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[Intervention Review]

Surgical versus non-surgical interventions in people with adolescent idiopathic scoliosis

Josette Bettany-Saltikov¹, Hans-Rudolf Weiss², Nachiappan Chockalingam³, Razvan Taranu⁴, Shreya Srinivas⁵, Julie Hogg¹, Victoria Whittaker¹, Raman V Kalyan⁶, Tracey Arnell⁷

¹School of Health and Social Care, University of Teesside, Middlesbrough, UK. ²Spinal Deformities Rehabilitation Services, Orthopedic Practice, Gensingen, Germany. ³Faculty of Health, Staffordshire University, Stoke-on-Trent, UK. ⁴Department of Trauma and Orthopaedics, Northumbria Healthcare NHS Foundation Trust, Ashington, UK. ⁵Northern Deanery, James Cook University Hospital, Middlesbrough, UK. ⁶James Cook University Hospital, Middlesbrough, UK. ⁷Newcastle College, Newcastle, UK

Contact address: Josette Bettany-Saltikov, School of Health and Social Care, University of Teesside, Victoria Road, Middlesbrough, Cleveland, TS13BA, UK. j.b.saltikov@tees.ac.uk

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ABSTRACT

Background

Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformity of the spine. While AIS can progress during growth and cause a surface deformity, it is usually not symptomatic. However, if the final spinal curvature surpasses a certain critical threshold, the risk of health problems and curve progression is increased. Interventions for the prevention of AIS progression include scoliosis-specific exercises, bracing, and surgery. The main aims of all types of interventions are to correct the deformity and prevent further deterioration of the curve and to restore trunk asymmetry and balance, while minimising morbidity and pain, allowing return to full function. Surgery is normally recommended for curvatures exceeding 40 to 50 degrees to stop curvature progression with a view to achieving better truncal balance and cosmesis. Short-term results of the surgical treatment of people with AIS demonstrate the ability of surgery to improve various outcome measures. However there is a clear paucity of information on long-term follow-up of surgical treatment of people with AIS.

Objectives

To examine the impact of surgical versus non-surgical interventions in people with AIS who have severe curves of over 45 degrees, with a focus on trunk balance, progression of scoliosis, cosmetic issues, quality of life, disability, psychological issues, back pain, and adverse effects, at both the short term (a few months) and the long term (over 20 years).

Search methods

We searched the Cochrane Back Review Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, four other databases, and three trials registers up to August 2014 with no language limitations. We also checked the reference lists of relevant articles and conducted an extensive handsearch of the grey literature.

Selection criteria

We searched for randomised controlled trials (RCTs) and prospective controlled trials comparing spinal fusion surgery with non-surgical interventions in people with AIS with a Cobb angle greater than 45 degrees. We were interested in all types of instrumented surgical interventions with fusion that aimed to provide curve correction and spine stabilisation.

Data collection and analysis

We found no RCTs or prospective controlled trials that met our inclusion criteria.

Main results

We did not identify any evidence comparing surgical to non-surgical interventions for AIS with severe curves of over 45 degrees.

Authors' conclusions

We cannot draw any conclusions.

PLAIN LANGUAGE SUMMARY

Surgical treatment compared to non-surgical treatment (braces, exercise, or observation) for teens with idiopathic scoliosis

Background

Scoliosis is a condition where the spine is curved in three dimensions (from the back the spine appears to be shaped like a 'c' or an 's'). It is often idiopathic, or of unknown cause. The most common type of scoliosis, adolescent idiopathic scoliosis (AIS), is discovered around 10 years of age or older, and is defined as a curve that measures at least 10 degrees (known as a Cobb angle, which is measured on an x-ray).

People with AIS usually have no symptoms, however the resulting surface deformity frequently negatively impacts adolescents. In addition, increased curvature of the spine can present health risks in adulthood. Different types of treatment, including physical therapy, bracing, and surgery, are advocated depending on the magnitude of the curvature and area affected, truncal balance, general health, level of function and satisfaction, and patient's and parent's treatment desire.

Surgery is normally recommended in curvatures exceeding 40 to 50 degrees to stop the progression of the curvature. Short-term results of surgical treatment are improvements on outcome measures relating to self image, some functional aspects, and pain. However, the structured long-term follow-up needed to make meaningful conclusions is lacking. Recent papers highlight the long-term complications of surgery, while other papers postulate that the medium- and long-term complication rates following modern scoliosis surgery are low when compared to older techniques.

Study characteristics

We searched the literature for both randomised controlled trials and prospective non-randomised studies with a control group examining the effects of surgical versus non-surgical treatments for teens with idiopathic scoliosis. The evidence is current to August 2014.

Key results

We identified no evidence examining the effectiveness of surgical interventions compared to non-surgical interventions for people with AIS. As a result, we cannot draw any conclusions regarding the benefits or harms of these treatments.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Surgical interventions compared with non-surgical Interventions in people with adolescent idiopathic scoliosis						
Patient or population: Adolescent Idiopathic Scoliosis Settings: Anywhere Intervention: Surgical intervention Comparison: Non-surgical intervention						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-surgical interventions	Surgical Interventions				
Changes in trunk balance	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group
Progression of scoliosis	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group
Cosmetic issues	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group

Quality of life	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group
Back pain	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group
Disability	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group
Psychological issues	See comment	See comment	Not estimable	0	See comment	We identified no randomised or non-randomised prospective studies with a control group

CI: confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Scoliosis is a complex, three-dimensional deformity of the spine that comprises a lateral curvature in the frontal plane (this is a vertical plane that divides the body into front and back halves), thoracic lordosis in the sagittal plane (this is a vertical plane that divides the body into right and left halves) and a posterior rib hump, which is produced by rotation of the vertebrae in the transverse plane (horizontal plane); this results in the posterior elevation of the rib cage on the convex side of the curve and a depression on the concave side (Bradford 1987). These underlying skeletal changes are usually reflected by a change in back shape, the unsightly shape of which is generally more of a concern to the patient than is the underlying skeletal deformity (White 1990). If left untreated, the condition results in altered spinal mechanics and degenerative changes that lead to pain, loss of spinal mobility, and possible loss of function or disability. Cardiac and respiratory dysfunction may accompany these symptoms, depending on the time of onset of the deformity (White 1990). There are also psychological consequences that result from the unsightly and deformed shape of the back: A restricted social life, lower marriage rate, higher divorce rate, fewer children per marriage, and increased psychiatric consultations, including eating disorders and increased suicide rate, have all been reported (Freidel 2002).

Scoliosis can also occur secondary to certain diseases and conditions that affect the nervous and muscular systems of the body. However, most cases of scoliosis (80% to 90%) are 'idiopathic', meaning the underlying cause is unknown. The most common form of scoliosis is adolescent idiopathic scoliosis (AIS), which appears in late childhood or adolescence -- a period of rapid growth (Kanayama 1996; Stokes 1996). According to the Scoliosis Research Society and the International Society on Scoliosis Orthopaedic Rehabilitation and Treatment (Negrini 2012), the prevalence of AIS in the general population is 2% to 3%. Nearly 10% of people with AIS will require some form of treatment, and up to 0.1% will eventually require surgery (Lonstein 2006).

AIS is more common in females. While it does not typically cause any health problems during growth, the resulting surface deformity frequently has a negative impact on adolescents that can give rise to quality-of-life issues and, in the worst cases, psychological disturbances (Reichel 2003). As the condition is most often painless, early diagnosis is difficult, especially in countries where school scoliosis screening is not implemented. External change to the body shape is minimal in the early stages, and most changes in back shape occur predominantly on the back of the trunk, which is difficult for patients to see, and can be concealed by clothing (Roaf 1980). Treatment of AIS is determined by the deformity itself. As most people with AIS progress during growth, the main aims of all interventions are to limit or stop the curvature pro-

gression, restore trunk balance (Goldberg 2002; Asher 2006), and prevent the long-term consequences of the deformity.

Description of the intervention

Interventions for the prevention of AIS progression include scoliosis-specific exercises, bracing, and surgery (Lenssinck 2005; Negrini 2005; Rowe 1997; Weiss 2006a). The goals of all interventions are to correct the deformity and prevent further deterioration of the curve (that is prevent progression) and to restore trunk symmetry and balance, while minimising morbidity and pain, allowing return to full function (Bridwell 1999; Lonstein 2006).

Non-surgical interventions

Scoliosis-specific exercises consist of individually adapted exercises that are taught to patients in a centre that is dedicated to scoliosis treatment. Patients learn an exercise protocol that is personalised according to their own medical and physiotherapeutic evaluation. On the other hand, usual generalised physiotherapy is more generic, consisting of low-impact stretching and strengthening activities like yoga, but can include many different exercise protocols.

Bracing is defined as the application of external supports to the trunk; these are usually rigid and are applied with the aim of achieving maximum correction of the pathological curve (Rigo 2006a). Treatment commences when the curve is diagnosed as progressive, or when it exceeds a threshold of 30 degrees Cobb angle (Lonstein 2006; Negrini 2005; Weiss 2006a). Braces generally need to be worn for a considerable period of time per day (at least 20 hours) over several years until the end of bone growth, which usually occurs at 16 years of age for girls and 18 years of age for boys (Katz 2001). This causes a significant negative impact on the quality of life of children and adolescents (Climent 1999; Fallstrom 1986; Noonan 1997).

Surgical interventions

Fusion is generally considered to be necessary when AIS exceeds a certain degree (approximately 45 to 50 degrees), when previous treatments have failed, or when AIS causes symptoms, but indications vary widely according to the preference of the treating physician/surgeon (Dolan 2007). The literature describes a large multitude and variety of interventions (Maruyama 2008), including different surgical approaches (posterior, anterior, or combined) and various types of metal implant systems.

Posterior fusion with instrumentation has long been a standard for the surgical treatment of AIS (Lonner 2007; Maruyama 2008). The Harrington technique and instrumentation was introduced in the 1960s, followed by the Cotrel-Dubousset instrumentation technique in 1980s (Kadoury 2009). The last two decades have

seen a gradual progression or shift of usage from hook-based instrumentation systems to hybrid-based systems (hooks and pedicle screws) to all-pedicle screw systems with more anchors to the spine. This shift has enabled greater and better anchorage and correction manoeuvres and reduced the implant failure rate (Olgun 2013).

Anterior instrumentation surgery was previously favoured for thoracolumbar and lumbar scoliosis, as it enabled shorter fusion levels. However, since the recent introduction and usage of all-pedicle screw construct posterior surgery, the use of anterior surgery has been limited (Maruyama 2008). Modern surgical techniques follow the principles of segmental spinal instrumentation, where each vertebra of the spine is attached to a metal rod by means of screws or hooks.

Modern surgical techniques are believed to reliably provide a better arrest of progression of the deformity and achieve greater correction of the curves in the coronal plane (30% to 90%) with minimal loss at follow-up (Westrick 2011). Furthermore, these techniques also achieve a spontaneous partial correction of the compensatory curves and improve appearance. A recent prospective multicentre study on the outcomes of surgical treatment using participant-based outcomes demonstrates the ability of surgery to improve some outcome measures at the two-year postsurgical follow-up (Merola 2002). However, there is a lack of high-quality prospective studies with a control group on long-term follow-up.

All types of spinal fusion surgery are associated with significant risk, both in the short term and long term. The short-term risk for spinal fusion surgery is estimated to be approximately 5%, while long-term risks over a lifetime are estimated to be much higher (Weiss 2008a), with reoperation rates ranging from 6% to 29% (Asher 2006). A recently published meta-analysis on 1565 participants with a mean follow-up of 14.9 years demonstrated a reoperation rate between 0% to 8.3% (Lykissas 2013), the highest incidence being related to the use of Harrington rods and the lowest to all-pedicle screws. The same study reported a mean infection rate of 3.6%, the lowest incidence being encountered with the use of all-pedicle screws (1.18%) and the highest with Harrington rods (5.5%).

How the intervention might work

Scoliosis-specific exercises can be used in three main clinical scenarios: (1) as the primary treatment of AIS for mild curves, (2) in conjunction with braces for moderate curves, and (3) during adulthood if the scoliosis curves exceed certain thresholds (Romano 2012). In the treatment of mild scoliosis, scoliosis-specific exercises can be used on curves greater than 10 to 15 degrees but less than 25 or 30 degrees Cobb. These intense three-dimensional spine-and-rib-cage-specific exercises are used to try to limit the progression of the curve and thereby avoid the need for a brace. This critical Cobb angle is generally regarded as the threshold for brace prescription (Lonstein 2006; Weiss 2006b). The key objec-

tives of physical exercise in mild cases of AIS include stabilisation of the spine, three-dimensional auto-correction of the pelvis, rib cage, and shoulders together with isometric muscle contractions (Romano 2012; Weiss 2006b).

Braces use external corrective forces to correct the trunk; this is usually achieved with the use of rigid supports. However, some braces (known as soft braces) are made of material similar to elastic bands that is comparable with materials used in physical therapy treatments (Coillard 2003; Rigo 2006a). The mechanical forces of the brace are used to straighten the spine and de-rotate the pelvis and shoulders to bring the whole body into normal alignment. Negrini 2010 states that the external and proprioceptive inputs due to bracing change the unnatural loading on the spine and rib cage, decrease asymmetrical movements, and improve neuromuscular control; this facilitates proper spinal growth, neuromotor reorganization, and changes in motor behaviours (Castro 2003; Coillard 2002; Grivas 2008; Lupporelli 2002; Negrini 2006c; Odermatt 2003; Smania 2008; Stokes 2006; Weiss 2004). Unfortunately, most braces have the disadvantage of not being very comfortable to wear, especially for long periods. Furthermore, weakening of the back muscles may occur if bracing is not combined with scoliosis-specific exercises.

The aim of surgical treatment of the scoliotic spine is to correct the spinal curvature (reduction of the Cobb angle) and fuse the spine with the help of bone grafts that allow the spine to heal to a solid and stable bone fusion mass (spinal fusion), supported by the instrumentation (Haher 2003).

Why it is important to do this review

After conducting a comprehensive literature search, we identified only two key reviews that addressed surgical versus non-surgical interventions for AIS (Hawes 2006a; Weiss 2008b). Hawes 2006a was a very comprehensive narrative review, and hence had all the biases and limitations generally associated with such reviews (Bettany-Saltikov 2012). Weiss 2008b, although entitled a “systematic review”, did not in actuality meet the criteria for a systematic review; the search strategy as well as the precise methods used to identify and select papers were not detailed. Furthermore, it was unclear which primary papers were included and/or excluded, and the processes for the methodological evaluation and data extraction of included primary papers, if undertaken, were not described.

The significant limitations of these two reviews strongly highlighted the need for a state-of-the-art Cochrane review. Additionally, it was important to undertake this review so that people with AIS with severe curves and their parents understand both the short- and long-term effects, as well as the side effects and consequences, of surgical and non-surgical interventions, and can make evidence-based decisions.

OBJECTIVES

To examine the impact of surgical versus non-surgical interventions in people with AIS who have severe curves of over 45 degrees, with a focus on trunk balance, progression of scoliosis, cosmetic issues, quality of life, disability, psychological issues, back pain, and adverse effects, at both the short term (a few months) and the long term (over 20 years).

METHODS

Criteria for considering studies for this review

Types of studies

For the primary analysis we intended to combine the results of randomised control trials (RCTs) and quasi-randomised control trials (QRCTs). We also planned to include prospective non-randomised studies (NRSs) with a control group because we anticipated finding very few RCTs. We planned to include primary studies that compared surgical interventions with non-surgical interventions.

Types of participants

We intended to include people with AIS who were diagnosed and managed when they were between 10 and 18 years of age, with a Cobb angle greater than 45 degrees (Negrini 2012). We planned to exclude studies on participants with early-onset scoliosis (infant or juvenile) and scoliosis secondary to other conditions.

Types of interventions

We intended to include all types of instrumented surgical interventions with fusion that aimed to provide curve correction and spine stabilisation. We planned to exclude studies describing non-instrumented spinal correction and fusion, because the outcomes these interventions provide have been shown to be no better than those seen with untreated scoliosis (Bradford 1987).

We aimed to compare instrumented surgical interventions with different types of non-surgical treatments, such as scoliosis-specific exercises, bracing, physiotherapy, chiropractic treatment, electrical stimulation, and other non-surgical interventions for people with AIS with severe curves of over 45 degrees.

Types of outcome measures

We planned to examine outcomes (primary and secondary) measured in the immediate term (perioperative to six weeks postoperative), the short term (results at the end of bone growth), within two years, and over the long term (results in adulthood and in old age).

Primary outcomes

1. Change in trunk balance, measured in centimetres:
 - i) Frontal (coronal) balance (refers to the plane that divides the body into front and back halves);
 - ii) Lateral trunk shift; and
 - iii) Apical vertebral translation.
2. Progression of scoliosis, measured by:
 - i) Cobb angle in degrees (absolute values);
 - ii) Angle of trunk rotation in degrees (absolute values);and
 - iii) Number of participants who progressed by more than 5 degrees Cobb (5 degrees Cobb is the standard clinical measure reported within various research papers and commonly used in clinical practice).
3. Cosmetic issues, as measured by:
 - i) Validated scales or questionnaires: Walter Reed Visual Assessment Scale (Pineda 2006), Spinal Appearance Questionnaire (Sanders 2007), Trunk Appearance Perception Scale (Bago 2010); and
 - ii) Topographic measurements: Integrated Shape Imaging System or Integrated Shape Imaging System 2 (Berryman 2008), Quantec (Oxborrow 2000), Formetric (Knott 2010), measured in angles and millimetres.
4. Quality of life as measured by:
 - i) Generic questionnaires: 36-Item Short Form Health Survey;
 - ii) Scoliosis-specific questionnaires: Scoliosis Research Society-22 (Asher 2003);
 - iii) Bad Sobernheim Stress Questionnaire (Weiss 2006b);and
 - iv) Brace Questionnaire (Vasiliadis 2006).
5. Psychological issues as measured by:
 - i) Specific psychological questionnaires evaluating such concepts as self esteem, self image, etc., using specific questionnaires and subscales of Scoliosis Research Society-22, Brace Questionnaire, 36-Item Short Form Health Survey.
6. Back pain and disability as measured by:
 - i) Validated scales measuring pain intensity and pain duration, such as the visual analogue scale, McGill Pain Questionnaire, and other validated specific questionnaires, as well as use of medication.

Secondary outcomes

Secondary outcomes were any adverse effects reported in any of the included studies, such as blood loss, pseudarthrosis (a false joint where the bone has not healed adequately), deep wound infection, neurological complications, delayed infections, pedicle screw misplacement, delayed paraparesis (weakness or partial paralysis in the lower limbs) as well as the loss of normal spinal function and decompensation (spinal imbalance), increased spinal deformity and death. We planned to report any adverse events in our

review, whether or not they were listed here.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases from inception to August 2014.

- Cochrane Back Review Group Trials Register (Cochrane Register of Studies (CRS))
- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
- MEDLINE (OvidSP, 1946 to July Week 5, 2014) and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP, 7 August 2014)
- EMBASE (OvidSP, 1980 to 2014 Week 31)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCO, 1981 to August 2014)
- PsycINFO (OvidSP, 2002 to August Week 1, 2014)
- Physiotherapy Evidence Database (PEDro, 1929 to August 2014)
- PubMed (1946 to August 2014)

The search strategy combined the study design filter for observational studies adapted from the Scottish Intercollegiate Guidelines Network with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE, so that the search captured all study designs. We combined the study design terms with blocks of search terms for the disorder and the interventions. The strategy included subject headings (for example MeSH) and was adapted for the other databases (see [Appendix 1](#) and [Appendix 2](#)).

Searching other resources

The following strategies were also used.

- Screening the reference lists of all relevant papers.
- Searching the main electronic sources of ongoing trials: UK Clinical Trials Gateway ([UKCTG](#)), [ClinicalTrials.gov](#), and the World Health Organization International Clinical Trials Registry Platform ([WHO ICTRP](#)) (see [Appendix 2](#)).
- Searching the grey literature, including conference proceedings and PhD theses completed since 1980. For the latter, we searched the Electronic Theses Online Service ([EThOS](#)) provided by the British Library, which is an 'open access single point digital repository of UK research theses'. See [Appendix 2](#) for the EThOS search strategy.
- Contacting investigators and authors in the field for information on unpublished or incomplete trials.

All searches included non-English language literature.

Data collection and analysis

Selection of studies

We first developed a study selection form on the basis of the inclusion criteria. This was piloted and tested for both intraobserver and interobserver reliability by two review authors, who then independently screened the search results by reading the titles and abstracts. Potentially relevant studies were obtained in full text, and once again they were independently assessed for inclusion by two review authors, who resolved any disagreement through discussion. A third review author was contacted if disagreements persisted. If a review author was also the author of a paper, another review author who had not authored any of the papers undertook the selection.

We did not select any papers before 1980 because research done on older instrumentation may not have been relevant. Although clear advances in the materials and the design of spinal instrumentation have been made since 1980, the surgical approach and training may still be the same.

We did not find any relevant RCTs, QRCTs, or NRSs with a control group. As such, we were unable to carry out most of the pre-stated methodology. We have therefore described the planned methods in [Appendix 3](#).

Data extraction and management

See [Appendix 3](#) for planned methodology.

Assessment of risk of bias in included studies

See [Appendix 3](#) for planned methodology.

Measures of treatment effect

See [Appendix 3](#) for planned methodology.

Unit of analysis issues

See [Appendix 3](#) for planned methodology.

Dealing with missing data

See [Appendix 3](#) for planned methodology.

Assessment of heterogeneity

See [Appendix 3](#) for planned methodology.

Assessment of reporting biases

See [Appendix 3](#) for planned methodology.

Data synthesis

See [Appendix 3](#) for planned methodology.

Subgroup analysis and investigation of heterogeneity

See [Appendix 5](#) for planned methodology.

Sensitivity analysis

See [Appendix 3](#) for planned methodology.

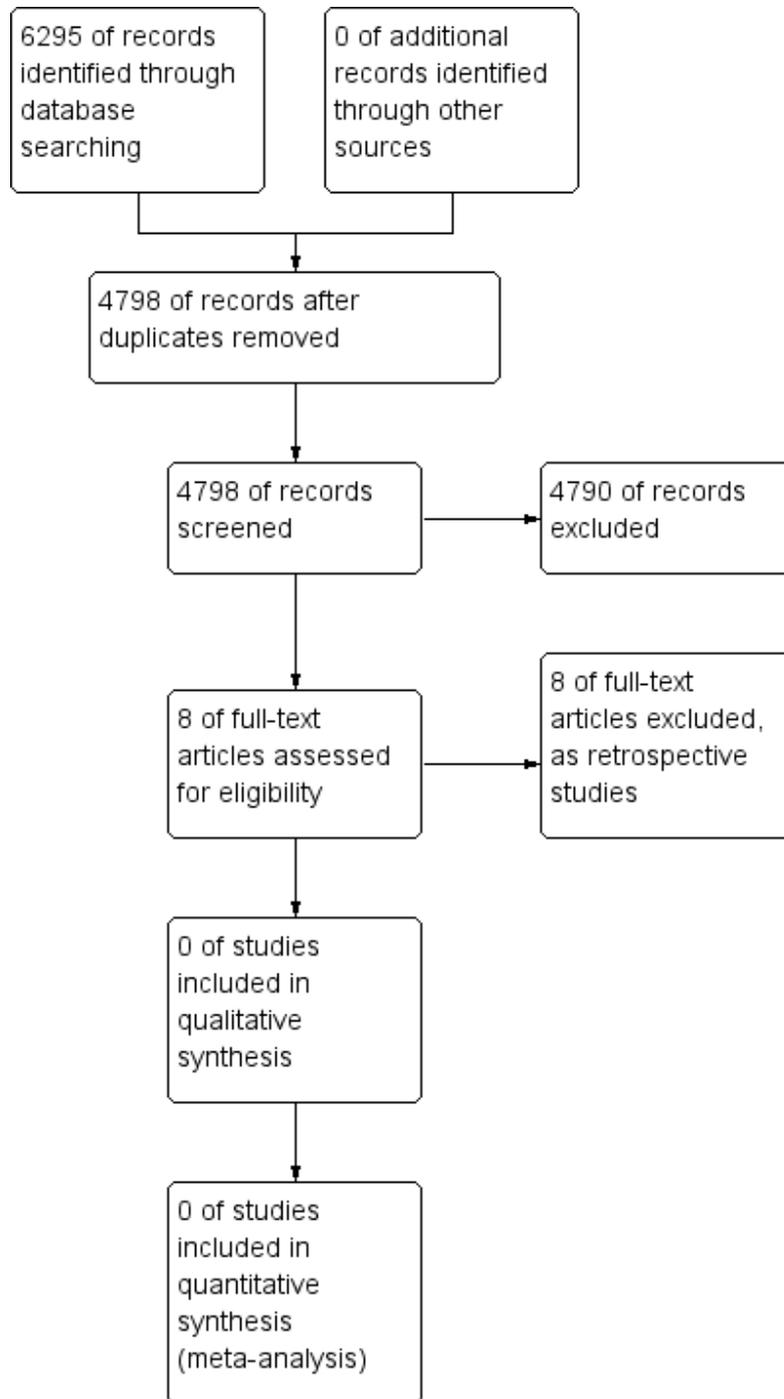
Clinical relevance of results

See [Appendix 3](#) for planned methodology.

RESULTS**Description of studies****Results of the search**

Our search of databases identified 4798 records. After screening the records, we assessed eight full-text articles, which we excluded because they were either retrospective cohort studies with a control group or retrospective case studies with a control group. There were no prospective studies with a control group (see study flow diagram, [Figure 1](#)).

Figure 1. Study flow diagram.



Excluded studies

The eight studies we excluded were all retrospective studies with a control group (Anderson 2006; Bunge 2007; Danielsson 2001; Danielsson 2001a; Danielsson 2001b; Danielsson 2003; Danielsson 2006; Pehrsson 2001). See [Characteristics of excluded studies](#) tables.

Risk of bias in included studies

We evaluated no studies for methodological quality.

Effects of interventions

See: [Summary of findings for the main comparison](#)

We did not identify any evidence comparing surgical to non-surgical interventions for people with AIS with severe curves of over 45 degrees ([Summary of findings for the main comparison](#))

DISCUSSION

Summary of main results

We did not identify any evidence of effectiveness of surgical compared to non-surgical interventions for people with AIS with severe curves of over 45 degrees.

Overall completeness and applicability of evidence

This review is technically considered to be an 'empty review' as we did not find any studies that met all the inclusion criteria. Nonetheless, this review provides important information regarding research gaps in this field, which is consistent with previously published reviews on this topic (Weiss 2008c; Weiss 2013).

Quality of the evidence

There is currently no randomised or non-randomised trial-based evidence from prospective studies with a control group comparing the effectiveness of surgical to non-surgical interventions for people with AIS with severe curves of over 45 degrees.

Potential biases in the review process

The most important potential bias is having missed any prospective controlled studies. However, given our extensive literature search, it is unlikely that we have missed any studies.

Agreements and disagreements with other studies or reviews

There is currently no randomised or non-randomised trial-based evidence from prospective studies with a control group that could be compared with other studies.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, we did not identify any evidence comparing surgical to non-surgical interventions for people with AIS with severe curves of over 45 degrees. We were therefore unable to draw any conclusions in this review.

Implications for research

In conclusion, we did not identify any evidence comparing surgical to non-surgical interventions for people with AIS with severe curves of over 45 degrees. We were therefore unable to draw any conclusions in this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2006	Retrospective study with a control group
Bunge 2007	Retrospective cross sectional study with a control group
Danielsson 2001	Retrospective study with a control group
Danielsson 2001a	Retrospective study with a control group
Danielsson 2001b	Retrospective study with a control group
Danielsson 2003	Retrospective study with a control group
Danielsson 2006	Retrospective study with a control group
Pehrsson 2001	Retrospective study with a control group

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. CBRG Trials Register, CENTRAL, MEDLINE, EMBASE and CINAHL search strategies

CBRG Trials Register

Last searched 11 August, 2014

#1 scoliosis

CENTRAL

Last searched 8 August, 2014

#1 MeSH descriptor: [Scoliosis] explode all trees

#2 scoliosis:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Orthopedic Procedures] explode all trees

#5 MeSH descriptor: [Orthopedic Fixation Devices] explode all trees

#6 "spine fusion" or "spinal fusion" or "spinal instrumentation" or spondylodesis:ti,ab,kw (Word variations have been searched)

#7 surg* or operat* or realign* or screw* or hybrid or wire* or hook* or sublaminar:ti,ab,kw (Word variations have been searched)

#8 #4 or #5 or #6 or #7

#9 MeSH descriptor: [Orthotic Devices] explode all trees

#10 braces:ti,ab,kw (Word variations have been searched)

#11 bracing:ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Exercise] explode all trees

#13 MeSH descriptor: [Physical Therapy Modalities] explode all trees

#14 MeSH descriptor: [Rehabilitation] explode all trees

#15 MeSH descriptor: [Drug Therapy] explode all trees

#16 non-surg* or nonsurg* or non-operat* or nonoperat* or conserv* or taping or tape* or immobilis* or immobiliz* or therap* or electrotherap*:ti,ab,kw (Word variations have been searched)

#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #3 and #8 and #17 Publication Year from 2013 to 2014, in Trials

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations

Last searched 8 August 2014

1. exp Spinal Diseases/
2. Scoliosis/
3. scoliosis.mp.
4. or/1-3
5. Orthopedics/
6. exp Surgical Procedures, Operative/
7. surgery.fs.
8. surg\$.tw.
9. operat\$.tw.
10. realign\$.tw.

11. spondylodesis.tw.
12. spine fusion.tw.
13. spinal fusion.tw.
14. spinal instrumentation.tw.
15. Bone Screws/
16. screw\$.tw.
17. hybrid.tw.
18. Bone Wires/
19. sublaminar.tw.
20. wire\$.tw.
21. hook\$.tw.
22. or/5-21
23. exp Rehabilitation/
24. rehabilit\$.tw.
25. rehabilitation.fs.
26. exp Physical Therapy Modalities/
27. Physical Therapy Speciality.mp.
28. physiotherapy.tw.
29. physical therapy.tw.
30. exp Exercise/
31. exercise\$.tw.
32. Exercise Movement Techniques/
33. exp Exercise Therapy/ (30988)
34. exp Musculoskeletal Manipulations/
35. Immobilization/
36. Braces/
37. brace\$.mp.
38. bracing.mp.
39. exp Orthotic Devices/
40. Orthopedic Equipment/
41. limit 40 to yr="1902 - 1975"
42. (non-surg\$ or nonsurg\$ or non-operat\$ or nonoperat\$ or conserv\$).tw.
43. (immobilis\$ or immobiliz\$ or therap\$ or taping or tape\$ or electrotherapy\$).tw.
44. or/23-43
45. 4 and 22 and 44
46. limit 45 to adolescent <13 to 18 years>
47. Adolescent/
48. adolescen\$.mp.
49. 47 or 48
50. 45 and 49
51. 46 or 50
52. Comparative Study/
53. exp Evaluation Studies/
54. exp Follow-Up Studies/
55. exp Prospective Studies/
56. exp Cross-Over Studies/
57. exp Epidemiologic Studies/
58. exp Case-Control Studies/
59. exp Cohort Studies/
60. exp Cross-Sectional Studies/
61. (cohort adj (study or studies)).mp.
62. cohort analy\$.mp.
63. (follow up adj (study or studies)).mp.

64. (observational adj (study or studies)).mp.
65. longitudinal.mp.
66. retrospective.mp.
67. cross sectional.mp.
68. control\$.mp.
69. prospective\$.mp.
70. volunteer.mp.
71. or/52-70
72. randomized controlled trial.pt.
73. controlled clinical trial.pt.
74. randomi#ed.ti,ab.
75. placebo.ti,ab.
76. drug therapy.fs.
77. randomly.ti,ab.
78. trial.ti,ab.
79. groups.ti,ab.
80. or/72-79
81. (Animals not (Humans and Animals)).sh.
82. 80 not 81
83. 71 not 81
84. 82 or 83
85. 51 and 84
86. limit 85 to yr=2013-2014
87. limit 85 to ed=20130705-20140808
88. 86 or 87

EMBASE

Last searched 8 August 2014

1. exp spine/
2. exp spine disease/
3. exp scoliosis/
4. exp idiopathic scoliosis/
5. scoliosis.mp.
6. or/1-5
7. orthopedics/
8. exp surgery/
9. su.fs.
10. surg\$.ti,ab.
11. operat\$.ti,ab.
12. realign\$.ti,ab.
13. spondylodesis.ti,ab.
14. spine fusion.ti,ab.
15. spinal fusion.ti,ab.
16. spinal instrumentation.ti,ab.
17. bone screw/
18. screw\$.ti,ab.
19. hybrid.ti,ab.
20. Kirschner wire/
21. sublaminar.ti,ab.
22. wire\$.ti,ab.
23. hook\$.ti,ab.
24. or/7-23

25. exp rehabilitation/
26. rehabilitat\$.ti,ab.
27. rh.fs.
28. exp physiotherapy/
29. physiotherapist/
30. physiotherapy.ti,ab.
31. physical therapy.ti,ab.
32. exp exercise/
33. exercise\$.ti,ab.
34. kinesiotherapy/
35. exp manipulative medicine/
36. immobilization/
37. brace/
38. brace\$.mp.
39. bracing.mp.
40. exp orthotics/
41. exp orthopedic equipment/
42. (non-surg\$ or nonsurg\$ or non-operat\$ or nonoperat\$ or conserv\$).ti,ab.
43. (immobilis\$ or immobiliz\$ or therap\$ or taping or tape\$ or electrotherap\$).ti,ab.
44. or/25-43
45. 6 and 24 and 44
46. limit 45 to adolescent <13 to 17 years>
47. adolescent/
48. adolescen\$.mp.
49. or/47-48
50. 45 and 49
51. 46 or 50
52. exp Clinical Study/
53. exp Case Control Study/
54. exp Family Study/
55. exp Longitudinal Study/
56. exp Retrospective Study/
57. exp Prospective Study/
58. exp Cohort Analysis/
59. (cohort adj (study or studies)).mp.
60. (case control adj (study or studies)).mp.
61. (follow up adj (study or studies)).mp.
62. (observational adj (study or studies)).mp.
63. (epidemiologic\$ adj (study or studies)).mp.
64. (cross sectional adj (study or studies)).mp.
65. exp Comparative Study/
66. evaluation study.mp.
67. follow-up study.mp. or exp Follow Up/
68. Crossover Procedure/
69. prospective\$.mp.
70. exp VOLUNTEER/
71. or/52-70
72. Clinical Article/
73. exp Clinical Study/
74. Clinical Trial/
75. Controlled Study/
76. Randomized Controlled Trial/
77. Major Clinical Study/

78. Double Blind Procedure/
79. Multicenter Study/
80. Single Blind Procedure/
81. Phase 3 Clinical Trial/
82. Phase 4 Clinical Trial/
83. crossover procedure/
84. placebo/
85. or/72-84
86. allocat\$.mp.
87. assign\$.mp.
88. blind\$.mp.
89. (clinic\$ adj25 (study or trial)).mp.
90. compar\$.mp.
91. control\$.mp.
92. cross?over.mp.
93. factorial\$.mp.
94. follow?up.mp.
95. placebo\$.mp.
96. prospectiv\$.mp.
97. random\$.mp.
98. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp.
99. trial.mp.
100. (versus or vs).mp.
101. or/86-100
102. 85 or 101
103. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
104. human/ or normal human/ or human cell/
105. 103 and 104
106. 103 not 105
107. 102 not 106
108. 71 not 106
109. 107 or 108
110. 51 and 109
111. limit 110 to yr=2013-2014
112. limit 110 to em=201326-201431
113. 111 or 112

CINAHL

Last searched 8 August 2014

v S85 S83 or S84

S84 S82 and EM 20130705-20140808

S83 S82 Limiters - Published Date: 20130701-20140831

S82 S77 OR S81

S81 S76 AND S80

S80 S78 OR S79

S79 adolescen*

S78 MH Adolescence+

S77 S34 AND S39 AND S75 Limiters - Age Groups: Adolescent: 13-18 years

S76 S34 AND S39 AND S75

S75 S56 OR S74

S74 S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73

S73 TI (immobilis* or immobiliz* or therap* or taping or tape* or electrotherap*) or AB (immobilis* or immobiliz* or therap* or taping or tape* or electrotherap*)
 S72 TI (non-surg* or nonsurg* or non-operat* or nonoperat* or conserv*) or AB (non-surg* or nonsurg* or non-operat* or nonoperat* or conserv*)
 S71 MH “Orthopedic Equipment and Supplies+”
 S70 orthotic*
 S69 (MH “Orthoses+”) OR “orthoses”
 S68 bracing
 S67 brace*
 S66 MH Immobilization
 S65 MH Manipulation, Orthopedic
 S64 MH Therapeutic Exercise+
 S63 TI exercise* or AB exercise*
 S62 MH Exercise+
 S61 TI “physical therapy” or AB “physical therapy”
 S60 TI physiotherapy or AB physiotherapy
 S59 MH Physical Therapists
 S58 MH Physical Therapy+
 S57 MH Rehabilitation+
 S56 (TI hook* or AB hook*) AND (S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55)
 S55 TI hook* or AB hook*
 S54 TI wire* or AB wire*
 S53 TI sublaminar or AB sublaminar
 S52 TI hybrid or AB hybrid
 S51 TI screw* or AB screw*
 S50 MH Orthopedic Fixation Devices
 S49 TI “spinal instrumentation” or AB “spinal instrumentation”
 S48 TI “spinal fusion” or AB “spinal fusion”
 S47 TI “spine fusion” or AB “spine fusion”
 S46 TI spondylodesis or AB spondylodesis
 S45 TI realign* or AB realign*
 S44 TI operat* or AB operat*
 S43 TI surg* or AB surg*
 S42 MW Surgery
 S41 MH Surgery, Operative+
 S40 MH Orthopedics
 S39 S35 OR S36 OR S37 OR S38
 S38 scoliosis
 S37 MH Scoliosis+
 S36 MH Spinal Diseases+
 S35 MH Spine+
 S34 S32 or S33
 S33 S30 not S31
 S32 S14 not S31
 S31 MH Animals
 S30 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
 S29 volunteer*
 S28 prospective*
 S27 control*
 S26 retrospective
 S25 longitudinal
 S24 “observational studies” or “observational study”

S23 “follow-up stud*” or “followup stud*”
 S22 “cohort analys*”
 S21 “cohort studies” or “cohort study”
 S20 MH Epidemiological Research+
 S19 MH Prospective Studies+
 S18 MH Evaluation Research+
 S17 MH Comparative Studies
 S16 latin square
 S15 MH Study Design+
 S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
 S13 MH Random Sample
 S12 random*
 S11 MW Drug Therapy
 S10 placebo*
 S9 MH Placebos
 S8 MH Placebo Effect
 S7 TI groups or AB groups
 S6 triple-blind
 S5 single-blind
 S4 double-blind
 S3 clinical W3 trial
 S2 “randomi?ed controlled trial*”
 S1 (MH “Clinical Trials+”)

Appendix 2. Other search strategies

PsycINFO

Last searched 8 August 2014

1 scoliosis.mp.

2 (surg* or operat* or realign* or spondylodesis or fusion or instrumentation or screw* or hook* or hybrid or wire* or sublaminar).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

3 (rehabilit* or therap* or physiotherapy or exercise* or braces or bracing or orthotic* or non-surg* or nonsurg* or non-operat* or nonoperat* or conserv* or immobilis* or immobiliz* or taping or tape* or electrotherapy).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

4 1 and 2 and 3

5 limit 4 to yr=2013-2014

PEDro

Last searched 8 August 2014

Abstract & Title: scoliosis

AND

Method: clinical trial

New records added since 05/07/2013

PubMed

Searched 11 August 2014. This search was designed to capture citations not indexed in MEDLINE.

(((((surg* or fus* or orthopedic* or instrument* or screw* or wire* or hook*[Title/Abstract])) OR (nonsurg* or non-surg or nonop* or non-op* or immobiliz* or immobilis* or exercise* or therap* or braces or bracing or taping or tape* or electrotherap* or rehab* or

conserv*[Title/Abstract])) AND (adolescen* AND scoliosis[Title/Abstract])) AND (“2013/07/05”[Date - Publication] : “3000”[Date - Publication])) NOT MEDLINE[sb]

UKCTG

Last searched August 2014
scoliosis

ClinicalTrials.gov

Last searched 8 August 2014
Condition: scoliosis

WHO ICTRP

Last searched 8 August 2014
Condition: scoliosis

EThOS

Last searched August 2014
scoliosis

Appendix 3. Planned Methodology

Data extraction and management

We planned to perform the review and meta-analyses following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would have performed the analyses using Review Manager (Review Manager (RevMan) 2014).

We had prepared a standardised data extraction form on the basis of all the inclusion criteria, which, had we identified any relevant trials, two review authors would have piloted and tested for intra- and interobserver reliability, and then used the form independently to extract data from the included papers. We would have extracted raw data, including information about the study design (RCT, QRCT, prospective controlled cohort study), study characteristics (country, recruitment modality, study funding, risk of bias), and participant characteristics (number of participants, age, sex, severity of scoliosis at baseline), as well as a description of experimental and comparison interventions, co-interventions, adverse effects, duration of follow-up, outcomes assessed and results, as well as any adverse effects. If a review author was the author of a paper, another review author would have undertaken the data extraction process. We would have discussed any disagreements and consulted a third review author if any disagreements persisted.

Assessment of risk of bias in included studies

We would have assessed the risk of bias for both randomised studies and NRSs using the criteria recommended by the Cochrane Back Review Group (Furlan 2009; Higgins 2011), together with items from the Downs and Black (Downs 1998) checklist, as outlined in Appendix 4. These criteria fall into five bias categories: selection bias, performance bias, attrition bias, detection bias, and selective outcome reporting. We piloted and tested the 'Risk of bias' assessment form for intraobserver and interobserver reliability. Two review authors would have independently assessed the internal validity of the included studies. The review authors would have resolved any disagreements by discussion, consulting a third independent review author if disagreements persisted. We planned to blind the 'Risk of bias' assessment to trial authors, institution, and journal. We planned to score the 'Risk of bias' criteria as high, low, or unclear and report these ratings in the 'Risk of bias' table. Next we would have rated the overall extent of risk of bias within each bias category (for example performance bias) as 'bias' or 'no bias'.

While it was difficult to provide an exhaustive list of all possible confounding variables at the start of the review, the review authors have experience in this field and are aware of most of the potential confounding variables that may occur when different treatment groups

are compared. These may have included, for instance, demographic variables such as age, Risser sign (bone maturity), curve location, and curve magnitude.

In regard to grading the quality of the evidence, we would not have downgraded evidence from studies judged 'no bias' for all five categories. We would have downgraded evidence by -1 point when three or fewer categories for each study were judged to have bias. We would have downgraded evidence by -2 points when four or more categories for each study were judged to have bias. See the [Data synthesis](#) section that follows for additional details on how we would have assessed the quality assessment for each outcome.

Measures of treatment effect

We planned to analyse dichotomous outcomes by calculating the risk ratio for each trial, with uncertainty in each result expressed by 95% confidence intervals. We planned to analyse continuous outcomes by calculating the weighted mean difference or the standardised mean difference with 95% confidence intervals.

Unit of analysis issues

In cases where three or more interventions were evaluated in a single study, we pre-stated in the protocol that we would include each pairwise comparison separately.

Dealing with missing data

For recent papers (within five years), we would have endeavoured to collect missing data by contacting the authors. When data were insufficient to be entered into the meta-analysis (even after contacting the authors), we had planned to report the results qualitatively in the 'Characteristics of included studies' table and the 'Summary of findings' tables.

Assessment of heterogeneity

In the protocol we stated that we would combine the outcome measures from individual trials through meta-analysis where possible (comparability of intervention and outcomes across trials) using a random-effects model. We would have used the I^2 statistic and the Chi^2 test (P less than 0.1) to indicate whether significant statistical heterogeneity was present. If a meta-analysis was not possible, we would have described the results from clinically comparable trials qualitatively in the text.

Assessment of reporting biases

To determine whether publication bias was present, we would have constructed funnel plots if at least 10 studies were available for the meta-analysis ([Sutton 2000](#)).

Data synthesis

In the protocol we stated that we would analyse dichotomous outcomes by calculating the risk ratio. We also planned that continuous outcomes would be analysed by calculating the mean difference when the same instrument was used to measure outcomes or the standardised mean difference when different instruments were used to measure outcomes. We would express uncertainty with 95% confidence intervals. It was postulated to combine outcome measures from the individual trials through meta-analysis where possible (clinical comparability of population, intervention/s and outcomes between trials) using a random-effects model. A P value of the Chi^2 test less than 0.1 would indicate significant statistical heterogeneity.

If meta-analysis was not possible, we would have described the results from clinically comparable trials qualitatively in the text. Regardless of whether sufficient data were available for the use of quantitative analyses to summarise the data, we would have assessed the overall quality of the evidence for each outcome. To accomplish this, we would have used the GRADE approach, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) and adapted in the updated Cochrane Back Review Group method guidelines ([Furlan 2009](#)). Factors that may have decreased the quality of the evidence included study design and risk of bias, inconsistency of results, indirectness (not generalisable), imprecision (sparse data), and other factors (for example reporting bias).

The quality of the evidence for a specific outcome would have been reduced by a level, according to the performance of the studies against the following five factors.

- High-quality evidence: Consistent findings had been noted among at least 75% of RCTs with low risk of bias; consistent, direct, and precise data and no known or suspected publication biases. Further research is unlikely to change the estimate or our confidence in the results.
- Moderate-quality evidence: One of the domains was not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low-quality evidence: Two of the domains were not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low-quality evidence: Three of the domains were not met. We are very uncertain about the results.
- No evidence: No studies were identified that addressed this outcome.

Subgroup analysis and investigation of heterogeneity

If we noted significant statistical heterogeneity, we would have performed a subgroup analysis to consider the effects of the following variables: age, bone age, Cobb degrees, type of surgery and braces, and exercise.

Sensitivity analysis

To incorporate the 'Risk of bias' assessment into the review process, we would have started by stratifying the intervention effects estimates by risk. If we saw differences in results among studies at different risks of bias, we would have performed sensitivity analyses, excluding studies with high risk of bias from the analysis. Alternatively, we would have presented the results for RCTs and QRCTs separately from those of longitudinal studies.

Clinical relevance of results

The review authors would also have assessed each trial for its clinical relevance by using the five questions outlined by [Shekelle 1994](#) and recommended by the Cochrane Back Review Group (see [Appendix 5](#)) ([Furlan 2009](#); [Van Tulder 2003](#)). We would have discussed all important outcomes for each comparison. In the protocol the review authors had also planned for the main conclusion to be clinical, as our main aim was to give clinicians, researchers, patients, and service users state-of-the-art information provided by relevant studies on this issue.

Appendix 4. Criteria for assessing risk of bias for internal validity for randomised and non-randomised studies (Downs and Black 1998; Furlan 2009)

Selection bias

Random sequence generation

Risk of selection bias is low if the investigators described a random component in the sequence generation process, such as referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing lots, minimising (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).

Risk of selection bias is high if the investigators described a non-random component in the sequence generation process, such as sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention.

If study is non-randomised, this will be rated as high bias.

Allocation concealment

Risk of selection bias is low if participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, Web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes.

Risk of bias is high if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on using an open random allocation schedule (for example a list of random numbers); assignment envelopes were used without appropriate safeguards (for example if envelopes were unsealed or non-opaque or were not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.

If study is non-randomised, this will be rated as high bias.

Selection bias (population)*

Risk of selection bias is low if participants in different intervention groups were recruited from the same population.

Selection bias (timing)*

Risk of selection bias is low if participants in different intervention groups were recruited over the same time. Surgical studies must be less than 10 years old for low risk of selection bias.

Adjustment for confounding*

Risk is low if no significant group differences were shown. Risk is high if the effect of the main confounders was not investigated or if no adjustment was made in the final analyses.

Performance bias**Blinding of participants**

Risk of performance bias is low if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if no blinding or incomplete blinding was performed, but the review authors judge that the outcome was not likely to be influenced by lack of blinding.

Blinding of personnel/care providers

Risk of performance bias is low if blinding of personnel was ensured and it was unlikely that the blinding could have been broken; or if no blinding or incomplete blinding was performed, but the review authors judge that the outcome was not likely to be influenced by lack of blinding.

Compliance (adherence)

Risk of bias is low if compliance with the interventions was acceptable on the basis of reported intensity/dosage, duration, number, and frequency for both index and control intervention(s). For single-session interventions (for example surgery), this item is irrelevant.

Co-interventions

Risk of bias is low if no co-interventions were provided, or if they were similar between index and control groups.

Attrition bias

Incomplete outcome data

Risk of attrition bias is low if no outcome data were missing; reasons for missing outcome data were unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data were balanced in numbers, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size, or missing data were imputed using appropriate methods (if dropouts were very large, imputation using even 'acceptable' methods may still suggest a high risk of bias). The percentage of withdrawals and dropouts should not exceed 20% for short-term follow-up and 30% for long-term follow-up and should not lead to substantial bias (these percentages are commonly used but are arbitrary and are not supported by the literature).

Intention-to-treat analysis

Risk of bias is low if all randomly assigned participants were reported/analysed in the group to which they were allocated by randomisation.

Measurement/detection

Blinding of outcome assessment

Risk of detection bias is low if blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if no blinding or incomplete blinding was performed, but the review authors judge that the outcome was not likely to be influenced by lack of blinding, or:

- for participant-reported outcomes in which the participant was the outcome assessor (e.g. pain, disability): Risk of bias for outcome assessors is low if risk of bias for participant blinding is low;
- for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between participants and care providers (e.g. co-interventions, length of hospitalisation, treatment failure), in which the care provider is the outcome assessor: Risk of bias for outcome assessors is low if risk of bias for care providers is low; and
- for outcome criteria that are assessed from data from medical forms: Risk of bias is low if the treatment or adverse effects of the treatment could not be noticed in the extracted data.

Timing of outcome assessments

Risk of bias is low if all important outcome assessments for all intervention groups were measured at the same time, or if analyses adjust for different lengths of follow-up.

Selective reporting

Data dredging

Risk of bias is low if all analyses were planned at the outset of the study.

Risk of bias is high if analyses were conducted retrospectively (for example retrospective unplanned subgroup analyses).

Outcome measures

Risk of reporting bias is low if the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way, or if the study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

Risk of reporting bias is high if not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (for example subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely, so that they cannot be entered into a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study.

*Items are relevant only to non-randomised studies.

Appendix 5. Questions for assessing clinical relevance

1. Are the participants described in detail so that you can decide whether they are comparable with those that you see in your practice?
Yes/No/Unsure
2. Are the interventions and treatment settings described well enough so that you can provide the same for your patients?
Yes/No/Unsure
3. Were all clinically relevant outcomes measured and reported?
Yes/No/Unsure
4. Is the size of the effect clinically important?
Yes/No/Unsure
5. Are the likely treatment benefits worth the potential harms?
Yes/No/Unsure

CONTRIBUTIONS OF AUTHORS

Substantial contributions to conception and design: Josette Bettany-Saltikov, Hans-Rudolf Weiss, Razvan Taranu, Shreya Srinivas, Nachiappan Chockalingam, Vicky Whittaker, Raman V Kalyan

Study search and selection: Julie Hogg, Josette Bettany-Saltikov, Hans-Rudolf Weiss, Razvan Taranu, Shreya Srinivas, Tracey Arnell, Raman V Kalyan

Drafting of the article: Josette Bettany-Saltikov, Hans-Rudolf Weiss, Razvan Taranu, Shreya Srinivas, Nachiappan Chockalingam, Vicky Whittaker, Raman V Kalyan, Tracey Arnell

Critical revision for important intellectual content: Josette Bettany-Saltikov, Hans-Rudolf Weiss, Razvan Taranu, Shreya Srinivas, Nachiappan Chockalingam, Vicky Whittaker, Raman V Kalyan

Final approval of the version to be published: Josette Bettany-Saltikov, Hans-Rudolf Weiss, Nachiappan Chockalingam.

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