials, where these are available and Google Scholar as well as key journals/grey literature will be searched from inception to 31 January 2022. An optimum search strategy has been developed to retrieve relevant articles which focuses on the following key terms: exercise, physical activity, fear of movement, kinesiophobia, spinal musculoskeletal pain, low back and neck pain. Search strategy for each database can be found in online supplemental file 2. Only articles published in English will be considered eligible.

Inclusion criteria

Studies published in peer-reviewed journals and grey literature will be included. Randomised controlled trials (RCT) and non-randomised studies of exercise/physical activity intervention will be included, where fear of movement/kinesiophobia is measured using a validated measure at baseline and at follow-up in people with non-specific spine-related pain. The selection criteria for inclusion/exclusion of studies will follow the Participants, Interventions, Comparators, Outcomes and Study design framework.

Population

Adults (≥18 years) with chronic non-specific spine-related pain (ie, neck, thoracic or LBP).

Study type

RCTs and non-randomised studies.

Intervention

Any form of active exercise/physical activity interventions for example, resistance training, motor control exercise, cardiovascular exercise, yoga, hydrotherapy, walking or Pilates will be reviewed. The term ‘exercise’ is commonly used to describe exercise or physical activity, which is planned, structured and repetitive and which serves to improve physical fitness. The exercise intervention/s should not include other forms of treatment apart from education. In the case of RCTs, then the control should be waitlist control, education only or passive therapies (eg, manual therapy or electrotherapy) only. RCTs
comparing two or more types of exercise interventions will be considered and the effects for each exercise intervention considered separately (eg, strengthening vs motor control exercises).

Comparator
In the case of RCTs, non-exercise training treatment comparator groups: true control (ie, no intervention provided), or receiving passive interventions only (eg, manual therapy or education) or general practitioner management.

Outcome measures
Studies will be required to include any validated measure of fear of movement or kinesiophobia such as the TSK25 and the Fear Avoidance Behaviour Questionnaire (FABQ), or any other validated measures to ascertain fear of movement/kinesiophobia.

Measures of effect
End of intervention between group differences will be measured in the case of RCTs and within group difference will be considered in the case of non-randomised study interventions. Mean difference or standardised mean difference (SMD) will be extracted with accompanying 95% CIs and p values where this is reported. Group effect size will be extracted and reported.

Exclusion criteria
1. Aged <18 years.
2. Patients with specific causes of spinal pain (eg, radiculopathy), spinal pathology or postsurgery.
3. Single case studies, case reports alongside any review articles, letters, editorials, studies with only abstracts and any other literature with no full text availability and articles not published in the English language will be excluded.

Preparing for eligibility screening
Before eligibility screening commences, search results identified by the outlined databases will be assembled into a digital library and organised by searched database using Endnote V.20 software (Clarivate Analytics) reference management software. Any duplicate articles will be identified and removed at this stage.

Study selection
Two reviewers (RS and FJ) will independently screen and identify studies potentially meeting the predetermined inclusion criteria by reading titles and abstracts within the digital library. Both reviewers will then select articles for full-text screening and independently apply eligibility criteria to select appropriate articles for inclusion in the review. They will resolve any disagreement over eligibility through consensus. If no resolution is reached a third reviewer (DF) will arbitrate any disagreement over study eligibility and resolve through discussion. An inclusion criteria checklist (Table 1) has been developed, based on study eligibility criteria, to ensure that studies are classified and interpreted appropriately. A PRISMA-P flow diagram will be provided to describe included and excluded studies along with reasons for exclusions.

Patient and public involvement
No patients or the public were directly involved in the design, writing or editing of this systematic review protocol. We will present the results of this review to our established patient and public involvement group at the Centre of Precision Rehabilitation for Spinal Pain, UK.

Data extraction
Data will be managed using the EndNote V.20 software (Clarivate Analytics), see http://www.endnote.com). This will enable reviewer’s ease of access, remove duplicates and review and store full texts and abstracts. Data from the included studies will be extracted independently by two reviewers. Any disagreement over the eligibility of a study will be resolved through discussions with a third reviewer. For missing data, attempts will be made to contact study authors at least twice by email and/or phone to gain further information. The following data items will be extracted from each study: authors and year of publication, study location, study design, participant’s characteristics and outcomes of interest (fear of movement or Kinesiophobia), sample size, follow-up time, setting and items associated with risk of bias, summary statistics and methods for statistical analysis. Details of intervention (duration, frequency, type of exercise/physical activity) and control/comparison group where appropriate; study methodology and outcomes and times of measurement/ follow-up), will be extracted and reported. Two reviewers will independently conduct data extraction from each study using a pre-defined data extraction sheet. Extracted outcome data will be preintervention and postintervention mean and SD. Data presented as medians or alternate measures of spread will be converted to mean and SD. When only figures are presented (rather than numerical data within text), data will be extracted and analysed where possible using software tool such as Web Plot Digitizer.27
Risk of bias (quality) assessment

The Cochrane Risk of Bias tool V.2 (RoB 2)\textsuperscript{28} will be used to assess the risk of bias of each of the included randomised trials. Risk of bias may include selection bias (random sequence generation and allocation concealment), performance bias (blinding of patients/research team), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). The Risk Of Bias in Non-randomised Studies of Interventions\textsuperscript{29} tool will be used to assess the risk of bias of non-randomised studies of interventions. Two reviewers (RS and FJ) will be involved in the quality assessment and any disagreements will be resolved through a third reviewer (DF). For this review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)\textsuperscript{30} working group methodology will be used to assess the quality of the pooled evidence.

Data analysis and synthesis

A pairwise random-effects meta-analysis will be conducted depending on effect measures reported in the studies and similarities between individual studies, interventions and outcomes,\textsuperscript{31} and the statistical heterogeneity, the assessment of whether genuine differences exist between results is low.\textsuperscript{32} Meta-analysis will be performed if heterogeneity between the studies is low ($I^2<50\%$). Variation in study outcome between studies will be evaluated using the I$^2$ statistical analysis. SMD and 95% CIs will be extracted and reported as effect estimates of fear of movement/kinesiophobia. SMD and associated Cohen’s D where available will be extracted and reported or calculable using Cohen’s D formula, effect size will be defined as small (0.0–0.2), medium (0.3–0.7) and large (>0.8). A 95% CI will also be calculated where possible. If the level of heterogeneity and risk of bias is high between studies and pooled analysis of the studies is not possible, a narrative summary of the outcome of the selected studies will be undertaken and presented in the final review. All analyses will be conducted in Stata V.17.0 (StataCorp).

Heterogeneity assessment

Univariate and multivariate meta-regression will be used to statistically examine sources of variation between studies, statistical significance will be set at ($p<0.05$). The following covariates: sample size, country, study setting and diversity of outcome measures will be further examined to explore sources of heterogeneity. Statistically significant covariates from univariate models will be included in a multivariate meta-regression model. Meta-regression will be performed in STATA using the ‘metareg’ command.\textsuperscript{33}

Analysis of subgroup or subsets

Subgroup analyses may be performed depending on the number of studies identified. Subgroup analyses will be performed to consider the following: (1) Exercise/physical activity type; (2) Pain location; (3) Outcome measure, for example, TSK versus FABQ. The level of heterogeneity across included studies and strength of evidence for heterogeneity will be examined using the Cochrane Q and I$^2$ statistics with associated 95% CI. An I$^2$ of 50% and above is considered a substantial level of heterogeneity.\textsuperscript{34} Depending on the level of heterogeneity (I$^2$ statistics) and study characteristics both fixed and random effect models may be used as summary effect measures. The fixed effect model based on Mantel-Haenszel\textsuperscript{35} will be used if tests of heterogeneity among studies are not significant, or the DerSimonian and Laird\textsuperscript{36} method will be used for random effect models because of potential heterogeneity between study variations in population, regions or assessment methods across studies. A minimum of two studies are generally considered sufficient to perform a meta-analysis.\textsuperscript{37}

Sensitivity analysis

A range of sensitivity analyses may be conducted to examine the methodological quality and potential sources of heterogeneity of the included studies. Sources of variations may include tool for assessment of fear of movement, sampling strategy, adequate response and type of exercise/physical activity. These will be stratified and separate sensitivity analyses conducted. A further analysis will be conducted excluding any studies with high risk of bias.

Narrative synthesis

If the level of heterogeneity is high between studies and pooled analysis of the studies is not possible, a narrative synthesis of the outcome of the selected studies will be examined in more nuanced detail and presented in the final review outlining the reasons for the results reported in each study.

Publication bias and overall quality of the evidence

Presence of publication bias will be assessed by visual inspection of the inverted funnel plot technique and by the Begg rank test\textsuperscript{38} and the Egger regression test.\textsuperscript{39} The magnitude of publication bias will be examined by the trim and fill method\textsuperscript{40} by estimating the number of missing studies because of publication bias and imputes missing effect sizes until the funnel plot is symmetrical. The effect size is re-estimated using standard meta-analysis method. The STATA command metatrtrim\textsuperscript{41} will be used to perform the non-parametric trim and fill method. The GRADE framework\textsuperscript{30} will be used to examine the quality and inconsistency between studies including publication bias, imprecision, inconsistency and indirectness of study results to the population. The quality of the summary evidence will be assessed as high, moderate, low or very low consistent with GRADE. The minimum number of studies recommended when examining publication bias is 10.\textsuperscript{12}

DISCUSSION

To the best our knowledge, this will be the first systematic review to explore whether different forms of exercise/
physical activity interventions are effective at modifying fear of movement/kinesiophobia in people with non-specific spine-related pain. This review will provide the strength of evidence supporting the efficacy of exercise/physical activity interventions in modifying fear of movement for people with spine-related pain. Furthermore, this review will explore which exercise/physical type are related to evidence of significant benefit.

The strengths and limitations identified in the included studies will be presented and described in the review. The strengths of this review include an in depth search strategy designed and adapted for each search database and robust quality appraisal and heterogeneity assessment to evaluate studies included in this review. Some potential limitations are likely to include between study heterogeneity in terms of diagnostic methods, study setting or country and publication bias. A narrative summary of the outcome of the selected studies will be presented in the final review to overcome this issue if necessary.

Implications of results
Based on the available evidence, the results of this review will help identify the most effective exercise/physical activity or type of exercise interventions, which are most beneficial at modifying reducing fear of movement in adults aged ≥18 years with non-specific spine-related pain.

ETHICS AND DISSEMINATION
This review does not require ethical approval as only existing published data available in scientific databases will be used. Findings of this systematic review will be presented for peer review in an appropriate journal. Any data generated from this systematic review will be made available from the corresponding author on reasonable request.

Twitter Deborah Falls @Deb_Falla

Contributors FJ, RS and DF contributed equally to the conception of this protocol. FJ and DF conceived the study design. FJ and RS drafted the first version of the protocol and was reviewed/revised by DF. The final version was drafted by FJ. The search strategy was developed by FJ and iteration discussed with DF and RS. The final version was approved by DF and RS. The search will be performed by RS. FJ and RS will perform initial screening for study selection. FJ and RS will collect data from the included studies and conduct quality assessment. FJ and RS will perform data analysis/synthesis. DF will ensure data extraction consistency. FJ, RS and DF drafted and critically reviewed the manuscript and approved the final version. DF is guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Ferokhan Jadhakhan http://orcid.org/0000-0002-4545-3703
Deborah Falls http://orcid.org/0000-0003-1689-6190

REFERENCES
1 Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. Pain 2016;157:791–6.
2 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet 2017;390:1211–59.
3 Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. Arch Intern Med 2009;169:251–8.
4 Parsons S, Breen A, Foster NE, et al. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. Fam Pract 2007;24:308–16.
5 Office for National Statistics. Sickness absence in the UK labour market, 2018. Available: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/datasets/sicknessabsenceintheuklabourmarket
6 Haldeman S, Carroll L, Cassidy JD. Findings from the bone and joint decade 2000 to 2010 Task force on neck pain and its associated disorders. J Occup Environ Med 2010;52:424–7.
7 Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J 2006;15:834–48.
8 Safiri S, Kolahi A-A, Hoy D, et al. Global, regional, and national burden of neck pain in the general population, 1990–2017: systematic analysis of the global burden of disease study 2017. BMJ 2020;368:m791.
9 Hoy D, March L, Woolf A, et al. The global burden of neck pain: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1309–15.
10 Abajobir AA, Abate KH, Abbafati C, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet 2017;390:1260–344.
11 Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000;85:317–32.
12 Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. Phys Ther 2011;91:700–11.
13 de Moraes Vieira EB, de Góes Salvetti M, Damianni LP, et al. The role of fear avoidance beliefs in chronic low back pain patients: coexistence and associated factors. Pain Manag Nurs 2014;15:593–602.
14 Wernli MM, Rasmussen-Barr E, Weiser S, et al. Self-Efficacy and fear avoidance beliefs in chronic low back pain patients: coexistence and associated factors. Pain Manag Nurs 2014;15:816–36.
15 Balci NC, Aytaar A, Atici E. The effect of aquatic and land exercises on pain, health related quality of life, kinesiophobia and disability in chronic low back pain: a randomized clinical trial. J Neurol Phys Ther 2012;36:1249–57.
16 Cruz-Diaz D, Romeu M, Velasco-Gonzalez C, et al. The effectiveness of 12 weeks of Pilates intervention on disability, pain and kinesiophobia in patients with chronic low back pain: a randomized controlled trial. Clin Rehabil 2018;32:1249–57.
17 Hanel J, Owen PJ, Held S, et al. Effects of exercise training on fear-avoidance in pain and pain-free populations: systematic review and meta-analysis. Sports Med 2020;50:2193–207.
18 Martinez-Calderon J, Flores-Cortés M, Morales-Asecnio JM, et al. Conservative interventions reduce fear in individuals with chronic

Jadhakhan F, et al. BMJ Open 2022;12:e060264. doi:10.1136/bmjopen-2021-060264
low back pain: a systematic review. Arch Phys Med Rehabil 2020;101:329–58.

19 Leonhardt C, Lehr D, Chenot J-F, et al. Are fear-avoidance beliefs in low back pain patients a risk factor for low physical activity or vice versa? A cross-lagged panel analysis. Psychosoc Med 2009;6:Doc01.

20 Elfving B, Andersson T, Grooten WJ. Low levels of physical activity in back pain patients are associated with high levels of fear-avoidance beliefs and pain catastrophizing. Physiother Res Int 2007;12:14–24.

21 Shamseer L, Moher D, Clarke M. Preferred reporting for systematic review and meta-analysis protocols (PRISMA-P). BMJ 2015;349:g7647.

22 Deeks JJ, Bossuyt PM, Gatsonis C. Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0.0. The Cochrane Collaboration, 2009.

23 McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, et al., eds. Cochrane Handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane, 2021.

24 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126–31.

25 French DJ, France CR, Vigneau F, et al. Fear of movement/(re) injury in chronic pain: a psychometric assessment of the original English version of the Tampa scale for kinesiophobia (TSK). Pain 2007;127:42–51.

26 Waddell G, Newton M, Henderson I, et al. A Fear-Avoidance questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain 1993;52:157–68.

27 Rohatgi A. WebPlotDigitizer - Extract data from plots, images, and maps, 2020. Available: https://automeris.io/WebPlotDigitizer/

28 Sterne JAC, Savović J, Page MJ, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:i4898.

29 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

30 Balshem H, Helfand M, Schünemann HJ, et al. Grade guidelines: 3. rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

31 Gagnier JJ, Moher D, Boon H, et al. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. BMC Med Res Methodol 2012;12:111.

32 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

33 Harbord RM, Higgins JPT. Meta-Regression in Stata. Stata Journal; 8:493–419, 2008. Available: http://www.stata-journal.com/article.html?article=sbe23_1

34 Higgins JP, Green S. Cochrane Handbook for systematic reviews of interventions, 2011. Available: http://www.mri.gov.lk/assets/Uploads/Research/Cochrane-Hand-book-text.pdf

35 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959:22:719–48.

36 DerSimonian R, Laird N. Meta-Analysis in clinical trials. Control Clin Trials 1986;7:177–88.

37 Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. J Educ Behav Stat 2010;35:215–47.

38 Begg CB, Mazumdar M. Operating characteristics of a RANK correlation test for publication bias. Biometrics 1994;50:1088–101.

39 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

40 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000b;56:455–63.

41 Sterne JAC, Newton HJ, Cox NJ. Meta-Analysis in Stata: an updated collection from the Stata Journal. College Station, TX: Stata Press, 2009.

42 Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.