Round 2

Interventions for preventing ankle ligament injuries

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Final version: submitted
ABSTRACT

Background
Ankle ligament injury is the most prevalent and universal sports injury. Prevention of ankle injuries could preserve health in people who participate in high-risk sports and those who have suffered a previous ankle ligament injury.

Objectives
To assess the effects (benefits and harms) of interventions for preventing ankle ligament injuries and re-injuries.

Methods
We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (5 January 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2014 Issue 12), MEDLINE (1946 to November Week 3 2014), MEDLINE In-Process & Other Non-Indexed Citations (5 January 2015), EMBASE (1980 to 2014 Week 52), SPORTDiscus (1985 to 5 January 2015), CINAHL (1937 to 5 January 2015), the World Health Organisation International Clinical Trials Registry Platform, ClinicalTrials.gov and reference lists. Randomised and quasi-randomised controlled trials evaluating interventions for preventing ankle ligament injuries were eligible. Two review authors independently performed study selection, risk of bias assessment and data extraction. Where appropriate, the results of comparable studies were pooled using the fixed-effect model.

Main results
A total of 47 trials, including 29,752 participants, were included. Although the interventions were heterogeneous, and outcomes varied, the data from 33 trials could be pooled for the primary outcome’ incidence of ankle ligament injury’. Overall the risk of bias in the pooled studies was low to moderate, but the more recent trials were of higher methodological quality. Most participants were high school athletes, recreational athletes (age mainly 18 to 35 years) or military recruits. The interventions tested in the included trials fell into seven main preventive strategies: footwear, taping, bracing, neuromuscular training, multifaceted exercise programs, insoles and stretching. All following results are pooled data for incidence of ‘total ankle sprains’. Two trials (1463 participants) showed that there is limited inconclusive evidence regarding the effectiveness of high-top shoes versus low-top shoes (OR 1.02, 95% CI 0.52 to 2.03). The only trial concerning taping versus controls (2,562 basketball player games) showed a significant reduction in the occurrence of ankle sprains (OR 0.44, 95% CI 0.24, 0.79). Nine trials (7886 participants) that compared the use of different brace types to controls showed a significant reduction in the occurrence of ankle sprains (OR 0.38, 95% CI 0.31 to 0.47). Nine trials (3845 participants) that compared neuromuscular training to controls showed a significant reduction in the occurrence of ankle sprains (OR 0.59, 95% CI 0.47 to 0.72). Six trials (6,412 participants) that compared multifaceted exercise programs to controls showed a significant reduction in the occurrence of ankle sprains (OR 0.55, 95% CI 0.43 to 0.71). Three trials that compared stretching to controls showed no effect in the occurrence of ankle sprains (OR 0.71 95% CI 0.44 to 1.13). Two trials (676 participants) investigated insoles versus controls which showed no effect in the occurrence of ankle sprains (OR 0.73, 95% CI 0.37 to 1.44). Finally, two trials (411 participants) that compared different brace types to neuromuscular training showed a
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Authors’ conclusions
Overall taping, bracing, neuromuscular training and multifaceted exercise programs are found to prevent ankle ligament injuries, although quality of studies is divers. For prevention of first-time ankle ligament injuries, evidence was only found for bracing. For prevention of recurrent ankle ligament injury, taping, bracing, neuromuscular training and multifaceted exercise programs all show benefits. Finally, high-top shoes, stretching and insoles do not prevent ankle injuries, although the quality of studies is low and evidence is limited for high top shoes and insoles.

BACKGROUND

Description of the condition
While people are encouraged to take part in sports and other physical activities because of the benefits to their health (Haskell 2007), participation in such activities generally increases the risk of injury. The ankle joint is the most common location of injury for many physical activities (Fong 2007). Most ankle injuries are acute sprains, involving injury to the ankle ligaments. The majority, up to 85% (Garrick 1973), of ankle sprains involve the lateral ligaments; these are situated on the outer side of the ankle. In the United States, the incidence rates of ankle sprain range from 2.15 per 1000 person-years in the general population (Waterman 2010a) to 58.4 per 1000 person-years in physically active populations (Waterman 2010b). About half of all ankle sprains occur during athletic activity, with basketball, football, and soccer being associated with the highest number of ankle sprains (Waterman 2010a). Injury to the lateral ligaments occurs as a result of a forced inversion (inward movement of the foot) while the foot is in plantar flexion (foot bent downwards) (Wexler 1998). In this vulnerable plantar flexed position, the bony stability of the ankle joint is minimal and the ligaments alone provide stability. Injury occurs to the anterior talofibular ligament first, followed to a varying degree by the calcaneofibular ligament. The posterior talofibular ligament is usually uninjured unless there is a frank dislocation of the ankle. Together, these ligaments form the lateral ligament complex. Clinically, lateral ligament injuries are graded 1, 2 or 3. Grade 1 (mild) involves a stretch (or sprain), grade 2 (moderate) involves a partial tear, and grade 3 (severe) involves a complete rupture (Kannus 1991). Most ankle sprains heal without residual complaints; however, up to one in three people re-injure their ankle (Bahr 1997 Beynnon 2001; Verhagen 2004b), which can result in disability and which can lead to chronic pain or instability in up to 40% of re-injured cases (Gerber 1998; Yeung 1994).

Description of the intervention
In an attempt to prevent (i.e. primary prevention) ankle sprains, ankle taping, braces, modified footwear and associated supports, adapted training regimens including ankle exercises, and injury awareness have been used (Handoll 2001). Secondary prevention (i.e. prevention of re-injury or recurrence) includes interventions such as neuromuscular training aimed at enhancing coordination and retraining proprioception (i.e. the sense of joint and muscular position). Neuromuscular training typically involves the use of ‘wobble boards’, also called ankle disks (Wester 1996). Neuromuscular...
training is also referred to as balance training, proprioceptive training, or sensorimotor training. Secondary prevention is a common treatment goal in the management of ankle sprains.

**How the intervention might work**
External support measures for the ankle joint were originally designed with the aim of mechanically restricting abnormal range of ankle motion. Historically, it was presumed that the support system that provides the best mechanical stabilisation would be the best system to prevent ankle injuries. Based on outcomes from clinical and mechanical studies, however, it is more likely that external measures act primarily by supporting neuromuscular function rather than by mechanically restricting the range of ankle motion (Hupperets 2009b; Verhagen 2000; Verhagen 2001). Neuromuscular (i.e. sensorimotor, proprioceptive, balance) training is a well-established secondary preventive measure. The rationale behind this kind of intervention is that athletes who sustain an ankle sprain have a higher risk of re-injury within one to two years of the injury (Bahr 1997 Ekstrand 1990; Verhagen 2004b). Besides ligamentous weakness, impairment of proprioception after an ankle sprain is generally thought to be the cause of the increased injury risk (Freeman 1965). It is assumed that neuromuscular training improves this deficit by re-establishing and strengthening the protective reflexes of the ankle (Karlsson 1993).

**Why it is important to do this review**
Ankle ligament injury is the most prevalent and universal sports injury. Prevention of ankle injuries could preserve health in people who participate in high-risk sports and those who have suffered a previous ankle ligament injury. Since the publication in 2001 of the previous Cochrane review in this area (Handoll 2001), several additional effectiveness studies have been completed. More recently, two systematic reviews have been published specifically exploring the preventive effect of external ankle supports (Dizon 2010) and neuromuscular training (Hubscher 2010). Since, none of the reviews compares the effects of the various preventive measures, a new synthesis of available literature is warranted to establish the effectiveness of preventive measures for acute lateral ligament injury of the ankle.

**OBJECTIVES**

To assess the effects (benefits and harms) of interventions for preventing ankle ligament injuries and re-injuries. It is anticipated that the population will consist predominantly of individuals, from adolescence to middle age, who are participating in regular sports and other physical activities. Where possible, individuals undergoing rehabilitation for ankle sprains were analysed separately.

The specific objectives of this review were to assess differences in outcomes between:
1. any intervention aimed at the prevention of ankle ligament injuries versus no intervention, and
2. different interventions aimed at the prevention of ankle ligament injuries.
METHODS

Criteria for considering studies for this review

Types of studies
Randomised and quasi-randomised (method of allocating participants to a treatment which is not strictly random; e.g. by date of birth, hospital record number or alternation) controlled trials evaluating interventions for preventing ankle ligament injuries were considered for inclusion.

Types of participants
Studies involving individuals at risk of, or who have had a previous, ankle ligament injury were eligible for inclusion. We expected that the majority of trial populations would fall into the adolescence to middle age category, which reflects the greater participation in high-risk activities for ankle sprains. This review also included people who have undergone rehabilitation after an ankle sprain.

Types of interventions
Any intervention, including use of (modified) footwear, external ankle supports, ankle taping, adapted training programmes including ankle exercises, co-ordination and/or neuromuscular training programmes, and injury awareness, that were applied to prevent ankle ligament injury, was eligible. Trials involving testing of preventative devices in laboratory conditions or trials that only reported intermediate outcome measures that had no proven relationship to clinical outcomes were excluded. Trials involving the rehabilitative treatment of ankle sprains were included, provided that the interventions under study were specifically intended to reduce the risk of re-injury, and that re-injury data were actively collected and reported.

Types of outcome measures
The reporting of ankle ligament injury was a criterion for study inclusion.

Primary outcomes
1. Incidence of ankle ligament injury;
2. Severity of ligament injuries to the ankle (grade, surgery considered); and
3. Patient-assessed ankle function (e.g. giving way, performance inhibition).

Secondary outcomes
1. Incidence of other lower extremity injuries;
2. Complications (e.g. fitness deficit, skin abrasions, other injuries);
3. Measures of health service utilisation or resource use (e.g. practitioner visits, costs of intervention); and
4. Compliance (adherence) to the intervention.

Search methods for identification of studies

Electronic searches
We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (5 January 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (The
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Cochrane Library, 2014 Issue 12), MEDLINE (1946 to November Week 3 2014), MEDLINE In-Process & Other Non-Indexed Citations (5 January 2015), EMBASE (1980 to 2014 Week 52), SPORTDiscus (1985 to 5 January 2015), and CINAHL (1937 to 5 January 2015). We also searched the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov for ongoing and recently completed trials. In MEDLINE, the subject specific strategy was combined with the sensitivity- and precision-maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011). In EMBASE, the subject-specific strategy was combined with the RCT search filter developed by the Scottish Intercollegiate Guidelines Network. Search strategies for CENTRAL, MEDLINE, EMBASE, SPORTDiscus, and CINAHL, can be found in Appendix 1. The searches were run in three stages: the initial search was undertaken in November 2011 and a top-up searches were run in January 2014 and January 2015. We did not apply any language or publication restrictions.

Searching other resources
We checked the reference lists of relevant studies and reviews, including the previous version of this review (Handoll 2011).

Data collection and analysis

Selection of studies
Initial study selection was performed independently by two review authors (KWJ and EV). Both authors examined titles and abstracts to produce a list of potentially relevant reports. Full texts were then retrieved and examined independently by the same review authors in order to obtain a final list of eligible reports. If consensus could not be achieved, a third party (PvdW) adjudicated.

Data extraction and management
Key information from each included study was independently extracted by two review authors (KWJ and EV) using a piloted data collection form. This form allowed the collection of information on the source, study eligibility, study design and methods, study participants, interventions used, outcome measures, and results. Attempts were made to contact the trial authors where the reports did not provide full information. Where necessary, consensus was reached by discussion.

Assessment of risk of bias in included studies
Risk of bias of all included studies was independently assessed by two review authors (KWJ and EV) using The Cochrane Collaboration’s ’Risk of bias’ tool (Higgins 2011). This tool assesses selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. The latter include bias from major imbalances in baseline characteristics, performance bias (from systematic differences in the care provided) and sponsorship bias (from funding sources). Where necessary, a third review author (PvdW) adjudicated on differences of opinion.
Measures of treatment effect
We calculated odds ratios (OR) with 95% confidence intervals (CI) for dichotomous data and mean differences (MD), or standardized mean differences (SMD) where different scales were used, with 95% CIs for continuous data.

Unit of analysis issues
Cluster randomisation may be used in some trials eligible for inclusion. When allocation is by a group of participants, such as a platoon or soccer team, unit of analysis errors are likely to result from the presentation of outcome by the individual participants. The risk of injury of such individuals cannot be considered independently of the cluster unit (platoon/team). Using statistical methods that assume, for example, that all participants’ chances of injury are independent ignores the possible similarity between outcomes for participants within the same platoon or team. This may underestimate standard errors and give misleadingly narrow confidence intervals, leading to the possibility of spurious positive findings (Bland 1997). Whilst we will present the overall results of these trials where available and we will use adjusted data if feasible, we will indicate these as cluster randomised trials and suggest cautious interpretation.

Dealing with missing data
Where necessary, we contacted trial authors for missing data, including intra-class correlation coefficients for cluster randomized trials.

Assessment of heterogeneity
Heterogeneity of the included studies was assessed by visual inspection of the analyses, along with consideration of the chi² test for heterogeneity and the I² statistic (Higgins 2002).

Assessment of reporting biases
Possible duplicate publications of the same studies were addressed by taking into account the following from each identified study: author names, study design, presented sample demographics, location and setting of the intervention.

Data synthesis
Where appropriate, the results of studies of comparable populations, interventions, comparison group, outcomes and design were pooled using the fixed-effect model. The individual and pooled statistics will be reported as either ORs, MDs or SMDs; all with 95% CIs.

Subgroup analysis and investigation of heterogeneity
Where possible, subgroup data by history of previous sprain were explored. We investigated whether the results of subgroups were significantly different by inspecting the overlap of 95% CIs, and performing the test for subgroup differences and the I² statistic available in RevMan.

Sensitivity analysis
Where possible, sensitivity analyses to evaluate the effects of various aspects of trial and review methodology, including the effect of missing data, inclusion of trials at high risk of bias, principally from lack of allocation concealment, or for which only abstracts were obtained, were conducted.
**RESULTS**

**Results of the search**

The search strategy developed for the review was highly sensitive; however, precision was very low (i.e. the search identified a large number of false positive results). We screened a total of 3,676 records from the following databases: the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (166 records); CENTRAL (977), MEDLINE (600), EMBASE (814), CINAHL (269), SPORTDiscus (292), the WHO ICTRP (221) and ClinicalTrials.gov (337). We also identified 20 potentially eligible studies from other sources (reference lists of included studies). After initial screening, we identified a total of 90 articles for potential inclusion, for which full reports were obtained where possible. Upon further analysis, 47 studies were included, 39 were excluded, and three are awaiting classification. There was one ongoing study. A flow diagram summarising the selection process of the studies is shown in Figure 1.
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Figure 1: flow diagram of the studies
Included studies
A total of 47 trials were included (29,752 participants). All manuscripts of the trials were available in English apart from Schroter 2005, which was published as a thesis in German. Most studies were indexed in COCHRANE, MEDLINE or EMBASE. Study details are briefly summarized below.

Design
The majority of included studies were individually randomised. Nineteen of the 47 included trials (40%) were cluster-randomised trials. In cluster-randomised trials, groups of individuals or centres rather than individuals are randomised to different interventions; therefore the ‘unit of allocation’ is the cluster, or the group (for example a soccer team). A promising thirteen of the nineteen cluster-randomised trials adjusted for clustering in their analyses.

Sample sizes
Included trials ranged in sample size from 47 (Nualon 2013) to 2562 (Garrick 1973). The median sample size was 450 participants.

Setting
The included trials were carried out in 16 countries. Most studies were performed in the United States (12 trials), followed by the Netherlands (7 trials), Denmark (5 trials), Sweden (4 trials), Finland and Norway (3 trials) and Australia (2 trials).

Participants
Overall, 64% of included participants were men. All participants were men in 16 trials, and women in eight trials. Most participants were high school athletes, recreational athletes (age mainly 18 to 35 years) or military recruits. Most trials were performed in basketball (10 trials), soccer (9 trials), ER patients (8 trials), military recruits (5 trials) and volleyball (3 trials). The inclusion/exclusion criteria and other participant details are listed for each study in the ‘Characteristics of included studies’.

Interventions
The interventions tested in the included trials fell into seven main preventive strategies versus controls: footwear (2 trials), taping (1 trial), bracing (9 trials), neuromuscular training (14 trials), multifaceted exercise programs (7 trials), insoles (2 trials) and stretching (3 trials). Seven trials involved the rehabilitative treatment of ankle sprains, provided that the outcomes included the risk of re-injury, including functional treatment (3 trials), operative reconstruction of the lateral ankle ligaments (2 trials), bracing (1 trial) and laser therapy (1 trial). The remaining trials included the following interventions: neuromuscular training + manual therapy (1 trial), hydrotherapy (1 trial), and a combined intervention including taping and warm-up (1 trial).

Outcomes
For the primary outcome ‘Incidence of ankle ligament injury’, we were able to pool data from 33 trials. ‘Severity of ligament injuries to the ankle’ (grade one to three) was often not available. ‘Patient assessed ankle function’ (e.g. giving way, performance inhibition) was only available in a minority of the studies. Secondary outcome ‘Incidence of other lower extremity injuries’ was mostly available, but varying definitions of injury did not
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allow pooling of data. No serious ‘complications’ of the interventions were reported. ‘Measures of health service utilisation or resource use’ were only reported by a few trials. Although various trials reported ‘compliance’ (adherence) to the interventions, definitions varied and pooling of the data was not possible.

Excluded studies
Thirty-nine studies that initially appeared to meet the inclusion criteria were excluded from this review on the basis of full text review. Most trials (16) were excluded because they did not include the outcome ‘recurrent sprains’. A large number of trials (10) were cohort studies and not randomised controlled trials and therefore excluded.

Studies awaiting classification
Three studies were awaiting classification.

Ongoing studies
There was one ongoing study.

Risk of bias in included studies
Details of the risk of bias assessment for each trial are shown in an overview in Figure 2. Review authors’ judgments about each risk of bias item presented as percentages across all included studies are shown in Figure 3.

Allocation
Risk of bias relating to adequacy of sequence generation was assessed as low in 55% of studies (26 trials), high in 15% (seven trials) and unclear in the reports of the remaining 30% of studies (14 trials). Concealment of allocation prior to group assignment was judged to carry low risk of bias in just 36% of studies (17 trials) and unclear in the remaining 64% of studies (28 trials).

Blinding
The risk and potential impact of bias as a result of non-blinding of participants and personnel was assessed to be low in 26% of included studies (12 trials), high in 36% (17 trials) and unclear in the remaining 38% of the studies (16 trials). Blinding of outcome measurement was judged to carry low risk of bias in 34% of included studies (16 trials), high in 32% (15 trials) and unclear in the remaining 34% of the studies (16 trials).

Incomplete outcome data
Fifty-one percent of studies (24 trials) was assessed as being at low risk of bias from incomplete outcome data, and 34% (16 trials) as at high risk of bias. In the remaining 15% (seven trials), risk of bias was unclear.

Selective reporting
We assessed risk of bias relating to selective reporting as low in 74% of studies (35 trials), high in 15% (seven trials), and to be unclear in the reports of the remaining 11% of studies (five trials).
Other potential sources of bias
Forty-nine percent of studies (23 trials) was assessed as being at low risk of bias from other sources, and 28% (13 trials) as at high risk of bias. In the remaining 23% of the studies (11 trials), risk of bias was unclear.
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
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Figure 3. Risk of bias graph: review author’s judgement about each risk of bias item presented as percentages across all included studies.

Effects of interventions
In presenting the results, comparisons are grouped into: ‘comparisons with control’, ‘comparisons of preventive measures’ and ‘comparisons of treatment modalities’. There were limited opportunities to pool data due to the heterogeneity of comparisons studied and outcomes reported. For the primary outcome ‘Incidence of ankle ligament injury’, we were able to pool data from 33 trials. Different definitions for incidence of ankle ligament injury were used. Accordingly, we were only able to pool a dichotomous outcome ‘occurrence of ankle sprain’ for ‘high-top shoes versus low-top shoes’, ‘bracing versus control’, ‘neuromuscular training versus control’, ‘multi-faceted exercise programs versus control’, ‘stretching versus control’, ‘insoles versus control’ and ‘bracing versus neuromuscular training’. Multi-faceted exercise programs were defined as neuromuscular training combined with focus on quality of movement during training and feedback from researchers, staff or team members.

Distinguishing primary and secondary prevention of ankle sprains was an important goal of this review, therefore we categorized our primary outcome in ‘total ankle sprains’, ‘new ankle sprains’ and ‘recurrent ankle sprains’. ‘Total ankle sprains’ included all sustained ankle sprains, ‘new ankle sprains’ included solely ankle sprains sustained by participants without a history of ankle sprains, ‘recurrent ankle sprains’ solely included ankle sprains sustained by participants with a history of ankle sprains, in the respective studies. For other outcomes pooling was hampered by inconsistent data reporting and variations in definition of the outcome measures.

COMPARISONS WITH CONTROL

1. High-top shoes versus control (low-top shoes)

1.1 Primary outcomes
Incidence of ankle ligament injury
Only two trials compared high-top versus low-top shoes (and/ or taping) in college basketball (Barrett 1993 and Garrick 1973). Pooled data showed no significant reduction in the occurrence of ‘total ankle sprains’ (OR 1.02, 95CI: 0.52 - 2.03 Figure 4,
Analysis 1.1 for high-top versus low-top shoes. For players without previous ankle injury, Garrick 1973 found no significant reduction in the occurrence of 'new ankle sprains' for players wearing high-top versus low-top shoes (19.0 vs 12.9 ankle sprains/1000 participant games respectively, no 95% CI provided). For previously injured players, Garrick 1973 did find a significant reduction in the occurrence of 'recurrent ankle sprains' for players wearing high-top versus low-top shoes (8.3 versus 19.9 ankle sprains/1000 participant games respectively, no 95% CI given). Barrett 1993 was not able to reproduce these findings.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High-top shoes</th>
<th>Low-top shoes</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett 1993</td>
<td>7</td>
<td>209</td>
<td>27.1%</td>
<td>1.34 [0.38, 4.88]</td>
</tr>
<tr>
<td>Garrick 1973</td>
<td>7</td>
<td>230</td>
<td>27.3%</td>
<td>0.91 [0.38, 2.10]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>438</td>
<td>1025</td>
<td>1.02 [0.52, 2.03]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 0.07 (P = 0.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Forest plot of comparison: High-top shoes versus Control (Low-top shoes), outcome: 1.1 Total ankle sprains.

Severity of ligament injuries to the ankle
Barrett 1993 reported that the severity of ankle injury did not differ significantly between the intervention groups, but the tables do not show the actual numbers. Garrick 1973 reported no separate data on severity of injury for high-top versus low-top shoes.

Patient-assessed ankle function
Not reported in these trials.

1.2 Secondary outcomes
Incidence of other lower extremity injuries
No significant difference in the incidence of other injuries were reported in either trial. Barrett 1993 found only three knee injuries in total, which occurred among athletes wearing each type of shoe. Garrick 1973 found a rate of 8.7 knee sprains/1000 participant games for high-top shoes versus 5.8 knee sprains/1000 participant games for low-top shoes.

Complications
Not reported in these trials.

Measures of service utilisation or resource use
Not reported in these trials.

Compliance (adherence) to the intervention
Barrett 1993 controlled compliance to the intervention by assignment of a monitor, whose task was to check the shoes in and out at every exposure. Garrick 1973 reported no specific method to control or measure compliance.
2. Bracing versus control

2.1 Primary outcomes

*Incidence of ankle ligament injury*

Nine trials (7,886 participants) compared the use of different brace types to controls (and in some to neuromuscular training, data not shown here) in basketball (McGuine 2011; Schroter 2005; Sitter 1994), soccer (Mohammadi 2007; Surve 1994; Tropp 1985), volleyball (Frey 2010), football (McGuine 2012) and military paratroopers (Amoroso 1998). Pooled data showed a significant reduction in the occurrence of 'total ankle sprains' (OR 0.38, 95% CI 0.31 to 0.47 Figure 5, Analysis 2.1), 'new ankle sprains' (OR 0.45, 95% CI 0.33 to 0.60 Figure 6, Analysis 2.2) and 'recurrent ankle sprains' (OR 0.22, 95% CI 0.13 to 0.35 Figure 7, Analysis 2.3) for bracing. The pooled data for 'total ankle sprains' and 'new ankle sprains' showed substantial statistical heterogeneity (I² = 48% and I² = 67%, respectively). McGuine 2012 was excluded from Analysis 2.2 and Analysis 2.3 because no actual numbers were presented; however, only hazard ratios (HR) were reported for acute ankle injury without a previous ankle injury (HR 0.43, 95% CI 0.23 to 0.82), and acute ankle injury with a previous ankle injury (HR 0.30, 95% CI 0.14 to 0.68).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoroso 1988</td>
<td>1 369</td>
<td>7 376</td>
<td>2.4%</td>
<td>0.14 (0.02, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Frey 2010</td>
<td>89 857</td>
<td>4 42</td>
<td>2.4%</td>
<td>0.97 (0.34, 2.78)</td>
<td></td>
</tr>
<tr>
<td>McGuine 2011</td>
<td>27 740</td>
<td>80 720</td>
<td>25.9%</td>
<td>0.39 (0.19, 0.78)</td>
<td></td>
</tr>
<tr>
<td>McGuine 2012</td>
<td>27 893</td>
<td>68 1068</td>
<td>21.7%</td>
<td>0.42 (0.27, 0.67)</td>
<td></td>
</tr>
<tr>
<td>Mohammadi 2007</td>
<td>2 20</td>
<td>6 20</td>
<td>2.5%</td>
<td>0.17 (0.03, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>3 100</td>
<td>24 125</td>
<td>7.1%</td>
<td>0.13 (0.04, 0.45)</td>
<td></td>
</tr>
<tr>
<td>Sitter 1994</td>
<td>11 709</td>
<td>35 812</td>
<td>11.7%</td>
<td>0.31 (0.16, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Surve 1994</td>
<td>48 244</td>
<td>75 260</td>
<td>20.1%</td>
<td>0.60 (0.40, 0.91)</td>
<td></td>
</tr>
<tr>
<td>Tropp 1965</td>
<td>2 60</td>
<td>30 171</td>
<td>5.2%</td>
<td>0.16 (0.04, 0.67)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>4272</strong></td>
<td><strong>3614</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.38 (0.31, 0.47)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 8.04 (P < 0.00001) Favour Brace Favour Control

Figure 5. Forest plot of comparison: Brace versus Control, outcome: 2.1 Total ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frey 2010</td>
<td>48 650</td>
<td>3 33</td>
<td>3.7%</td>
<td>0.78 (0.22, 2.59)</td>
<td></td>
</tr>
<tr>
<td>McGuine 2011</td>
<td>28 619</td>
<td>75 618</td>
<td>50.7%</td>
<td>0.32 (0.20, 0.56)</td>
<td></td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>0 45</td>
<td>7 66</td>
<td>4.3%</td>
<td>0.09 (0.00, 1.67)</td>
<td></td>
</tr>
<tr>
<td>Sitter 1994</td>
<td>10 702</td>
<td>29 722</td>
<td>18.9%</td>
<td>0.35 (0.17, 0.71)</td>
<td></td>
</tr>
<tr>
<td>Surve 1994</td>
<td>32 117</td>
<td>33 129</td>
<td>16.1%</td>
<td>1.19 (0.62, 2.21)</td>
<td></td>
</tr>
<tr>
<td>Tropp 1965</td>
<td>1 52</td>
<td>11 95</td>
<td>5.3%</td>
<td>0.15 (0.02, 1.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2105</strong></td>
<td><strong>1664</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.45 (0.33, 0.60)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 5.40 (P < 0.00001) Favour Brace Favour Control

Figure 6. Forest plot of comparison: Brace versus Control, outcome: 2.2 New ankle sprains.
Interventions for preventing ankle ligament injuries

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M.H, Fixed, 95% CI</th>
<th>Odds Ratio M.H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frey 2010</td>
<td>43</td>
<td>307</td>
<td>1</td>
<td>9</td>
<td>2.2%</td>
<td>1.30 [0.16, 10.69]</td>
<td></td>
</tr>
<tr>
<td>McGuine 2011</td>
<td>1</td>
<td>121</td>
<td>1</td>
<td>3</td>
<td>102</td>
<td>4.3%</td>
<td>0.28 [0.03, 2.60]</td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>0</td>
<td>55</td>
<td>15</td>
<td>5</td>
<td>59</td>
<td>12.8%</td>
<td>0.03 [0.00, 0.44]</td>
</tr>
<tr>
<td>Sitter 1994</td>
<td>1</td>
<td>90</td>
<td>5</td>
<td>6</td>
<td>87</td>
<td>9.0%</td>
<td>0.15 [0.02, 1.29]</td>
</tr>
<tr>
<td>Surve 1994</td>
<td>16</td>
<td>127</td>
<td>42</td>
<td>131</td>
<td>47.7%</td>
<td>0.31 [0.16, 0.58]</td>
<td></td>
</tr>
<tr>
<td>Tropp 1985</td>
<td>4</td>
<td>45</td>
<td>19</td>
<td>75</td>
<td>15.4%</td>
<td>0.07 [0.01, 0.52]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>745</td>
<td>463</td>
<td>100.0%</td>
<td>1</td>
<td>2.3%</td>
<td>0.22 [0.13, 0.35]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 7.43, df = 5 (P = 0.19); I² = 33%
Test for overall effect: Z = 6.03 (P < 0.00001)

Figure 7. Forest plot of comparison: Brace versus Control, outcome: 2.3 Recurrent ankle sprains.

Severity of ligament injuries to the ankle

In three trials, injury severity was reported clinically as grades one to three (Amoroso 1998; Sitler 1994; Surve 1994), in three trials days lost from sports participation were reported (McGuine 2011; McGuine 2012; Schroter 2005), in one trial only location of the injury was reported (Frey 2010), and in two trials injury severity was not reported at all (Mohammadi 2007; Tropp 1985). Amoroso 1998 found a lower occurrence of the more severe injuries in the brace compared to the control group (brace: one grade 1 sprain versus control: four grade 1 and three grade 3 sprains). Surve 1994 found a significantly lower incidence of the more severe ankle sprains in the previously sprained ankles of the brace (Sport-Stirrup) group compared to the control group (0.14/1000h vs 0.77/1000h; P < 0.001). Sitler 1994 found no significant difference (P > 0.45) in the severity of injuries (grade 1 vs grade 2 and 3) occurring in the brace versus control groups. McGuine 2011 and McGuine 2012 found no significant difference in the number of days lost from sports participation in the brace compared to the control group (5 versus 6 days; P = 0.23 and 5 versus 5 days P = 0.99, respectively). Schroter 2005 reported only total days lost from sports participation for all participants, not per treatment group.

Patient-assessed ankle function

McGuine 2011 was the only trial that reported some form of patient-assessed ankle function, through the Foot and Ankle Ability Measure (FAAM)-Sport. However, only used this measure to demonstrate similarities in the groups at baseline.

2.2 Secondary outcomes

Incidence of other lower extremity injuries

Three trials reported other lower extremity injuries. Amoroso 1998 found no significant difference in other injury categories between the brace and control groups. McGuine 2011 found that the incidence of acute knee injury was similar between the brace and control group (0.26 versus 0.20; HR 1.31, 95% CI 0.60 to 2.89). The incidence of other lower extremity injury was 0.61 (95% CI 0.32 to 1.19) in the brace group and 0.33 (95% CI 0.20 to 0.53) in the control group. Comparison of first-time events between the groups failed to demonstrate a statistical difference (HR 1.78, 95% CI 0.92 to 3.44). In contrast, McGuine 2012 found no significant difference in the incidence of lower extremity injuries with the use of lace-up bracess in football. Both McGuine studies found no increased risk of acute knee injuries with a laceup brace in basketball and football.
Interventions for preventing ankle ligament injuries

Sitler 1994 found a comparable incidence of knee injuries in the brace versus control group (9/812 versus 8/789; \( P = 0.69 \)). Schroter 2005 reported only total numbers of other injuries, not per treatment group.

**Complications**
None reported in these nine trials.

**Measures of service utilisation or resource use**
Schroter 2005 reported primary treatment (RICE: rest, ice, compression, elevation), medical treatment and time lost from sports participation. None of the other studies reported measures of service utilisation or resource use.

**Compliance (adherence) to the intervention**
In four trials compliance was controlled for by trainers/coaches (Amoroso 1998; Frey 2010; McGuine 2011; McGuine 2012; Surve 1994), in one trial by the researchers (Sitler 1994) and in three trials compliance was not controlled for or measured at all (Mohammadi 2007; Schroter 2005; Tropp 1985). No comparisons based on adherence were reported.

3. Neuromuscular training versus control

3.1 Primary outcomes

**Incidence of ankle ligament injury**
Fourteen trials (5,213 participants) compared neuromuscular training to controls in basketball (Eils 2010; Emery 2007; McGuine 2006; Schroter 2005), soccer (Emery 2010; Engebretsen 2008; Söderman 2000), volleyball (Verhagen 2004a), handball (Wedderkopp 1999; Wedderkopp 2003), recreational athletes (Holme 1999; Hupperets 2009a; Wester 1996) and general patients presenting to an emergency department (ED) (Van Rijn 2007). Pooled data showed a significant reduction in the occurrence of ‘total ankle sprains’ (OR 0.56 95%CI 0.45 to 0.69 Figure 8, Analysis 3.1) and ‘recurrent ankle sprains’ (OR 0.54, 95% CI 0.41 to 0.71 Figure 9, Analysis 3.3). There was no significant reduction in the occurrence of ‘new ankle sprains’ (OR 0.55, 95% CI 0.29 to 1.02 Figure 10, Analysis 3.2).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NM training</th>
<th>M-H, Fixed, 95% CI</th>
<th>Control</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emery 2007</td>
<td>62</td>
<td>0.68 [0.45, 0.96]</td>
<td>434</td>
<td>0.68 [0.45, 0.96]</td>
</tr>
<tr>
<td>Emery 2010</td>
<td>14</td>
<td>0.43 [0.25, 0.70]</td>
<td>380</td>
<td>0.43 [0.25, 0.70]</td>
</tr>
<tr>
<td>Holme 1993</td>
<td>23</td>
<td>0.59 [0.35, 1.02]</td>
<td>323</td>
<td>0.59 [0.35, 1.02]</td>
</tr>
<tr>
<td>McGuine 2006</td>
<td>13</td>
<td>0.53 [0.26, 1.10]</td>
<td>116</td>
<td>0.53 [0.26, 1.10]</td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>23</td>
<td>0.53 [0.26, 1.10]</td>
<td>392</td>
<td>0.53 [0.26, 1.10]</td>
</tr>
<tr>
<td>Söderman 2000</td>
<td>13</td>
<td>1.21 [0.62, 2.81]</td>
<td>62</td>
<td>1.21 [0.62, 2.81]</td>
</tr>
<tr>
<td>Verhagen 2004a</td>
<td>29</td>
<td>0.50 [0.35, 0.76]</td>
<td>392</td>
<td>0.50 [0.35, 0.76]</td>
</tr>
<tr>
<td>Wedderkopp 1999</td>
<td>14</td>
<td>0.10 [0.05, 0.20]</td>
<td>111</td>
<td>0.10 [0.05, 0.20]</td>
</tr>
<tr>
<td>Wedderkopp 2003</td>
<td>1</td>
<td>0.55 [0.05, 6.22]</td>
<td>77</td>
<td>0.55 [0.05, 6.22]</td>
</tr>
<tr>
<td>Wester 1996</td>
<td>6</td>
<td>0.28 [0.08, 0.96]</td>
<td>24</td>
<td>0.28 [0.08, 0.96]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2075</td>
<td>0.48 [0.40, 0.59]</td>
<td>2007</td>
<td>0.48 [0.40, 0.59]</td>
</tr>
<tr>
<td>Total events</td>
<td>177</td>
<td></td>
<td>321</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 32.92, \text{df}=9 (P = 0.00001); P = 73\% \)

Test for overall effect: \( z = 7.19 (P < 0.00001) \)
Interventions for preventing ankle ligament injuries

Figure 8. Forest plot of comparison: Neuromuscular Training versus Control, outcome: 3.1 Total ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NM training</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engström 2008</td>
<td>13</td>
<td>102</td>
<td>0.64 [0.30, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Holme 1993</td>
<td>26</td>
<td>46</td>
<td>0.14 [0.03, 0.61]</td>
<td></td>
</tr>
<tr>
<td>Hupperets 2009a</td>
<td>55</td>
<td>256</td>
<td>0.56 [0.38, 0.82]</td>
<td></td>
</tr>
<tr>
<td>McGuine 2006</td>
<td>11</td>
<td>89</td>
<td>0.88 [0.30, 2.66]</td>
<td></td>
</tr>
<tr>
<td>Schnetter 2005</td>
<td>7</td>
<td>56</td>
<td>0.42 [0.18, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Van Rijn 2007</td>
<td>135</td>
<td>49</td>
<td>0.84 [0.35, 2.06]</td>
<td></td>
</tr>
<tr>
<td>Wester 1996</td>
<td>5</td>
<td>24</td>
<td>0.29 [0.09, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>622</td>
<td>648</td>
<td>0.54 [0.41, 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1093
Heterogeneity: Ch² = 5.51, df = 6 (P = 0.48), I² = 0%
Test for overall effect: Z = 4.46 (P < 0.0001)

Figure 9. Forest plot of comparison: Neuromuscular exercises versus Control, outcome: 3.3 Recurrent ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NM training</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuine 2006</td>
<td>12</td>
<td>284</td>
<td>0.53 [0.28, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Schnetter 2005</td>
<td>4</td>
<td>63</td>
<td>0.50 [0.17, 1.71]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>344</td>
<td>365</td>
<td>0.55 [0.29, 1.02]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 163
Heterogeneity: Ch² = 0.03, df = 1 (P = 0.98), I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)

Figure 10. Forest plot of comparison: Neuromuscular Training versus Control, outcome: 3.2 New ankle sprains.

Eils 2010 was excluded from Analysis 3.1 because the unit of observation was the single participation in sports, not the player. They reported a reduction in ankle sprains for neuromuscular training (OR 0.35, 95% CI 0.15 to 0.84). Analysis of players who had previously sustained an ankle injury revealed no difference between neuromuscular training and control groups (OR 1.6, 95% CI 0.76 to 3.55) regarding subsequent ankle injuries. Emery 2007 was excluded from Analysis 3.3 because they only reported a higher relative risk, but no specific numbers, for ankle ligament injury in players with a history of lower extremity injury in the previous year (RR 1.52, 95% CI 1.07 to 2.14). This also applied to Emery 2010, because they only reported a higher adjusted incidence rate ratio of 2.29 (95% CI 1.23 to 4.28) for ankle ligament injury in players with an earlier lower extremity injury in the previous year. Verhagen 2004a performed a subgroup analysis for players with a history of ankle sprains which also showed a lower risk of ankle sprains in favour of the intervention group (RR 0.4, 95% CI 0.2 to 0.8). Söderman 2000 reported that there was no significant difference between the groups in the number of re-injuries, including the number of recurrent ankle sprains, although no absolute numbers of recurrent injuries were reported.

Severity of ligament injuries to the ankle

In three trials days lost from sports participation were reported (Emery 2007; Emery 2010; Engebretsen 2008), in one trial (Hupperets 2009a) injury severity was sub grouped in self-reported injuries, time-loss injuries and injuries leading to costs, and in five trials injury severity was not reported at all (Eils 2010; Van Rijn 2007; Verhagen...
Interventions for preventing ankle ligament injuries

2004a, Söderman 2000; Wester 1996). Three trials (Emery 2010; Engebretsen 2008; McGuine 2006) reported no significant difference in the distribution of ankle sprain severity among the groups. The same was found by Emery 2007 for all acute ankle injuries; however, ankle sprains were not specified. Hupperets 2009a found fewer recurrent ankle sprains for neuromuscular training versus controls that led to loss of sports time (RR 0.53, 95% CI 0.32 to 0.88), and recurrent ankle sprains that led to healthcare costs or lost productivity costs (RR 0.25, 95% CI 0.12 to 0.50). Although Wedderkopp 1999 reported severity of sustained injuries during the interventions, this was not specified for ankle sprains.

**Patient-assessed ankle function**

Only two trials (Van Rijn 2007; Wester 1996) reported patient assessed ankle function. Van Rijn 2007 reported that there was no significant difference in full subjective recovery after one year (control 42% vs intervention 53%), where a score of 10 on a 11-point scale (0-10) represented full recovery (OR of full recovery 1.59, 95% CI 0.73 to 3.49). Wester 1996 reported no significant difference in pain at walking or sports at 1, 6 and 12 weeks.

**3.2 Secondary outcomes**

**Incidence of other lower extremity injuries**

Seven trials reported and specified other lower extremity injuries. Emery 2007 and Emery 2010 reported a trend towards a reduction in lower-extremity injury and knee sprain injuries in the neuromuscular training group compared to the control group, however these were not statistically significant findings. Verhagen 2004a found a significantly higher risk of overuse knee injuries in the intervention group (RR 5.0, 95% CI 1.1 to 24.3) by subgroup analysis for players with a history of knee injuries. Schroter 2005 did not find a significant difference in knee injuries between the intervention groups (neuromuscular training 0.86% vs Control 2.40%). Söderman 2000 found a significant difference in the distribution of injury severity (minor, moderate, and major) between the intervention and the control groups (p=0.02), but did not specify if this concerned lower extremity injuries. Wedderkopp 1999 found a significant lower number of traumatic lower extremity injuries in the neuromuscular training group (OR 0.10, 95% CI 0.05 to 0.20).

**Complications**

Besides the higher risk of overuse knee injuries reported by Verhagen 2004a, no complications were reported in these trials.

**Measures of service utilisation or resource use**

Verhagen 2004a performed a cost-effectiveness evaluation of the intervention (balance board training in warm-up), which was reported in a separate paper (Verhagen 2005). The total costs per player (including the intervention material) were significantly higher in the intervention group (€ 36.99, SD: 93.87) than in the control group (€ 18.94, SD: 147.09). The cost of preventing one ankle sprain was approximately € 444. Sensitivity analysis showed that a proprioceptive balance board training program aimed only at players with previous ankle sprains could be cost effective over a longer period of time. Hupperets 2009a performed a cost-effectiveness evaluation of the intervention (home-based balance board training), which was reported in a separate paper (Hupperets 2010). Statistically significant differences in total costs were found per athlete (MD –€
Interventions for preventing ankle ligament injuries

69, 95% CI –€ 200 to –€ 2) and per injured athlete (MD –€ 332, 95% CI –€ 741 to –€ 62) in favour of the intervention group. None of the other trials reported measures of service utilisation or resource use.

Compliance (adherence) to the intervention

In five trials compliance was controlled by trainers/coaches (Emery 2007; Emery 2010; McGuine 2006; Schroter 2005; Wedderkopp 1999; Wedderkopp 2003), in one trial (Holme 1999) compliance was controlled by physical therapists (supervised training), in four trials self-reported compliance was measured (Engebretsen 2008; Hupperets 2009a; Söderman 2000; Van Rijn 2007) and in three trials compliance was not controlled for or measured at all (Eils 2010; Verhagen 2004a; Wester 1996). McGuine 2006 reported, that even in trainer-controlled training sessions 9% of the intervention group was noncompliant. Emery 2007 registered self-reported compliance to be fair (60%) for the home-based part of the neuromuscular training. Emery 2010 registered self-reported compliance to the home-programme as poor (< 15%). Engebretsen 2008 and Hupperets 2009a rated compliance with their training programs as poor, with only 27.5% and 23% fully compliant participants respectively. In Van Rijn 2007 the intervention group received once weekly training under supervision of a physical therapist, while both groups also received home exercises. They reported a compliance of 74% for the intervention group versus below 18% for the control group for these home exercises. Söderman 2000 divided the intervention group into two subgroups: those who had performed at least 70 training sessions (44% of the participants) and those who had trained between 35 and 69 times (56% of the participants). No significant difference was found in the number of traumatic injuries or injured players between these two subgroups.

4. Multifaceted exercise programs versus control

4.1 Primary outcomes

Incidence of ankle ligament injury

Seven trials (6,592 participants) compared ME programs to controls in soccer (Ekstrand 1983; Labella 2011; Soligard 2008), basketball (Labella 2011; Longo 2012), handball (Olsen 2005), floorball (Pasanen 2008), military conscripts (Parkkari 2011). Pooled data showed a significant reduction in the occurrence of ‘total ankle sprains’ (OR 0.55, 95% CI 0.43 to 0.71 Figure 11, Analysis 4.1). Four trials (Longo 2012; Olsen 2005; Parkkari 2011; Soligard 2008) reported only acute ankle injuries, not specifying ankle sprains. As earlier research showed that 85% (Garrick 1973) of acute ankle injuries concern ankle sprains, these acute ankle injuries were considered ankle sprains, and thus included. The pooled data for ‘total ankle sprains’ showed moderate statistical heterogeneity (I² = 36%) Ekstrand 1983 only reported the number of teams, six in each intervention group, but not the number of participants. This study did find significantly fewer sprains in the intervention group, which included taping and was therefore excluded from the pooled analysis.
Interventions for preventing ankle ligament injuries

**Severity of ligament injuries to the ankle**
Although most trials reported overall injury severity as minor or severe, this was not further specified for ankle sprains (Ekstrand 1983; Longo 2012; Olsen 2005; Soligard 2008). In two trials injury severity was not reported at all (Labella 2011; Pasanen 2008). Parkkari 2011 reported the total loss of off-duty days from military service because of injuries, however did not specify days lost because of ankle sprains.

**Patient-assessed ankle function**
None of the trials reported patient-assessed ankle function.

### 4.2 Secondary outcomes

**Incidence of other lower extremity injuries**
While all trials reported and specified other lower extremity injuries, definitions varied, which precluded pooling of the data. Five of the seven trials found significantly fewer lower extremity injuries in the intervention groups (Labella 2011; Longo 2012; Olsen 2005; Pasanen 2008). Ekstrand 1983 reported a significant overall reduction of injuries of 75% in the intervention group. Longo 2012 found a significantly lower risk for lower extremity injuries in the intervention group (FIFA 11+, OR 0.40, 95% CI 0.19 to 0.84). Labella 2011 found a significant reduction in the incidence of lower extremity injuries (1.78 versus 4.19 per 1000 athletic exposures). Olsen 2005 reported a significant reduction in all injuries (RR 0.49, 95% CI 0.36 to 0.68) and lower extremity injuries (RR 0.51, 95% CI 0.36 to 0.73). Parkkari 2011 found a significant reduction in incidence of acute upper extremity injuries in the intervention subgroup of men with moderate to high baseline aerobic fitness (HR 0.37, 95% CI 0.14 to 0.99). Pasanen 2008 reported significantly fewer non-contact leg injuries (RR 0.34, 95% CI 0.20 to 0.57) in the intervention group. Soligard 2008 found fewer lower extremity injuries in the intervention group, but not significantly (RR 0.71, 95% CI 0.49 to 1.03).

**Complications**
None of the trials reported complications of the ME Programs.
**Measures of service utilisation or resource use**
Labella 2011 reported the costs associated with training a group of 15 to 20 coaches in the implementation of the intervention being $80 per coach. Parkkari 2011 reported a significant overall reduction in training time loss in the intervention group due to injuries (HR 0.55, 95% CI 0.29 to 1.04), although days lost because of ankle sprains were not specified. None of the other trials reported measures of service utilisation or resource use.

**Compliance (adherence) to the intervention**
In most trials compliance was controlled by trainers/coaches (Ekstrand 1983; Labella 2011; Olsen 2005; Pasanen 2008). Overall the reported compliance to the interventions was good. Labella 2011 reported the self-reported compliance of the coaches to the coach implemented warm-up including neuromuscular training to be good (used in 80% of practice sessions). Olsen 2005 found a high compliance (87%) to their coach led warm-up, although the definition of full compliance was not given. Parkkari 2011 reported a high compliance in the military setting, an average 83% of the conscripts attended the training sessions. Pasanen 2008 found a fair compliance as 74% of the intended training sessions were carried out by the intervention teams as planned. Soligard 2008 reported a good compliance, as overall 77% of the prescribed training sessions were performed by the intervention teams. The only trial reporting 100% compliance was Longo 2012, although it is not clear how compliance to the program was measured.

**5. Taping versus control**

**5.1 Primary outcomes**

**Incidence of ankle ligament injury**
Only one trial (Garrick 1973) compared taping as intervention to a control group. In this trial, 2,562 basketball player games were studied. High-top shoes and taped ankles were significantly more effective (P = 0.025 rate 6.5 sprains/1000 player games) in preventing an ankle sprain than high-top shoes and untaped ankles or low-top shoes and untaped ankles (rate respectively 30.4 and 33.4 sprains/1000 player games). Overall, taping showed a significant reduction in the occurrence of ankle sprains (OR 0.44, 95% CI 0.24 to 0.79). Participants with a history of a previous ankle sprains were about twice as likely to be injured as the previously uninjured participants (27.7 vs 13.9 sprains/1000 player games).

**Severity of ligament injuries to the ankle**
In this trial, injury severity was reported as mild, moderate or severe, comparable to the more commonly used grading system (grades 1, 2 or 3). Most ankle sprains were mild. Of the taped group almost all (16 of 17) sprains were mild, and the remaining injury was moderate. In the control group about 20% of the 36 sprains were moderate, and two were severe.

**Patient-assessed ankle function**
Not reported in this trial.
5.2 Secondary outcomes

**Incidences of other lower extremity injuries**
A total of eleven knee sprains was reported. Seven of these were sustained in the untaped groups, compared to four in the taped groups. Because of the small numbers of knee sprains no formal analysis was performed.

**Complications**
Not reported in this trial.

**Measures of service utilisation or resource use**
Not reported in this trial.

**Compliance to the intervention**
Not reported in this trial.

6. Stretching versus control

6.1 Primary outcomes

**Incidences of ankle ligament injury**
Three trials (2842 participants) compared stretching versus control for the prevention of lower extremity injuries, including ankle sprains, in army recruits (Pope 1998; Pope 2000) and civil servants engaged in recreational running (van Mechelen 1993). Pooled data showed no effect in the occurrence of ‘total ankle sprains’ (OR 0.71, 95% CI 0.44 to 1.13). In addition, Pope 1998 measured ankle dorsiflexion range at baseline to investigate whether this would influence incidence of ankle sprains, or other lower extremity injuries. It was found that participants with a low range of ankle dorsiflexion were at greater risk of sustaining an ankle sprain (likelihood ratio 7.65, P 0.006).

**Severity of ligament injuries to the ankle**
Not reported in these trials.

**Patient-assessed ankle function**
Not reported in these trials.

6.2 Secondary outcomes

**Incidences of other lower extremity injuries**
The overall rate of lower extremity injuries in the intervention groups did not differ significantly from the control groups for the three studies (Pope 1998 HR 0.92, 95% CI 0.52 to 1.61; Pope 2000 HR 0.95, 95% CI 0.77 to 1.18; van Mechelen 1993 HR 1.31, 95% CI 0.69 to 2.47).

**Complications**
Not reported in these trials.

**Measures of service utilisation or resource use**
Not reported in these trials.
Compliance (adherence) to the intervention
Pope 1998 and Pope 2000 reported instructor based compliance control to the stretching exercises. Van Mechelen 1993 reported moderate compliance to the intervention. Sixty-eight percent of the intervention group performed the warm-up, 64% performed the cooling down and 47% performed the stretching exercises (control group 21%, 8% and 5 %, respectively).

7. Insoles versus control

7.1 Primary outcomes
Incidence of ankle ligament injury
Two trials (676 participants) investigated insoles versus controls to prevent lower extremity injuries (including ankle sprains) in military conscripts (Bensel 1986; Larsen 2002). Pooled data showed no effect in the occurrence of 'total ankle sprains' (OR 0.73, 95% CI 0.37 to 1.44).

Severity of ligament injuries to the ankle
Not reported in these trials.

Patient-assessed ankle function
Not reported in these trials.

7.2 Secondary outcomes
Incidence of other lower extremity injuries
Bensel 1986 reported comparable numbers of lower extremity disorders for all intervention groups. Larsen reported significantly fewer conscripts with shin splints in the intervention group; 5 vs 24 (P = 0.005).

Measures of service utilisation or resource use
Larsen 2002 calculated costs as numbers needed to prevent (NNP) multiplied by cost per pair of insoles, which was approximately US $19. The cost for preventing one case of shin splints was US $101. To prevent at least one case of off-duty days, the cost was US $3750.

Compliance (adherence) to the intervention
Bensel 1986 reported similar numbers (70%) of participants in the three groups reported having always worn the insoles in their boots. Larsen 2002 reported good compliance rates, only 9 of the 58 (16%) military conscripts did not comply to the intervention.
COMPARISONS OF PREVENTIVE MEASURES

8. Taping versus bracing

8.1 Primary outcomes

**Incidence of ankle ligament injury**
Only one trial (Mickel 2006) compared taping to bracing in high school football. The overall incidence of ankle sprains was 0.80/1000 exposures. There was no significant difference of the incidence of ankle sprains in the intervention groups (0.77 versus 0.83, respectively, P > 0.05).

**Severity of ligament injuries to the ankle**
All six ankle sprains were grade 1 sprains.

**Patient-assessed ankle function**
Not reported in this trial.

8.2 Secondary outcomes

**Incidence of other lower extremity injuries**
There were no clinically evident fractures or “high” (disruption of the inferior tibiofibular syndesmosis) ankle sprains reported in either group.

**Complications**
Not reported in this trial.

**Measures of service utilisation or resource use**
Costs of bracing and taping were calculated, including materials and time to apply the brace or tape. Costs per braced/taped ankle per season were US$ 30/US$ 776 respectively, therefore bracing was found to be dominant over taping.

**Compliance (adherence) to the intervention**
The correct application of the ankle stabilizer was explained to the participants and supervised by the head athletic trainer of each participating team. In the ankle taping group, team athletic trainers performed each ankle taping before practice and games.

9. Brace versus neuromuscular training

9.1 Primary outcomes

**Incidence of ankle ligament injury**
Four trials (705 participants) compared the use of different braces to neuromuscular training in soccer (Tropp 1985), basketball (Schroter 2005), volleyball (Stasinopoulos 2004) and recreational athletes (Janssen 2014a). Pooled data showed a significant reduction in the incidence of 'total ankle sprains' (OR 0.35, 95% CI 0.13 to 0.94 Figure 12, Analysis 9.1) and 'recurrent ankle sprains' (OR 0.54, 95% CI 0.32 to 0.92 Figure 13, Analysis 9.3) in favour of bracing. Pooled data showed no significant difference in the occurrence of 'new ankle sprains' (OR 0.24, 95% CI 0.04 to 1.37 Figure 14, Analysis 7.2).
Interventions for preventing ankle ligament injuries

### Figure 12. Forest plot of comparison: Brace versus Neuromuscular Training, outcome: 9.1 Total ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace</th>
<th>NM training</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Schroter 2006</td>
<td>3</td>
<td>100</td>
<td>13</td>
<td>116</td>
</tr>
<tr>
<td>Tropp 1985</td>
<td>2</td>
<td>60</td>
<td>7</td>
<td>135</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>5</td>
<td>160</td>
<td>20</td>
<td>251</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td>160</td>
<td>20</td>
<td>251</td>
</tr>
<tr>
<td>Heterogeneity: CH²= 0.82, df=1 (P=0.37); I²=0%</td>
<td>Test for overall effect: Z = 2.03 (P=0.04)</td>
<td>Favoours Brace</td>
<td>Favoours NM training</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 13. Forest plot of comparison: Brace versus Neuromuscular Training, outcome: 9.3 Recurrent ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace</th>
<th>NM training</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Janssen 2014a</td>
<td>17</td>
<td>113</td>
<td>29</td>
<td>107</td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>3</td>
<td>56</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>Stasinopoulos 2004</td>
<td>6</td>
<td>17</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Tropp 1985</td>
<td>1</td>
<td>44</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>229</td>
<td>242</td>
<td>44</td>
<td>251</td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>242</td>
<td>44</td>
<td>251</td>
</tr>
<tr>
<td>Heterogeneity: CH²= 4.43, df=3 (P=0.21); I²=33%</td>
<td>Test for overall effect: Z = 2.27 (P=0.02)</td>
<td>Favoours Brace</td>
<td>Favoours NM training</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 14. Forest plot of comparison: Brace versus Neuromuscular Training, outcome: 9.2 New ankle sprains.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Brace</th>
<th>NM training</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Schroter 2005</td>
<td>0</td>
<td>45</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>Tropp 1985</td>
<td>1</td>
<td>52</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>97</td>
<td>137</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Heterogeneity: CH²= 0.26, df=1 (P=0.61); I²=0%</td>
<td>Test for overall effect: Z = 1.61 (P=0.11)</td>
<td>Favoours Brace</td>
<td>Favoours NM training</td>
<td></td>
</tr>
</tbody>
</table>

### Severity of ligament injuries to the ankle
Janssen 2014a found no significant difference in time loss injuries and injuries resulting in costs between the interventions. Schroter 2005 reported only total days lost from sports participation for all participants, not per treatment group. Stasinopoulos 2004 and Tropp 1985 did not report injury severity.

### Patient-assessed ankle function
Not reported in these trials.

### 9.2 Secondary outcomes

#### Incidence of other lower extremity injuries
Schroter 2005 reported only total numbers of other injuries, not per treatment group. The other three trials did not report other lower extremity injuries.
Complications
None reported in these trials.

Measures of service utilisation or resource use
Janssen 2014a did not report costs, but these were collected and were published in a separate publication (Janssen 2014b). Bracing was found to be the dominant intervention over both neuromuscular training and the combination of both measures, providing a more effective and less expensive measure. The study only ascertained the cost effectiveness of the prevention of recurrent ankle sprains. Other clinical consequences of ankle sprains were not taken into account. Schroter 2005 reported primary treatment (Rest, Ice, Compression, Elevation), medical treatment and time lost from sports participation. None of the other studies reported measures of service utilisation or resource use.

Compliance (adherence) to the intervention
Janssen 2014a showed that self-reported compliance varied from 45% in the training group, measured during the 2 months of neuromuscular training prescription, to 23% in the brace group, measured during the 12 months of ankle brace prescription during sports. In the combi group 28% fully complied to 2 months of training combined with 2 months of bracing. Compliance was not controlled for or measured at all in the remaining trials.

COMPARISONS OF TREATMENT MODALITIES
As these trials were mainly aimed at primary treatment and not at the prevention of ankle sprains, these were eventually excluded from the final review (Ardevol 2002; Beynnon 2006; Bleakley 2010; Nualon 2013; Cleland 2013; Pihlajamäki 2010; Pijnenburg 2003; De Bie 1998).
DISCUSSION

Summary of main results
A total of 47 trials (29,752 participants) concerning interventions for preventing acute ankle ligament injuries were included in this review. Although the interventions were heterogeneous, and outcomes varied, the data from 33 trials could be pooled for the primary outcome ‘incidence of ankle ligament injury’. Overall the risk of bias in the pooled studies was moderate, but the more recent trials were of better methodological quality. The available data allowed categorisation of acute lateral ankle sprains in ‘total ankle sprains’, ‘new ankle sprains’ and ‘recurrent ankle sprains’. For the other primary outcomes, ‘severity of ligament injuries to the ankle’ and ‘patient-assessed ankle function’, and the secondary outcomes ‘complications’, ‘measures of service utilisation or resource use’, and ‘compliance (adherence) to the intervention’, the available data varied considerably in definition or the outcomes were not available at all, and therefore pooling was not possible. This was also the case for the secondary outcomes ‘complications’, ‘measures of service utilization or resource use’, and ‘compliance (adherence) to the intervention’. In this discussion we decided to focus on the primary outcome ‘incidence of ankle ligament injury’ only, because of substantial clinical heterogeneity in the other outcomes studied. We recommend a uniform core set of outcomes to be included in future studies to overcome this issue in ‘Implications for research’.

Most participants were high school athletes, recreational athletes (age mainly 18 to 35 years) or military recruits. Twenty of the included trials found significant effects of the interventions studied. The interventions tested by the included trials fell into five main preventive strategies: footwear, taping, bracing, neuromuscular training, and multifaceted exercise programs.

Two trials reported the effect of high-top versus low-top shoes for prevention of ‘total ankle sprains’ (Analysis 1.1). One trial (Garrick 1973) did find a significant reduction in the occurrence of ‘recurrent ankle sprains’ in favour of players wearing high-top versus low-top shoes, but Barrett 1993 was not able to reproduce these findings. Moreover, the study by Garrick 1973 was at “high” risk of bias. Although taping is arguably the most popular preventive method for ankle sprains, only one RCT (Garrick 1973) provided limited evidence of low quality to support its preventive use. Garrick 1973 reported high-top shoes combined with tape to be significantly more effective in preventing ankle sprains than high-top shoes alone in basketball.

Nine trials compared the use of ankle braces to controls in various athletic populations, and delivered evidence of moderate quality to support bracing for prevention of both ‘total’ and ‘recurrent ankle sprains’ (Analysis 2.1; Analysis 2.3). There is evidence of low quality to support ankle bracing for prevention of ‘new ankle sprains’ (Analysis 2.2). Although different ankle brace-types were used in these trials, evidence was strongest for semi-rigid (5 studies) and lace-up (2 studies) ankle braces. The pooled data for ‘total ankle sprains’ and ‘new ankle sprains’ showed substantial statistical heterogeneity. The study mainly responsible for this heterogeneity is Surve 1994. This was the only study where participants with a history of previous ankle injury wore braces on both ankles, while participants without previous injury only wore a brace on the dominant ankle.
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Thirteen trials compared neuromuscular training to controls, mainly in basketball, soccer and in patients with an ankle sprain presenting at an ED. There is evidence of moderate quality for the effectiveness of neuromuscular training for prevention of 'total ankle sprains' and 'recurrent ankle sprains' (Analysis 3.1 and Analysis 3.3). There was inconclusive evidence of very low quality for an effect in the prevention of 'new ankle sprains' (Analysis 3.2). A possible explanation is that an effect for 'total ankle sprains' was found only because of the large effect on 'recurrent ankle sprains' in this 'total'. Not all studies supplied the data to separate these two categories. Moreover, only two studies allowed extraction of 'new ankle sprains' data, therefore the question on the effectiveness of neuromuscular training as primary preventive measure remains to be solved.

Seven trials compared multifaceted exercise programs to controls. There is evidence of high quality to support multifaceted exercise programs for prevention of 'total ankle sprains' (Analysis 4.1). The pooled data showed moderate statistical heterogeneity, likely due to the varied interventions and participants (clinical diversity). The data in these studies were of insufficient detail to allow pooling of 'recurrent ankle sprains' and 'new ankle sprains'. Two trials compared stretching to controls in military recruits. There is evidence of moderate methodological quality of no effect of stretching for prevention of 'total ankle sprains' (Analysis 5.1). Only one trial (Mickel 2006) compared bracing to taping in high school football. This trial found limited inconclusive evidence of low quality regarding bracing versus taping for the prevention of 'total ankle sprains'.

Finally, limited evidence of very low quality was found for the superiority of bracing over neuromuscular training in preventing 'total ankle sprains' and 'recurrent ankle sprains' (Analysis 7.1 and Analysis 7.3). Given the fact that the data of only two and four studies could be pooled respectively, cautious interpretation of these estimates is required. Furthermore, inconclusive evidence of very low quality was found for bracing versus neuromuscular training in preventing 'new ankle sprains' (Analysis 7.2).

Overall completeness and applicability of evidence
In interpreting the results of this review, one should be aware of the variation in the participants (college students, active population, recreational athletes, elite-athletes), setting (teams / individual athletes), duration of the intervention and the follow-up (weeks to a year), and the type of intervention tested.

The vast majority of these trials were performed in men (age: mainly 18 to 35 years), although some recent trials were performed in females. The limited data and analysis of female participants in the included trials means we cannot provide separate evidence of effectiveness for each sex. A recent epidemiological study showed a comparable incidence rate ratio for ankle sprain for males versus females. This study also showed that males between fifteen and twenty-four years old had higher rates of ankle sprain than their female counterparts, whereas females over thirty years old had higher ankle sprain rates than their male counterparts (Waterman 2010a).

The participants in the included trials were mainly recreational athletes, although a minority also concerned military recruits, elite and high school athletes. Therefore the evidence in this review is only applicable to active populations. It is assumed that more sedentary populations could also benefit from the presented preventive measures, but
motivation and physical condition at study onset may be important confounders of outcome. Preventive 'taping' refers to traditional sportstape, or Leukotape, which is non-elastic and mechanically decreases plantar flexion and inversion movements. Although taping is also thought to increase proprioception, it remains unclear to which extent the preventive effect of taping can be contributed to each quality (Raymond 2012). Elastic 'kinesio taping', also called 'cure taping' or 'medical taping' is rapidly increasing in popularity. There are no reports of RCTs that included 'medical taping' as preventive measure. A recent review on preventive effects of 'kinesio taping' (Williams 2012) concluded that a beneficial effect for proprioception regarding grip force sense error is likely, but no positive outcome for ankle proprioception was found. Overall, the evidence for the effectiveness of taping is limited and is not applicable to 'kinesio taping'.

Verhagen 2004a found a higher risk of overuse knee injuries in the intervention group by subgroup analysis for players with a history of knee injuries. There were no other reports on serious adverse effects of the interventions included in this review. Compliance is of major concern in the translation of the evidence to daily practice. A per protocol analyses from a study on neuromuscular training (Verhagen 2011) showed that significantly fewer recurrent ankle sprains were found in the fully adherent group compared to the group that was not adherent. Nevertheless, more than a quarter of the included trials did not describe the methods for monitoring or ensuring compliance.

Evidence on resource use or service utilisation was limited. Only three trials included an economic evaluation (Hupperets 2010; Janssen 2014a; Verhagen 2005). It was shown that a proprioceptive balance board training programme aimed at players with previous ankle sprains could be cost effective over a longer period of time. Evidence for the cost-effectiveness of preventive ankle bracing is lacking, although one trial (Mickel 2006) on bracing versus taping concluded that the cost of taping an ankle far surpassed the cost of bracing for a single season. The duration of most trials was only one year, or one season, while a substantial part of the reported injuries concerned recurrent injuries. It is assumed, but not proven, that after an index ankle ligament injury the risk of a recurrent injury is increased for as long as one year. Proper studies with a longer follow-up are scarce, while a higher risk of subsequent injury could become manifest in the next playing season, and therefore an underestimation of the risk of subsequent injury is likely.

Quality of the evidence
The quality of the evidence included in this review is moderate. Each included trial was assessed for risk of bias in seven domains. In about 25% of the assessments, there was insufficient information to make a judgment, particularly in the domain of 'allocation concealment' (64%). Only two of the 42 included trials (5%) were assessed as low risk of bias in all seven domains. Twenty trials (48%) were assessed as at low risk of bias in four or more of the seven domains, whereas eight trials (19%) were assessed as at high risk of bias in three or more of the seven domains. The trials scored well in the domains 'random sequence generation' and 'selective reporting'; 60% and 71% of trials respectively were assessed as being at low risk of bias. Only 29% and 36% of trials were assessed as at low risk of bias in the domains 'blinding of participants and personnel' and 'blinding of outcome assessment', respectively. Although it is true that blinding of both participants and personnel is difficult in clinical trials, more effort could have been taken to ensure blinding of outcome assessment.
Seventeen of the 42 included trials (40%) were cluster-randomised trials. In cluster-randomised trials, groups of individuals or centres rather than individuals are randomised to different interventions; therefore the ‘unit of allocation’ is the cluster, or the group. This method of randomisation is mainly applied to avoid ‘contamination’ across interventions when trial participants are managed within the same setting, for example a soccer club. A promising thirteen of the seventeen cluster-randomised trials adjusted for clustering in their analyses. The assessment of bias relies on adequate reporting of the trial methods. Recently a new update of the CONSORT statement (Schulz 2010), which is an evidence-based, minimum set of recommendations for reporting RCTs, was published to guide adequate reporting. Although this method of reporting is gaining in popularity, it was adopted in only a minority of the included trials, even when they were of recent date.

**Potential biases in the review process**

We tried to minimize publication bias by performing a comprehensive and sensitive search of multiple relevant databases. Our search strategies were developed and performed by the Cochrane Trials Search Co-ordinator, specialised in musculoskeletal conditions, and we included trials identified in languages other than English. Despite this professional search support, we cannot rule out the possibility that some trials have been missed. We minimised selection bias in the review process by having two authors who independently screened studies for inclusion, extracted data and assessed risk of bias (KWJ and EV). Finally, we followed a priori protocol and the Cochrane Handbook in the methods employed in this review.

**Agreements and disagreements with other studies or reviews**

In this Cochrane review we focused on the primary and secondary prevention of ankle sprains. Overall 20% to 50% of people who sustain a lateral ankle sprain continue to suffer from lateral ankle instability, characterised by persistent recurrent ankle sprains or a feeling of giving way. If this continues for longer than six months, the term ‘chronic ankle instability’ (CAI) is used. For treatment of CAI we refer to the Cochrane review: 'Interventions for treating chronic ankle instability' (De Vries 2011).

A former Cochrane review (Handoll 2001) found good evidence for the beneficial effect of ankle supports to prevent ankle sprains during high-risk sporting activities (e.g. soccer, basketball). This is in line with the current findings of our systematic review. The cost effectiveness of external ankle supports in prevention of recurrent ankle sprains was just recently reported dominant over neuromuscular training and the combined intervention by Janssen 2014b, though these results need to be confirmed by others.

With respect to the evidence for neuromuscular training progress has been made. While Handoll 2001 found limited evidence for the reduction in ankle sprain recurrences through neuromuscular (ankle disk) training over a decade ago, the current meta analyses shows ‘Total ankle sprains’ and ‘Recurrent ankle sprains’ can be prevented by this intervention.

We found 12 other relevant systematic reviews on the prevention of ankle sprains (Aaltonen 2007; Dizon 2010; Hubscher 2010; Kadakia 2003; Kaplan 2011; McGuine 2006; McKeon 2008; Sitler 1995; Thacker 1999; Verhagen 2000; Verhagen 2010; Zech
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2009). These reviews mainly selected the RCTs that were included in this review. Therefore, we will only discuss the most recent reviews. In general their findings were in line with the current results.

In the review of Dizon 2010 on the effectiveness of external ankle support seven trials of moderate quality were included. The main finding was the reduction of ankle sprain by 69% (OR 0.31, 95% CI 0.18 to 0.51) with the use of ankle braces and reduction of ankle sprain by 71% (OR 0.29, 95% CI 0.14 to 0.57) with the use of ankle tape among previously injured athletes, mainly based on the same studies currently included. No type of ankle support was found to be superior than the other. Hubscher 2010 included seven methodologically well-conducted studies on neuromuscular training, although not all of them were randomised. Pooled analysis revealed that multi-intervention training was effective in reducing ankle sprains (RR 0.50, 95%CI 0.31 to 0.79). Balance training alone resulted in a significant risk reduction of ankle sprains (RR 0.64, 95% CI 0.46 to 0.90).

The most recent review Kaplan 2011, which included 19 RCTs, mainly confirmed our findings. They concluded that semi-rigid ankle braces or aircasts are more effective than taping to reduce the incidence of sprains. They also found that neuromuscular training could improve sensori-motor control in previously injured ankles, such that the risk equaled that of healthy ankles. They advised change of rules to limit contact between players and introduction of harsher penalties for foul play. While Verhagen 2010 hypothesized in their review that: "A combination of an external prophylactic measure (tape or brace) with neuromuscular training will achieve the best preventive outcomes with minimal burden for the athlete.\text{"}, a recent RCT (Janssen 2014a; Janssen 2014b) that compared neuromuscular training versus bracing versus the combination of the interventions could not confirm this. It was found that bracing was superior over neuromuscular training with respect to incidence of self-reported recurrences and costs.
AUTHORS’ CONCLUSIONS

Implications for practice
Overall taping, bracing, neuromuscular training and multifaceted exercise programs are found to prevent ankle ligament injuries, although quality of studies is diver. For prevention of first time ankle ligament injuries, evidence was only found for bracing. For prevention of recurrent ankle ligament injury, taping, bracing, neuromuscular training and multifaceted exercise programs all show benefits. Finally, high-top shoes, stretching and insoles do not prevent ankle injuries, although the quality of studies is low and evidence is limited for high top shoes and insoles.

Implications for research
Over the last decade well designed trials have contributed substantially to the available evidence for interventions preventing ankle ligament injuries in athletes. Although taping is arguably the most popular preventive method for ankle sprains, available evidence is limited, and additional well-designed and reported randomised controlled trials are needed to determine the effectiveness of this intervention in different populations. While stronger evidence was found for neuromuscular training and ankle bracing, optimal duration of these interventions is still to be determined. Furthermore, adequate monitoring and reporting of compliance are required in future investigations. A major issue in extracting and synthesising the available evidence, other than ‘incidence of ankle ligament injury’, was the substantial clinical heterogeneity in the outcomes studied. We therefore recommend a uniform set of outcomes to be included in future studies. In addition to ‘incidence of ankle ligament injury’, this core set of outcomes should include ‘severity of ligament injuries to the ankle’, ‘patient-assessed ankle function’, ‘complications’, ‘measures of health service utilization or resource use’, and ‘compliance (or adherence) to the intervention’. Furthermore, studies with a longer follow-up are necessary, to prevent an underestimation of the risk of subsequent injury. Although there is limited evidence for the economic benefits of neuromuscular training and bracing from a societal point of view, more trials are needed regarding the cost-effectiveness of neuromuscular training, bracing and other interventions for preventing ankle ligament injuries.

A crucial step for the athletic and physically active population in benefiting from (cost-)effective interventions is the implementation of these interventions in practice. Therefore, more implementation studies are needed. Design, conduct, and reporting of trials should meet the contemporary standards of the CONSORT statement.

ACKNOWLEDGEMENTS
We would specifically like to thank Dr Helen Handoll for her valuable comments about drafts of this protocol. Furthermore, we would like to thank Joanne Elliott for the design of the search strategies and Lindsey Elstub for her advice and support.

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The authors would like to acknowledge the previous work by Handoll et al (Handoll 2001) as the foundation of the current review.
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REFERENCES

Aaltonen 2007

Beynnon 2001

Bland 1997

De Vries 2011

Dizon 2010

Ekstrand 1990

Fong 2007

Gerber 1998

Handoll 2001

Haskell 2007

Higgins 2002

Higgins 2011

Hubscher 2010

Hupperets 2009b

Hupperets 2010

Janssen 2014b
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Kadakia 2003

Kannus 1991

Kaplan 2011

Karlsson 1993

Lefebvre 2011

McKeon 2008

Raymond 2012

Schulz 2010

Sitler 1995

Thacker 1999

Verhagen 2000

Verhagen 2001

Verhagen 2004b

Verhagen 2005

Verhagen 2010

Verhagen 2011

Waterman 2010a
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Waterman 2010b

Wexler 1998

Williams 2012

Yeung 1994

Zech 2009

References to other published versions of this review

Handoll 2011

Janssen 2011

References to studies included in this review

Amoroso 1998

Ardevol 2002

Barrett 1993

Bensel 1986

Beynnon 2006

Bleakley 2010

Cleland 2013
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- **De Bie 1998**

- **Eils 2010**

- **Ekstrand 1983**

- **Emery 2007**

- **Emery 2010**

- **Engebretsen 2008**

- **Frey 2010**

- **Garrick 1973**

- **Holme 1999**

- **Hupperets 2009a**

- **Janssen 2014a**

- **Labella 2011**

- **Larsen 2002**

- **Longo 2012**

- **McGuine 2006**

- **McGuine 2011**
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McGuine 2012

Mickel 2006

Mohammadi 2007

Nualon 2013

Olsen 2005

Parkkari 2011

Pasanen 2008

Pihlajamäki 2010

Pijnenburg 2003

Pope 1998

Pope 2000

Schroter 2005

Sitler 1994

Söderman 2000

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**Soligard 2008**

**Stasinopoulos 2004**

**Surve 1994**

**Tropp 1985**

**Van Mechelen 1993**

**Van Rijn 2007**

**Verhagen 2004a**

**Wedderkopp 1999**

**Wedderkopp 2003**

**Wester 1996**

* Indicates the major publication for the study
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