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http://dx.doi.org/10.1002/acr.22797

Title	Lateral wedge insoles for reducing biomechanical risk factors for medial knee osteoarthritis progression : a systematic review and meta-analysis
Authors	Arnold, JB, Wong, DX, Jones, R, Hill, CL and Thewlis, D
Publication title	Arthritis Care & Research
Publisher	Wiley
Type	Article
USIR URL	This version is available at: http://usir.salford.ac.uk/id/eprint/37792/
Published Date	2016

Lateral wedge insoles for reducing biomechanical risk factors for medial knee osteoarthritis progression: a systematic review and meta-analysis

John B. Arnold, PhD[1], Daniel X. Wong[1], Richard K. Jones, PhD[2, 3], Catherine L. Hill, MBBS, FRACP, MSc, MD[4, 5], Dominic Thewlis, PhD[1, 6]

[1]Alliance for Research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, School of Health Sciences, University of South Australia, Adelaide, Australia;
[2]School of Health Sciences, University of Salford, Frederick Road, Salford, UK;
[3]Arthritis Research UK Epidemiology Unit, Centre for Musculoskeletal Research, University of Manchester, Oxford Road, Manchester, UK;
[4]Department of Rheumatology, The Queen Elizabeth Hospital, Woodville Road, Woodville, Adelaide, Australia;
[5]The Health Observatory, School of Medicine, The University of Adelaide, Woodville, South Australia, Australia
[6]Centre for Orthopaedic and Trauma Research, University of Adelaide, Adelaide, Australia;

Corresponding author

John B. Arnold
Alliance for Research in Exercise, Nutrition and Activity (ARENA)
Sansom Institute for Health Research
School of Health Sciences , University of South Australia
GPO Box 2471, Adelaide, Australia 5001
T: +61 8 8302 1207; F: +61 8 8302 2766; E-mail: john.arnold@unisa.edu.au

Running title

Lateral wedge insoles for knee OA

Keywords

knee osteoarthritis, biomechanics, insole, gait

Word Count: 3792

Objective

Lateral wedge insoles are intended to reduce biomechanical risk factors of medial knee osteoarthritis (OA) progression, such as increased knee joint load; however, there has been no definitive consensus on this topic. The aim of this systematic review and meta-analysis was to establish the within-subject effects of lateral wedge insoles on knee joint load in people with medial knee OA during walking.

Methods

Six databases were searched from inception until February 13th 2015. Included studies reported on the acute biomechanical effects of lateral wedge insoles in people with medial knee osteoarthritis during walking. Primary outcomes of interest relating to the biomechanical risk of disease progression were the 1st and 2nd peak external knee adduction moment (EKAM) and knee adduction angular impulse (KAAI). Eligible studies were pooled using random-effects meta-analysis.

Results

Eighteen studies were included with a total of 534 participants. Lateral wedge insoles resulted in a small but statistically significant reduction in the 1st peak EKAM (SMD: -0.19; 95% CI -0.23 − -0.15) and 2nd peak EKAM (SMD: -0.25; 95% CI -0.32 − -0.19) with a low level of heterogeneity (I^2 = 5% and 30%, respectively). There was a favourable but small reduction in the KAAI with lateral wedge insoles (SMD: -0.14; 95% CI -0.21 − -0.07, I^2 =31%). Risk of methodological bias scores (Quality Index) ranged from 8 to 13 out of 16.

Conclusions

Lateral wedge insoles cause small reductions in the EKAM and KAAI in people with medial knee OA during walking. At present, they appear ineffective at attenuating structural changes in people with medial knee OA as a whole and may be better suited to targeted use in biomechanical phenotypes associated with larger reductions in knee load.

Systematic Review Registration (PROSPERO): CRD42015015392

Significance and Innovations

- This review presents the first comprehensive synthesis of studies investigating the effect of lateral wedge insoles on biomechanical risk factors for medial knee osteoarthritis progression, such as medial knee joint loading
- This review of 18 studies found lateral wedge insoles had a small statistically significant effect on reducing the 1st and 2nd peak external knee adduction moment and knee adduction angular impulse
- Biomechanical effects of lateral wedge insoles persisted regardless of whether a sham insole or footwear was used as the comparison condition
- Variability in patient response highlights the need to consider the potential of lateral wedge insoles to attenuate disease progression in specific biomechanical phenotypes

The local mechanical environment plays an important role in the pathogenesis of knee osteoarthritis (OA) (1). Knee joint loading, estimated using surrogate measures such as the external knee adduction moment (EKAM), has been implicated in both the development of knee pain and radiographic progression of medial knee OA in older adults (2, 3). Knee load during walking is also positively associated with levels of subchondral bone change (4), worsening of bone marrow lesions (5), cartilage loss (6) and progression to total knee replacement in those with established disease (7). Non-invasive interventions aimed at reducing knee load during walking may therefore hold potential to slow disease progression in people with medial knee OA.

The medial knee compartment more commonly shows radiographic disease, proposed to be a result of bearing a greater proportion of load (~60%) compared to the lateral compartment (~40%) during walking (8). The EKAM has been used as a proxy for medial knee joint load and a reduction in the EKAM represents a change in medial to lateral distribution and a relative lowering of the medial compartment load (9). The area underneath the EKAM curve, the knee adduction angular impulse (KAAI), represents the cumulative effect of the EKAM over the stance phase (10). High medial knee loading during walking estimated using the EKAM and KAAI is predictive of structural progression in knee OA (3, 6, 11), and as they are modifiable factors with conservative interventions, are potential targets to slow disease progression.

Lateral wedge insoles are in-shoe devices that lower medial tibiofemoral compartment load to potentially reduce the deleterious effects of aberrant mechanics in knee OA. Originally described in 1987 by Yasuda & Sasaki (12), they consist of a simple wedged insole with an elevated lateral profile and angle of inclination facing toward the outside of the heel. Variations to this design have been described, ranging from shortened devices covering only the heel (13), to modifications of over-the-counter arch supports (14).The elevated lateral profile of lateral wedge insoles shifts the point of application of the ground reaction force (centre of pressure) toward the outside of the foot, shortening the ground reaction force lever arm on the inside of the knee and reducing the EKAM (15).

The clinical and biomechanical effects of lateral wedge insoles in people with medial knee OA have been extensively studied. Recommendations feature in clinical guidelines for the conservative management of knee OA, including those from the American College of Rheumatology (ACR) (16) and Osteoarthritis Society International (OARSI) (17). However, recommendations remain inconsistent. Internationally, some guidelines issue a conditional recommendation (16, 17), whilst others do not recommend use of lateral wedge insoles on the basis of equivocal evidence of any benefit on pain or knee function (18). A recent meta-analysis demonstrated an effect of lateral wedge insoles on pain outcomes below the minimally clinical important difference for OA (19). However, to our knowledge, there remains no comprehensive meta-analysis of their effect on biomechanical risk factors for knee OA progression, such as knee load. The objective of this review was to determine the within-subject effects of lateral wedge insoles on biomechanical risk factors for disease progression (EKAM and KAAI) in patients with medial knee OA during walking.

Methods

Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (20). This protocol for this review was registered on the international prospective register of systematic reviews (PROSPERO), registration number (CRD42015015392).

Search Strategy

The PICO (Population, Intervention, Comparison and Outcome) framework was used to define the search strategy. The electronic databases Medline (via OvidSP), EMBASE (via OvidSP), CINAHL (via EBSCOhost), AMED (via OvidSP), Scopus and Web of Science (via ISI Web of Knowledge) were searched from inception to February 13th 2015. Searches were limited to studies on adults aged ≥18 years published in English. The Medical Subject Headings (MeSH) were used for keywords where available, with an example of the full search terms and combinations provided in Supplementary File 1. Search terms included a mixture of words relating to gait kinetics, kinematics and muscle activity to maximise the chance of retrieving relevant studies as these outcomes are frequently reported together. Each database was searched by two independent researchers to ensure reproducibility, with agreement required on the number of search hits achieved in each database before screening was initiated.

Eligibility Criteria

To be included in this review, studies must have been peer-reviewed journal articles investigating the biomechanical effects of laterally wedged insoles in adults with knee osteoarthritis during walking. All study designs were considered, as long as they included a within-group comparison of baseline versus insole conditions in people with medial knee OA. Eligible designs included (but were not limited to): randomised controlled trials (RCTs), Quasi-RCTs, non-RCTs, cohort studies, case-control and case-series. Systematic and narrative reviews were eligible for the purposes of manual reference list searching only to identify any studies missed in the primary search. Conference abstracts and unpublished data were not eligible.

Studies must have investigated a lateral wedged insole, defined as an in-shoe orthotic device with an angle of inclination towards the lateral border of the foot. No restrictions were made regarding the features of insoles (i.e. length – heel or full-length), degree of angulation, density or presence of concurrent arch support in the device. For prospective studies, only baseline data inferring the immediate effects of lateral wedge insoles were used. Studies allowing greater than a one month wear-in period were excluded, as this is the longest time period where effects are shown not to decline with continued wear (21).

As this review was focused on the biomechanical effects specific to lateral wedge insoles, studies must have included a comparison condition where the insole was not used during walking. This could be either in the same footwear but with the insole removed or in the same footwear with a sham device (thin flat insole) that is theoretically biomechanically ‘inert’ relative to the laterally wedged insole. This allowed the type of footwear, which can itself independently alter knee biomechanics, to be controlled within studies. Studies testing ‘variables stiffness’ shoes, were not eligible as although these devices work by the same mechanism, other design features may impact upon their effects and it is unclear if shoe features could be held constant across testing conditions (22, 23). Primary outcome variables of interest were specific due to their relevance to disease progression included features of the external knee adduction moment; the 1st peak EKAM, 2nd peak EKAM and the area under the EKAM curve, the knee adduction angular impulse (KAAI).

Study inclusion

All articles from searching of electronic databases were aggregated in bibliographic software (Endnote® X7, Thomson Reuters, Philadelphia, USA), where duplicate references were removed and cross-checked between two researchers to ensure agreement. The eligibility criteria were applied to the title and abstract by two independent researchers, with the retained articles again cross-checked. The retained articles were retrieved in full-text and screened according to the criteria, with the final remaining articles forming the results of the systematic review. Discrepancies in eligibility assessment made by two independent researchers were first resolved by discussion, with the opinion of a third researcher sought if consensus was not reached. Reference lists of the final included studies were manually searched for any relevant articles not identified in the initial search.

Critical Appraisal of Risk of Methodological Bias

Critical appraisal of each individual study was carried out by two independent reviewers using a modified version of the Quality Index (24). Similar to previous systematic reviews, we elected to use an abridged version containing 16 items relevant to a range of study designs, whilst still being applicable to randomised studies. The 16 items assessed the reporting quality, external validity and internal validity (bias and confounding). Each study was scored with the tool with each item graded as Yes (1 point), No (0 points) or unable to determine (0 points) to give a total score out of 16.

Data Extraction

Point estimates of effects including descriptive (means, medians, standard deviations, change scores) and inferential statistical information (p-values, confidence intervals) were extracted and cross-checked by two reviewers (JA and DW). Where different wedge angulations were given between participants and raw data were available, the mean value was computed. When adequate data was reported, standardised mean differences were calculated as the mean difference in the biomechanical parameter between the insole and no-insole conditions, divided by the pooled standard deviation with adjustment for small sample sizes (Hedges *g:* SMD)(25). Where not reported, the standard error of the mean difference and correlations between outcomes were estimated from P-values using the equivalent T-statistic (26). When this was not possible, an imputation approach was taken where the standard error of the mean difference was estimated using the lowest correlation estimate from other studies (26). If more information was required from that provided in the paper, authors were contacted directly to provide necessary data (relevant data from two studies was provided immediately).

Data Synthesis and Analysis

Meta-analysis was performed in Review Manager (RevMan) software (version 5.2, Cochrane Collaboration, Oxford, UK) using the inverse variance method, where the contribution of effect sizes from individual studies is weighted on sample size and their precision of the estimate. Significant heterogeneity across studies was anticipated due to differences in the distribution of participant characteristics (i.e. severity of OA), therefore a random-effects model was used to more conservatively estimate the pooled effect of the intervention. Sensitivity analysis according to the presence of a neutral (flat) insole was also performed when possible to assess the effect of this feature of study design to alter the biomechanical differences between conditions, as it has previously been shown to influence clinical outcomes (19). Publication bias was assessed using funnel plots and Egger's regression test using STATA (v14, StataCorp, College Station, TX, USA).

Statistical heterogeneity was assessed using the Chi^2 test and Cochran's *Q* statistic, which determines whether observed differences in results between studies differ due to chance alone, and the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Guidelines from the Cochrane Collaboration were followed for the interpretation of heterogeneity, where 25, 50 and 75% represent low, moderate and high heterogeneity, respectively (27). Effect sizes were interpreted as 0.2 (small), 0.5 (medium) and 0.8 (large) (28). To contextualise the effect sizes, the overall pooled estimates were back-transformed into original units using reference data from the largest study (15) (n=73) with mean and standard deviations of 3.82 SD 0.78 (Nm/%BW*Ht) for the 1st peak EKAM and 1.26 SD 0.37 (Nm.s/BW*Ht) for the KAAI.

Results

Three hundred and eighty three (383) records were identified. After assessing eligibility against the criteria, 48 studies were retained for full-text review. Eighteen studies met all eligibility criteria and were included in the final review (Figure 1). Eleven review articles were identified on the topic, but searching of reference lists yielded no additional studies not identified in the primary search. Authors of two studies provided additional data to allow effect sizes to be calculated (29, 30).

****Figure 1 here****

Study Characteristics

The 18 eligible studies included a total of 534 participants. All but four studies were within-subjects repeated measures designs, with the remaining being randomised trials (30-33). Four studies reported the use of the American College of Rheumatology (ACR) criteria (31, 34-36), with ten stating cut-offs regarding the severity of knee pain (13, 21, 29, 31, 32, 34, 36-39), most commonly >3/10 on a visual analog scale (21, 31, 32, 34, 37, 38, 40). This definition varied across studies according to the activity, with pain recalled during walking (29, 39), walking two blocks and/or climbing stairs (36), weight bearing activities (38) on most days of the past month (21, 32, 41). All studies included radiographic assessment of tibiofemoral OA. This was most commonly defined as Kellgren-Lawrence Grade 2 and above (21, 29, 31, 32, 34, 37-40, 42). Presence of medial joint space narrowing greater than lateral (13, 21, 29, 32, 33, 35, 36, 39, 41) and/or varus knee alignment (30, 36, 40, 42, 43) were used to limit participants to those with medial tibiofemoral OA.

Two studies reported the effects of heel wedges (43, 44), 14 studies investigated full-length insoles and two studies included both heel and full-length insoles (40, 45). The most common insole inclination angle was five degrees (21, 29, 32, 33, 36, 39-41, 45), with insole angles ranging from four (42) to 11 degrees (34). The presence of a concomitant medial arch support was common with four studies modifying generic insoles(31, 37, 38, 45) and three used a bespoke design (29, 33, 39). Fourteen studies prescribed the same insole to all participants, with the remaining four using a customised amount based on comfort and/or pain level (31, 35, 37, 38). A flat insole was the comparison condition in four studies(31, 34, 37, 38), seven studies used participants' own footwear (21, 30, 32, 36, 40, 42, 45) , five studies used standardised footwear(29, 33, 35, 39, 44), one study used both a flat insole and participants own footwear (41) and one study did not report the type of footwear (43). Walking speed was either controlled across conditions within a threshold of each participants' preferred speed(21, 31, 32, 36-38, 40), self-selected by participants but comparable across conditions (35, 41, 43), uncontrolled and not taken into account or reported(29, 30, 33, 34, 39, 42, 44) or the method was not reported but walking speed remained similar(45). Table 1 and Table 2 summarise the characteristics of included studies and participants.

****Table 1 here****

****Table 2 here****

Knee joint loading

1st peak external knee adduction moment (EKAM)

Eighteen studies reported the effect of lateral wedge insoles on the 1st peak EKAM, of which 13 used a shoe-only comparison and five used a neutral (flat) insole. As some studies made multiple comparisons with different insole angles, a total of 27 comparisons were included in the data synthesis (20 shoe comparison, seven neutral (flat) insole comparison) (Table 3).

The overall pooled effect estimate suggested that lateral wedge insoles resulted in a statistically significant reduction in the 1st peak EKAM (SMD = -0.19 [95% CI -0.23 − -0.15], $p < 0.001$), with a low level of statistical heterogeneity ($Chi^2 = 26.7$, $p = 0.42$, $I^2 = 3\%$) (Figure 2). This represents a small effect size and equates to an absolute change in the 1st peak EKAM of approximately 0.15 %BW*Ht. Subgroup comparisons yielded similar results, with the pooled effect similar in both shoe-only (SMD= -0.20 [95% CI -0.25 − -0.14]) and neutral (flat) insole comparisons (SMD = -0.22 [95% CI -0.30 − -0.13]). Egger's regression test for funnel plot asymmetry were not statistically significant, indicating weak evidence of publication bias for the 1st peak EKAM ($\beta = -0.61$, SE 0.37 $p = 0.111$) (Supplementary File 2).

****Figure 2 here****

2nd peak external knee adduction moment (EKAM)

Eight studies reported the effect of LWI on the 2nd peak EKAM; seven studies with a shoe-only comparison, one study with a neutral (flat) insole comparison and one study reported both comparisons. A total of 12 comparisons were included in the data synthesis (Table 3).

Overall, LWI resulted in a statistically significant reduction in the 2nd peak EKAM (SMD = -0.25 [95% CI -0.31 − -0.18], $p < 0.001$), with a low to medium level of statistical heterogeneity ($Chi^2 = 14.8$, $p = 0.19$, $I^2 = 26\%$) (Figure 3).

There was also evidence for differences according to subgroup analysis, with comparisons relative to shoe-only conditions resulting in a larger pooled effect (SMD = -0.29 [95% CI -0.35 − -0.22]) than neutral (flat) insole comparisons (SMD = -0.15 [95% CI -0.24 − -0.06]). Egger's regression test for funnel plot asymmetry were not statistically significant, indicating weak evidence of publication bias for the 2nd peak EKAM ($\beta = -0.29$, SE 1.27 $p = 0.822$).

****Figure 3 here****

Knee adduction angular impulse (KAAI)

Nine studies with a total of 11 comparisons were reported for the effect of LWI on the KAAI, with all but one comparing the LWI to a shoe-only condition (Table 3). The overall pooled estimate indicated a statistically significant reduction in the KAAI with LWI (SMD = -0.14 [95% CI -0.21 − -0.07], p <0.001), with a low level of statistical heterogeneity (Chi^2 = 14.44, p = 0.15, I^2 = 31%) (Figure 3). The pooled effect size equates to an absolute change in the KAAI of approximately 0.05 Nm.s/BW*Ht. Egger's regression test for funnel plot asymmetry were not statistically significant, indicating weak evidence of publication bias for the KAAI (β = -0.53, SE 1.19 p = 0.663).

****Figure 4 here****

****Table 3 here****

Risk of Bias

The modified index scores of included publications ranged from eight to 13 out of 16 (Table 1). Scoring agreement from two reviewers was evident on 271 of 288 items (agreement = 94%). Less than half of studies satisfactorily described their employed intervention clearly (item 4) with most neglecting to report the density of the insole material. Inadequate reporting of sampling methods for recruitment (item 8) and reporting of the proportion of participants who agreed to participate from the initial recruitment (item 9) was also common. All studies also failed to report if they blinded the assessors during the analysis of primary outcome measures (item 11). Full risk of bias scoring is provided in Supplementary File 3.

Discussion

This meta-analysis has demonstrated that lateral wedge insoles cause small reductions on biomechanical risk factors for disease progression (EKAM and KAAI) in people with medial knee OA. Proxies for medial relative to lateral compartment load were reduced with the use of lateral wedge insoles, including the 1st peak EKAM, 2nd peak EKAM and KAAI, irrespective of the presence of a neutral insole or footwear comparison.

This is the first meta-analysis on the effect of lateral wedge insoles on parameters of medial knee joint load (EKAM and KAAI) relevant to disease progression in people with knee OA. One previous review attempted to perform quantitative comparisons but did not establish pooled effect estimates (46). This review is therefore the most definitive, up-to-date and comprehensive analysis on this issue to clarify the effects of lateral wedge insoles on biomechanical risk factors for knee OA progression.

Lateral wedge insoles were associated with a modest reduction in the EKAM, questioning their potential to attenuate structural changes considering the effect of elevated knee load on risk for disease progression. A meta-analysis of prospective studies reported 1.9 times increased odds of OA progression for every 1 unit increase in the peak EKAM (%BW*Ht) (47). The overall effects revealed in this review on the 1st peak EKAM equates to a minimal reduction of 0.15 %BW*Ht. This may, in part, may explain the findings from randomised trials that lateral wedge insoles did not reduce the rate of cartilage loss over 12 months (48) or the rate of joint space narrowing over 2 years (49). Conversely, an alternate explanation is the inclusion of all participants with knee OA in previous clinical trials, despite up to 23% showing paradoxical increases in medial knee joint load with the use of lateral wedge insoles (29, 32). Recent evidence indicates that individuals with greater eversion of the ankle/subtalar complex during walking are more likely to decrease their EKAM when using a lateral wedge insole (50). Prescription based on biomechanical response and use of insoles only in individuals who show reductions in knee joint loading (biomechanical phenotypes) appears more appropriate to increase the likelihood of a favourable long-term response regarding the attenuation of structural changes. This would limit their application and benefit to a smaller number of individuals, but is still likely to be significant considering the overall prevalence of knee OA and projected rise due to population ageing and rising obesity levels (51). Further research investigating targeted use of lateral wedge insoles in biomechanical phenotypes likely to benefit is required to fully interrogate their potential to limit disease progression.

An important issue regarding knee load exposure in osteoarthritis is the concept of cumulative loading (52). Despite associations between the EKAM and disease progression, the KAAI has been proposed as a more useful measure to account for both the duration and magnitude of loading in knee OA. Indeed, the KAAI but not the peak EKAM has been associated with medial tibiofemoral cartilage loss over 12 months (6) and 2 years (11). Although the overall reduction in the peak EKAM and KAAI with lateral wedge insoles per step was small, it may surmount to a large cumulative effect imparted on the knee over the course of the day (52). This should be considered when interpreting the findings of this review and future research on load modifying interventions in knee osteoarthritis.

Unlike the results of a meta-analysis on the effect of lateral wedge insoles on pain (19), no subgroup differences according to use of a neutral (flat) insole were observed for the 1st peak EKAM. A subgroup difference was observed for the 2nd peak EKAM, with studies without a neutral insole comparison reporting smaller effect sizes. This is inconsistent with concern that flat insoles are not biomechanically inert, and considering the results of this meta-analysis and others (19), appears more relevant to the placebo effect and pain outcomes rather than knee loading.

The main limitation to this review was the available body of evidence, which primarily consisted of peer-reviewed single-group crossover studies testing the immediate effect of insoles. Numerous RCTs on lateral wedge insoles have been published, but report only pain outcomes (19) and data on their acquired or long term biomechanical effects are scarce (31). We assessed for the presence of publication bias by using funnel plots and formal testing which revealed weak evidence for an effect, strengthening the inferences from this review. An imputation approach for some comparisons was used to derive standard errors for effect sizes, however we took the most conservative approach by using the lowest correlation estimate amongst studies with all available data (26). The variability in measurement approach for the EKAM is also worthy of mention, however given the relative consistency in findings across studies this appears to have not had a major influence. The use of the EKAM to infer knee load in previous studies is also contentious as the contribution of muscle forces to joint load is not considered. However, clinical relevance was maintained in this review by the focus on outcomes that have demonstrated links with disease progression (3, 6).

In conclusion, lateral wedge insoles have a small effect on reducing medial knee joint load in people with medial knee OA. The magnitude of the changes observed in the EKAM and KAAI equates to minimal absolute reduction in knee joint load. At present, lateral wedge insoles appear ineffective at attenuating structural changes in people with medial knee OA as a whole. Recent evidence suggests they may be better suited to targeted use in biomechanical phenotypes associated with larger reductions in knee load, with future clinical trials required to investigate this potential.

Acknowledgements and Funding

We would like to acknowledge all authors who provided additional data. No sources of funding were obtained for this systematic review.

Competing Interest Statement

RKJ may receive royalties from Salford Insole™, a manufacturer of lateral wedge insoles.

All other authors declare no conflicts of interest.

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Table 1. Characteristics of included studies and intervention

Authors	Country	Clinical criteria	Intervention	Comparisons	Applied	QI Score (/16)
Abdallah et al. (2011) (34)	Egypt	ACR criteria Pain VAS (≥30 mm)	6° and 11° full length lateral wedge insoles with medial arch supports	Neutral insole	Bilateral	8
Barrios et al. (2013) (31)	United States	ACR criteria[a] Pain VAS (≥3/10)	8° full length lateral wedge insoles (customised via subjective comfort) and adhered to off the shelf insoles	Neutral insole	Unilateral	13
Butler et al. (2007) (37)	United States	Pain VAS (≥3/10)	9° full length lateral wedge insoles (customised via subjective comfort) and adhered to off the shelf insoles adhered to the neutral orthoses	Neutral insole	Unilateral	7
Butler et al. (2009) (38)	United States	Pain VAS (≥3/10) during weight bearing activities	10° full length lateral wedge insoles (customised via subjective comfort) and adhered to off the shelf insoles	Neutral insole	Unclear	9
Duivenvoorden et al. (2015) (30)	The Netherlands	Pain VAS (/10) mean: 6 SD 3, WOMAC (/100) mean: 47 SD 19	6° full length lateral wedged insole	Own shoes	Unclear	9
Hinman et al. (2012) (32)	Australia	Pain VAS (>3/10 upon walking) & on most days of past month WOMAC pain (/20) mean: 7 SD 3; function (/68) mean: 25 SD 13	5° full length non customised standard lateral wedged insoles	Own shoes	Bilateral	12
Hinman et al. (2009) (21)	Australia	Pain VAS (>3/10 upon walking) & on most days of past month WOMAC pain (/20) mean: 6 SD 3; function (/68) mean: 20 SD 14	5° full length non customised lateral wedged insoles	Own shoes	Bilateral	11
Hinman et al. (2008a) (13)	Australia	Pain VAS (>3/10 upon walking) & on most days of past month WOMAC pain (/20) mean: 8 SD 3; mean stiffness: 4 SD 2; function (/68) mean: 24 SD 11	5° full length and rearfoot lateral wedged insoles	Own shoes	Bilateral	9
Hinman et al. (2008b) (36)	Australia	Pain Likert-type scale average (>3/11), on most days of previous month and when walking 2 blocks and/or climbing stairs WOMAC pain (/20) mean: 9 SD 3; function (/68) mean: 30 SD 11	5° full length non customised standard lateral wedged insoles	Own shoes	Bilateral	10
Jones et al. (2013a) (39)	United Kingdom	Mild pain walking on flat surface during the past week (in KOOS pain subscale)	5° full length lateral wedged insoles; one with medial arch support, one without	Standardised shoe	Bilateral	9

Authors	**Country**	**Clinical criteria**	**Intervention**	**Comparisons**	**Applied**	**QI Score (/16)**
Jones et al. (2013b) (33)	United Kingdom	Symptomatic medial compartment OA confirmed by surgeon and x-rays. WOMAC pain (/100) mean 50 SD 15.7; stiffness (/100) mean 61.5 SD 20.3; function (/100) mean 54.2 SD 13.9	5° full length lateral wedged insoles with medial arch support	Standardised shoe	Bilateral	10
Jones et al. (2014) (29)	United Kingdom	Mild pain walking on flat surface during the past week (in KOOS pain subscale)	5° full length lateral wedged insoles; one with medial arch support, one without	Standardised shoe	Bilateral	10
Kerrigan et al. (2002) (41)	United States	Knee pain on most days of recent month	5° and 10° full length lateral wedged insoles	Flat insole + own shoes	Unclear	9
Leitch et al. (2011) (44)	Canada	Clinical diagnosis of OA confined primarily to medial tibiofemoral compartment	4° and 8° heel wedge placed underneath the insole on the lateral side of the shoe	Standardised shoe	Unilateral	10
Maly et al. (2002) (45)	United States	Medial compartment OA confirmed by physician and x-rays. WOMAC total (/96): 38 SD 14; mean pain (/20): 7 SD 3; mean stiffness (/8): 3 SD 1; mean function (/68): 26 SD 10	5° valgus heel wedge (modified off-the-shelf orthosis)	Routine footwear	Bilateral	8
Moyer et al. (2013) (35)	Canada	ACR criteria Symptoms at medial TFJ KOOS mean pain: 49.3 SD 15.9; mean symptoms: 37.5 SD 11.2; mean ADL: 54.3 SD 15.3; mean sport & rec: 18.8 SD 14; mean KOOS QoL: 23.8 SD 13.7	3°, 6° and 9° full length lateral wedge insole (customised via subjective comfort)	Standardised shoes	Unilateral	9
Pagani et al. (2012) (42)	Germany	WOMAC (11pt scale) mean pain: 9.8 SD 3.7 mean stiffness: 7.8 SD 2.8	4° full length lateral wedged insole	Own shoes	Bilateral	9
Shimada et al. (2006) (43)	Japan	Not reported	6° heel wedge (10 mm height)	Not reported	Bilateral	8

[a] stated inclusion criteria were consistent with ACR criteria, but all criteria not reported as assessed

Table 2. Characteristics of participants in included studies

Authors	***n***	**Gender (M:F)**	**Age (years)**	**Height (m)**	**Body mass (kg)**	**BMI (kg/m^2)**	**Bilateral knee OA included**	**Radiographic features**	**KL Grade**			
									1	**2**	**3**	**4**
Abdallah et al. (2011) (34)	21	0:21	54.1 (7.4)	1.57 (0.06)	84.1 (8.7)	NR	NR	KL Grade ≥2 FTA: 176 - 180°(varus)	NR	NR	NR	NR
Barrios et al. (2013) (31)	38[a]	NR	62.6 (7.4)	NR	NR	33.6 (7.6)	Yes	KL Grade ≥2 medial tibiofemoral compartment	0	8	6	5
Butler et al. (2007) (37)	20	9:11	63 (6)	NR	NR	33.4 (7.8)	Yes	KL Grade ≥2 medial tibiofemoral compartment	0	7	6	7
Butler et al. (2009) (38)	30	13:17	63.1 (6.8)	NR	NR	33.8 (6.9)	NR	KL Grade ≥2 medial tibiofemoral compartment	0	9	9	11
Duivenvoorden et al. (2015) (30)	42	14:28	54 (7)	NR	NR	30 (5)	NR	KL Grade ≥1 Hip-Knee-Ankle angle (°varus): 7 SD 4	15	8	18	1
Hinman et al. (2012) (32)	73	28:45	63.3 (8.4)	1.67 (0.09)	77.2 (14.5)	27.7 (3.6)	Yes	Medial tibiofemoral osteophytes & JSN medial > lateral KL Grade 2 & 3 Mechanical axis: 180.9° SD 2.6 (0.9°valgus)	0	41	32	0
Hinman et al. (2009) (21)	20	8:12	63.5 (9.4)	1.69 (0.07)	83.1 (14.2)	NR	Yes	Medial tibiofemoral osteophytes & JSN medial > lateral; KL Grade 2 & 3	0	8	12	0
Hinman et al. (2008a) (13)	13	6:7	59.7 (6.2)	1.69 (0.14)	81.0 (20.4)	NR	Yes	Medial tibiofemoral osteophytes KL Grade 2 & 3 Mechanical axis: (°): 178.1 SD 2.9 (1.9° varus)[b]	0	7	6	0
Hinman et al. (2008b) (36)	40	16:24	64.7 (9.4)	1.64 (0.09)	79 (12)	29.6 (4.2)	Yes	Medial tibiofemoral osteophytes Mechanical axis: 174.5 SD 4.7 (5.5°varus)	3	10	11	16
Jones et al. (2013a) (39)	51	29:22	59.6 (8.9)	1.69 (0.08)	90.3 (17.9)	31.6 (5.07)	Yes	KL grade 2 or 3 & JSN medial > lateral; no tricompartment OA	0	22	29	0

Authors [reference]	*n*	Gender (M:F)	Age (years)	Height (m)	Body mass (kg)	BMI (kg/m^2)	Bilateral knee OA included	Radiographic features	KL Grade (n=)			
									1	2	3	4
Jones et al. (2013b) (33)	28	16:10	66.3 (8.2)	1.75 (0.13)	88.7 (15.1)	NR	NR	Medial JSN; no lateral or PFJ OA	0	10	18	0
Jones et al. (2014) (29)	70	43:27	60.3 (9.6)	1.69 (0.09)	87.3 (18.5)	30.5 (4.9)	NR	KL grade 2 or 3 & JSN medial > lateral compartment, no tibiofemoral + PFJ OA	0	17	25	0
Kerrigan et al. (2002) (41)	15	8:7	69.7 (7.6)	1.67 (0.07)	83.9 (11.9)	NR	NR	KL Grade ≥3 Presence of definite osteophyte & medial JSN (but not lateral)	0	0	10	5
Leitch et al. (2011) (44)	12	5:7	48 (9)	1.72 (0.11)	90.5 (16.8)	30.45 (4.22)	NR	All KL Grades	2	2	3	5
Maly et al. (2002) (45)	12	9:3	60 (9.39)	NR	99.1 (15.8)	32.42 (5.03)	NR	NR	NR	NR	NR	NR
Moyer et al. (2013) (35)	16	8:8	55 (7.0)	NR	NR	32 (6.2)	No	KL Grade ≥1 & JSN medial > lateral Mechanical axis: 173.4° (6.6° varus)	2	5	6	3
Pagani et al. (2012) (42)	10	2:8	57.5 (7.1)	1.68 (0.04)	78.8 (12.2)	28 (4.3)	NR	KL Grade ≥2 Mean varus malalignment (°varus): 2.1 SD 1.2[c]	0	6	4	0
Shimada et al. (2006) (43)	23	6:17	67.0 (8.7)	1.50 (0.07)	60.3 (7.1)	NR	Yes	KL Grade ≥1 Mechanical axis: 6.2° varus SD 4.4	11	11	13	11

All values are reported as mean (standard deviation) unless otherwise indicated

[a] total sample size was 38 but 19 allocated to insole group

[b] FTA angle computed from A-P knee x-ray and regression equation

[c] hip-knee-ankle angle estimated from motion capture data

NR: not reported; PFJ: patellofemoral joint; QI: Downs & Black Quality Index

Table 3. Summary of comparisons across 18 studies included in the analysis of the 1st peak external knee adduction moment (EKAM), 2nd peak EKAM and knee adduction angular impulse (KAAI)

Authors	**Information available**	**Unit of measure**	**Study comparisons**		**SMD (A-B)**	**SE (A-B)**	**Correlation used**
			Condition (A)	**Comparator (B)**			
1st peak knee adduction moment (EKAM)							
Abdallah et al. 2011	Treatment specific summaries, correlation assumed	Nm/kg	6° full length wedged insole	Flat insole	-0.18	0.17	0.70
Abdallah et al. 2011b	Treatment specific summaries, correlation assumed	Nm/kg	11° full length wedged insole	Flat insole	-0.31	0.17	0.70
Barrios et al. 2013	Treatment specific summaries, correlation assumed	Nm/kg m	8° full length wedged insole[a]	Flat insole	-0.19	0.18	0.70
Butler et al. 2007	Treatment specific summaries, *P* values (t-test)	Nm/kg*m	9° full length wedged insole	Flat insole	-0.25	0.09	0.92
Butler et al. 2009	Treatment specific summaries, *P* values (t-test)	Nm/kg*m	10° full length wedged insole	Flat insole	-0.24	0.09	0.88
Duivenvoorden et al. 2015	Treatment specific summaries, correlation assumed	NR	6° full length wedged insole	Participant’s own shoes	-0.10	0.13	0.70
Hinman et al. 2008a	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.53	0.23	0.72
Hinman et al. 2008b	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° heel wedge	Participant’s own shoes	-0.32	0.23	0.70
Hinman et al. 2008c	Treatment specific summaries, correlation assumed	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.21	0.12	0.70
Hinman et al. 2009	Treatment specific summaries, correlation assumed	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.32	0.17	0.70
Hinman et al. 2012	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.28	0.08	0.74
Jones et al. 2013a	Treatment specific summaries, correlation assumed	Nm/kg	5° full length wedged insole	Standardised shoe†	-0.14	0.11	0.70
Jones et al. 2013b	Treatment specific summaries, correlation assumed	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.14	0.11	0.70
Jones et al. 2013c	Treatment specific summaries, *P* values (t-test)	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.54	0.15	0.70
Jones et al. 2014	Group differences, correlation assumed	Nm/kg	5° full length wedged insole	Standardised shoe†	-0.14	0.04 [d]	0.95[e]
Jones et al. 2014b	Group differences, correlation assumed	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.27	0.08 [d]	0.94[e]

Kerrigan et al. 2002	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	5° full length wedged insole	Participant's own shoes	-0.22	0.08	0.96
Kerrigan et al. 2002b	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	5° full length wedged insole	Flat insole	-0.16	0.08	0.96
Kerrigan et al. 2002c	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	10° full length wedged insole	Participant's own shoes	-0.37	0.10	0.93
Kerrigan et al. 2002d	Treatment specific summaries, correlation assumed	N.m/kg.m	10° full length wedged insole	Flat insole	-0.30	0.20	0.70
Leitch et al. 2011	Treatment specific summaries, correlation assumed	%BW*Ht	4° heel wedge	Standardised shoe*	-0.05[c]	0.22	0.70
Leitch et al. 2011b	Treatment specific summaries, correlation assumed	%BW*Ht	8° heel wedge	Standardised shoe*	-0.10[c]	0.22	0.70
Maly et al. 2002	Treatment specific summaries, correlation assumed	Nm/kg	5° full length wedged insole[a]	Routine footwear	0.15	0.26	0.70
Maly et al. 2002b	Treatment specific summaries, *P* values (F-test)	Nm/kg	5° heel wedge	Routine footwear	-0.07	0.05	0.99
Moyer et al. 2013	Treatment specific summaries, correlation assumed	%BW*Ht	4° full length wedged insole[a]	Standardised shoe^	-0.09	0.19	0.70
Pagani et al. 2012	Treatment specific summaries, correlation assumed	Nm/kg	4° full length wedged insole	Participant's own shoes	-0.19	0.25	0.70
Shimada et al. 2006	Treatment specific summaries, *P* values (t-test)	Nm/kg	6° heel wedge[b]	NR (footwear assumed)	-0.20	0.05	0.97
2nd peak knee adduction moment (EKAM)							
Butler et al. 2007	Treatment specific summaries, *P* values (t-test)	Nm/kg*m	9° full length wedged insole	Flat insole	-0.06	0.11	0.89
Hinman et al. 2008a	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° full length wedged insole	Participant's own shoes	-0.33	0.12	0.92
Hinman et al. 2008b	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° heel wedge	Participant's own shoes	-0.16	0.11	0.93
Hinman et al. 2008c	Treatment specific summaries, correlation assumed	%BW*Ht	5° full length wedged insole	Participant's own shoes	-0.31	0.07	0.89
Hinman et al. 2009	Treatment specific summaries, correlation assumed	%BW*Ht	5° full length wedged insole	Participant's own shoes	-0.15	0.11	0.89
Jones et al. 2013c	Treatment specific summaries, *P* values (t-test)	Nm/kg	5° full length wedged insole[a]	Standardised shoe†	-0.49	0.10	0.89
Kerrigan et al. 2002	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	5° full length wedged insole	Participant's own shoes	-0.27	0.07	0.96
Kerrigan et al. 2002b	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	5° full length wedged insole	Flat insole	-0.16	0.06	0.97
Kerrigan et al. 2002c	Treatment specific summaries, *P* values (t-test)	N.m/kg.m	10° full length wedged insole	Participant's own shoes	-0.32	0.08	0.95

Kerrigan et al. 2002d	Treatment specific summaries, correlation assumed	N.m/kg.m	10° full length wedged insole	Flat insole	-0.22	0.12	0.89
Moyer et al. 2013	Treatment specific summaries, correlation assumed	%BW*Ht	4° full length wedged insole [a]	Standardised shoe^	-0.22	0.13	0.89
Pagani et al. 2012	Treatment specific summaries, correlation assumed	Nm/kg	4° full length wedged insole	Participant’s own shoes	-0.17	0.15	0.89
Knee adduction angular impulse (KAAI)							
Barrios et al 2013	Treatment specific summaries, correlation assumed	Nm.s.kg.m	8° full length wedged insole	Insole comparison	-0.01	0.09	0.68
Duivenvoorden et al. 2015	Treatment specific summaries, correlation assumed	NR	6° full length wedged insole	Participant’s own shoes	-0.02	0.09	0.68
Hinman et al. 2009	Treatment specific summaries, correlation assumed	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.14	0.18	0.68
Hinman et al. 2012	Treatment specific summaries, *P* values (t-test)	%BW*Ht	5° full length wedged insole	Participant’s own shoes	-0.21	0.06	0.86
Jones et al. 2013a	Treatment specific summaries, correlation assumed	Nm/kg	5° full length wedged insole	Standardised shoe†	-0.16	0.09	0.68
Jones et al. 2013b	Treatment specific summaries, correlation assumed	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.16	0.09	0.68
Jones et al. 2013c	Treatment specific summaries, *P* values (t-test)	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.57	0.16	0.68
Jones et al. 2014	Group differences, correlation assumed	Nm/kg	5° full length wedged insole	Standardised shoe†	-0.17	0.09[d]	0.74[e]
Jones et al. 2014b	Group differences, correlation assumed	Nm/kg	5° full length wedged insole [a]	Standardised shoe†	-0.13	0.09[d]	0.72[e]
Moyer et al. 2013	Treatment specific summaries, correlation assumed	%BW*Ht	4° full length wedged insole [a]	Standardised shoe^	-0.02	0.09	0.68
Pagani et al. 2012	Treatment specific summaries, correlation assumed	Nm/kg	4° full length wedged insole	Participant’s own shoes	-0.14	0.25	0.68

[a] with medial arch support

[b] 10 mm height equates to 6 degree angulation as reported in Duivenvoorden et al (2015)

[c] values obtained from figures

[d] pooled standard deviation computed from SD of difference scores as raw values not reported

[e] correlation computed taking into account comparator standard deviation only as intervention not reported

†Ecco – Zen, Bredebro, Denmark

^ New Balance, Boston, MA, USA; *New Balance 882, Boston, MA, USA; NR: not reported

Figure legends

Figure 1: PRISMA flowchart of study selection.

Figure 2: Forest plot of data pooling for the 1st peak external knee adduction moment (EKAM). Solid squares indicate the effect size and horizontal bars the 95% confidence interval (95% CI). Solid diamonds represent the pooled estimate. Included studies were weighted based on the standard error of the effect size.

Figure 3: Forest plot of data pooling for the 2nd peak external knee adduction moment (EKAM) and knee adduction angular impulse (KAAI). Solid squares indicate the effect size and horizontal bars the 95% confidence interval (95% CI). Solid diamonds represent the pooled estimate. Included studies were weighted based on the standard error of the effect size.

Figure 1. PRISMA flowchart of study selection.

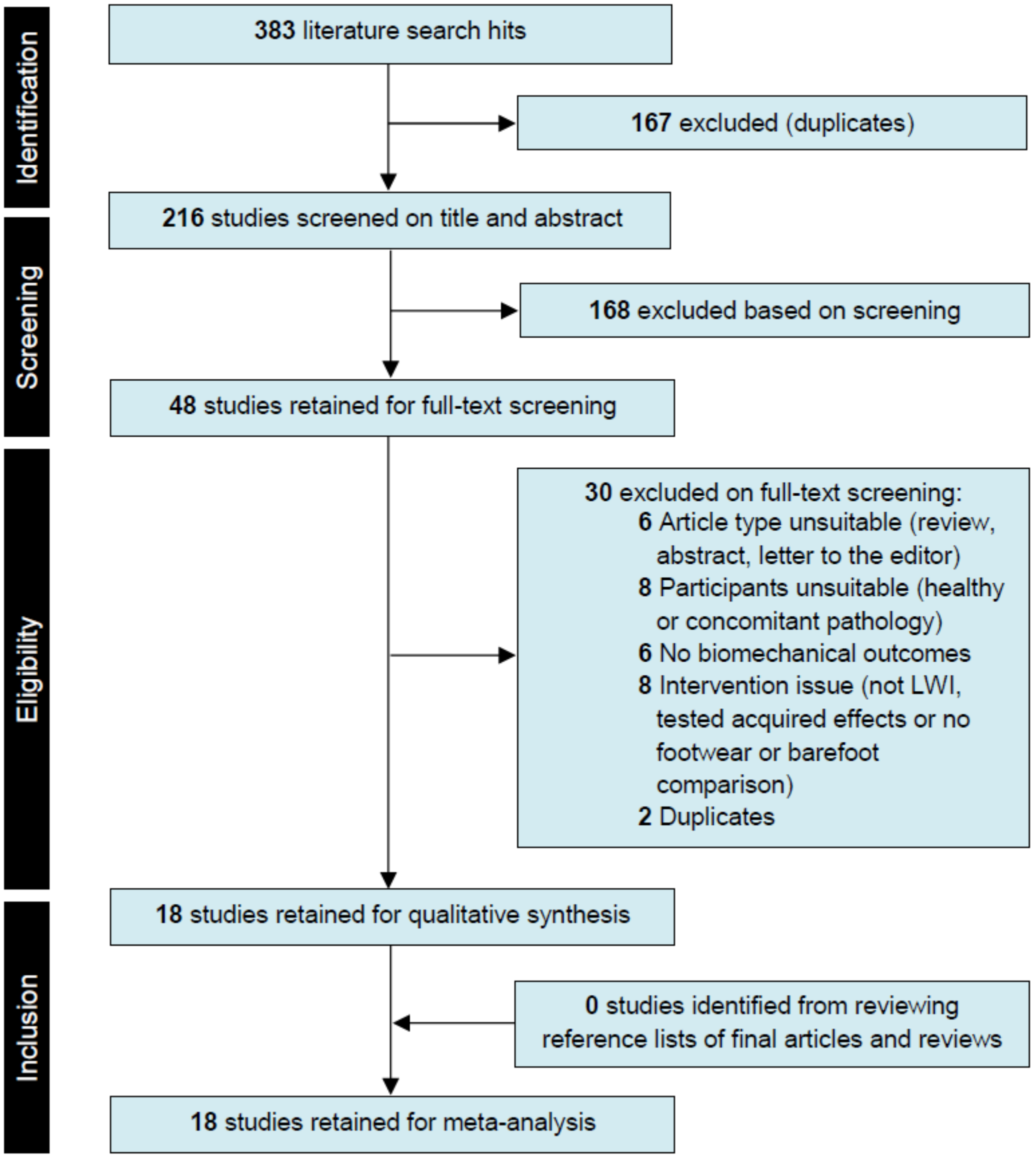
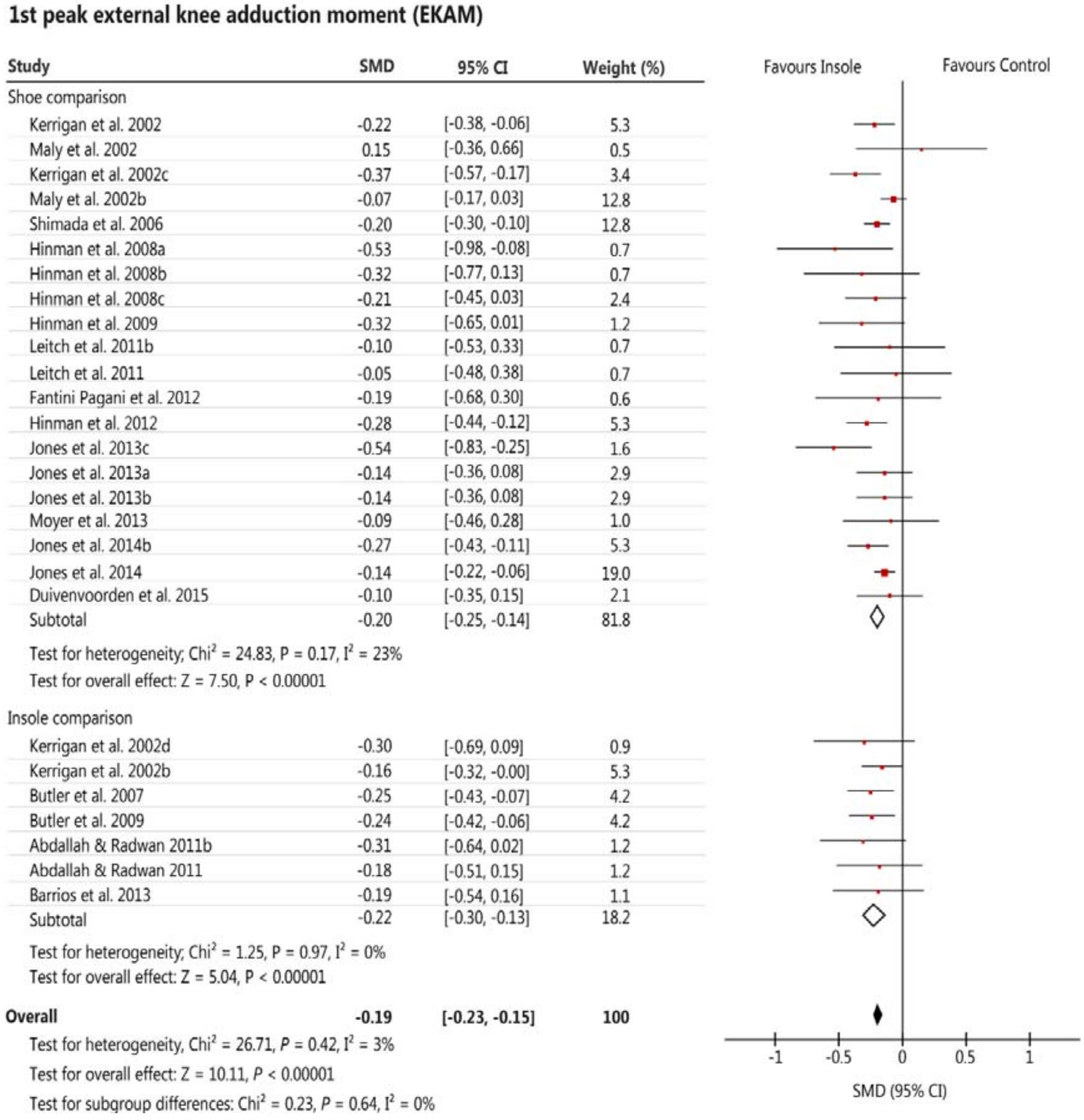


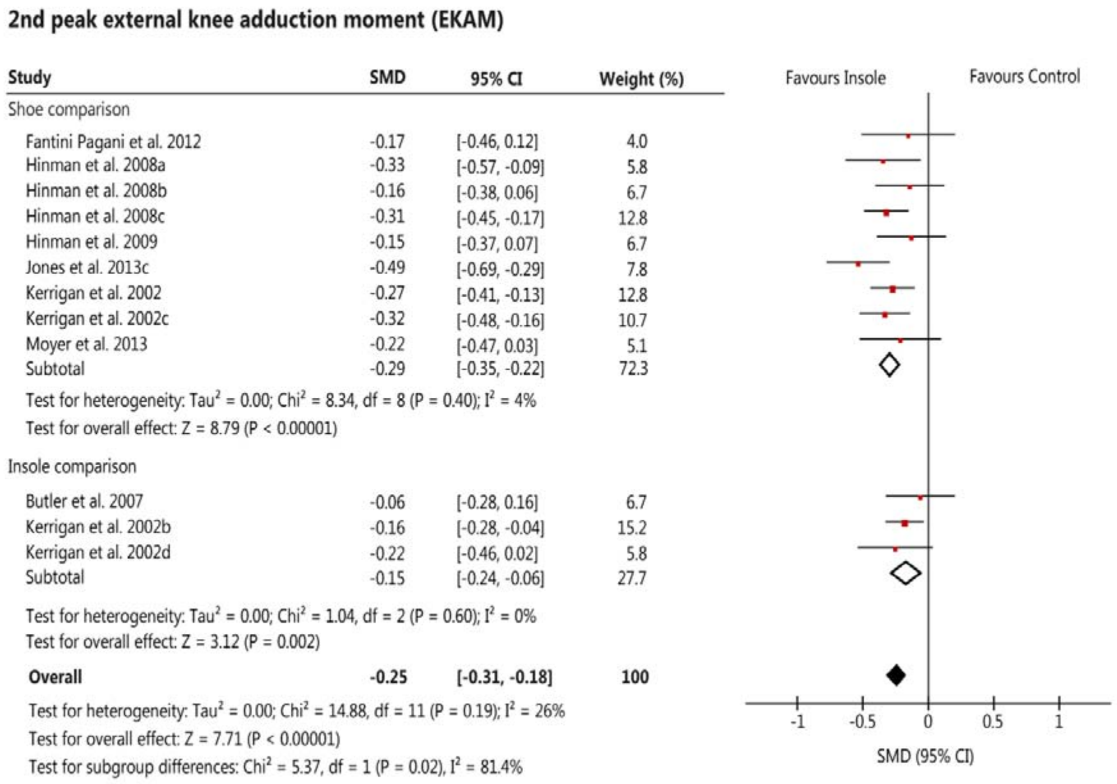
Figure 2. Forest plot of data pooling for the 1st peak external knee adduction moment (EKAM). Solid squares indicate the effect size and horizontal bars the 95% confidence interval (95% CI). Solid diamond represents the pooled estimate. Included studies were weighted based on the standard error of the effect size.



1st peak external knee adduction moment (EKAM)

Study	SMD	95% CI	Weight (%)
Shoe comparison			
Kerrigan et al. 2002	-0.22	[-0.38, -0.06]	5.3
Maly et al. 2002	0.15	[-0.36, 0.66]	0.5
Kerrigan et al. 2002c	-0.37	[-0.57, -0.17]	3.4
Maly et al. 2002b	-0.07	[-0.17, 0.03]	12.8
Shimada et al. 2006	-0.20	[-0.30, -0.10]	12.8
Hinman et al. 2008a	-0.53	[-0.98, -0.08]	0.7
Hinman et al. 2008b	-0.32	[-0.77, 0.13]	0.7
Hinman et al. 2008c	-0.21	[-0.45, 0.03]	2.4
Hinman et al. 2009	-0.32	[-0.65, 0.01]	1.2
Leitch et al. 2011b	-0.10	[-0.53, 0.33]	0.7
Leitch et al. 2011	-0.05	[-0.48, 0.38]	0.7
Fantini Pagani et al. 2012	-0.19	[-0.68, 0.30]	0.6
Hinman et al. 2012	-0.28	[-0.44, -0.12]	5.3
Jones et al. 2013c	-0.54	[-0.83, -0.25]	1.6
Jones et al. 2013a	-0.14	[-0.36, 0.08]	2.9
Jones et al. 2013b	-0.14	[-0.36, 0.08]	2.9
Moyer et al. 2013	-0.09	[-0.46, 0.28]	1.0
Jones et al. 2014b	-0.27	[-0.43, -0.11]	5.3
Jones et al. 2014	-0.14	[-0.22, -0.06]	19.0
Duivenvoorden et al. 2015	-0.10	[-0.35, 0.15]	2.1
Subtotal	-0.20	[-0.25, -0.14]	81.8
Test for heterogeneity; Chi^2 = 24.83, P = 0.17, I^2 = 23%			
Test for overall effect: Z = 7.50, P < 0.00001			
Insole comparison			
Kerrigan et al. 2002d	-0.30	[-0.69, 0.09]	0.9
Kerrigan et al. 2002b	-0.16	[-0.32, -0.00]	5.3
Butler et al. 2007	-0.25	[-0.43, -0.07]	4.2
Butler et al. 2009	-0.24	[-0.42, -0.06]	4.2
Abdallah & Radwan 2011b	-0.31	[-0.64, 0.02]	1.2
Abdallah & Radwan 2011	-0.18	[-0.51, 0.15]	1.2
Barrios et al. 2013	-0.19	[-0.54, 0.16]	1.1
Subtotal	-0.22	[-0.30, -0.13]	18.2
Test for heterogeneity; Chi^2 = 1.25, P = 0.97, I^2 = 0%			
Test for overall effect: Z = 5.04, P < 0.00001			
Overall	**-0.19**	**[-0.23, -0.15]**	**100**
Test for heterogeneity, Chi^2 = 26.71, *P* = 0.42, I^2 = 3%			
Test for overall effect: Z = 10.11, *P* < 0.00001			
Test for subgroup differences: Chi^2 = 0.23, *P* = 0.64, I^2 = 0%			

Figure 3. Forest plot of data pooling for the 2nd peak external knee adduction moment (EKAM) and knee adduction angular impulse (KAAI). Solid squares indicate the effect size and horizontal bars the 95% confidence interval (95% CI). Solid diamond represents the pooled estimate. Included studies were weighted based on the standard error of the effect size.



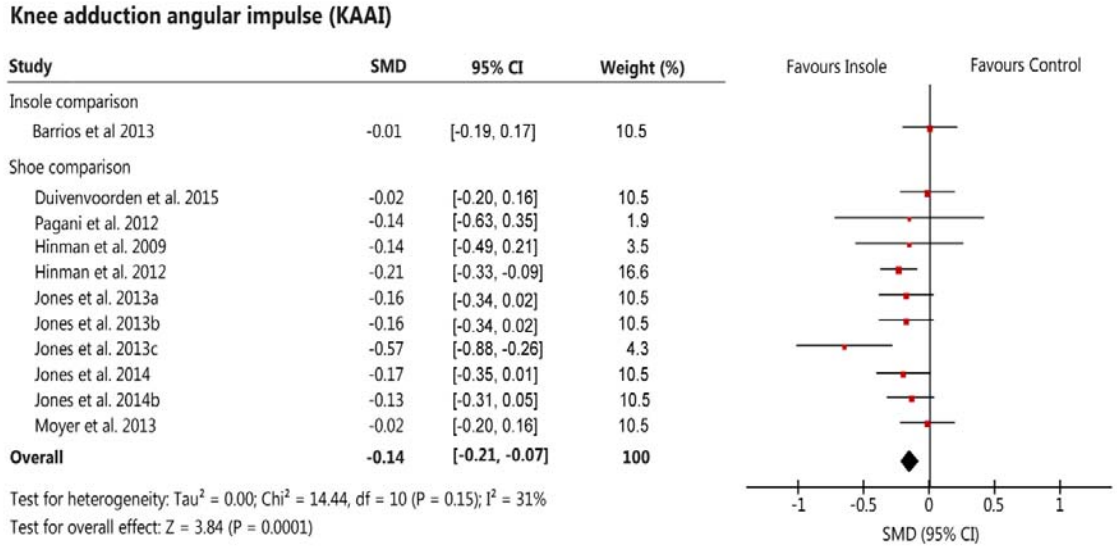
2nd peak external knee adduction moment (EKAM)

Study	SMD	95% CI	Weight (%)
Shoe comparison			
Fantini Pagani et al. 2012	-0.17	[-0.46, 0.12]	4.0
Hinman et al. 2008a	-0.33	[-0.57, -0.09]	5.8
Hinman et al. 2008b	-0.16	[-0.38, 0.06]	6.7
Hinman et al. 2008c	-0.31	[-0.45, -0.17]	12.8
Hinman et al. 2009	-0.15	[-0.37, 0.07]	6.7
Jones et al. 2013c	-0.49	[-0.69, -0.29]	7.8
Kerrigan et al. 2002	-0.27	[-0.41, -0.13]	12.8
Kerrigan et al. 2002c	-0.32	[-0.48, -0.16]	10.7
Moyer et al. 2013	-0.22	[-0.47, 0.03]	5.1
Subtotal	-0.29	[-0.35, -0.22]	72.3
Test for heterogeneity: Tau² = 0.00; Chi² = 8.34, df = 8 (P = 0.40); I² = 4%			
Test for overall effect: Z = 8.79 (P < 0.00001)			
Insole comparison			
Butler et al. 2007	-0.06	[-0.28, 0.16]	6.7
Kerrigan et al. 2002b	-0.16	[-0.28, -0.04]	15.2
Kerrigan et al. 2002d	-0.22	[-0.46, 0.02]	5.8
Subtotal	-0.15	[-0.24, -0.06]	27.7
Test for heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.60); I² = 0%			
Test for overall effect: Z = 3.12 (P = 0.002)			
Overall	**-0.25**	**[-0.31, -0.18]**	**100**

Test for heterogeneity: Tau² = 0.00; Chi² = 14.88, df = 11 (P = 0.19); I² = 26%

Test for overall effect: Z = 7.71 (P < 0.00001)

Test for subgroup differences: Chi² = 5.37, df = 1 (P = 0.02), I² = 81.4%



Knee adduction angular impulse (KAAI)

Study	SMD	95% CI	Weight (%)
Insole comparison			
Barrios et al 2013	-0.01	[-0.19, 0.17]	10.5
Shoe comparison			
Duivenvoorden et al. 2015	-0.02	[-0.20, 0.16]	10.5
Pagani et al. 2012	-0.14	[-0.63, 0.35]	1.9
Hinman et al. 2009	-0.14	[-0.49, 0.21]	3.5
Hinman et al. 2012	-0.21	[-0.33, -0.09]	16.6
Jones et al. 2013a	-0.16	[-0.34, 0.02]	10.5
Jones et al. 2013b	-0.16	[-0.34, 0.02]	10.5
Jones et al. 2013c	-0.57	[-0.88, -0.26]	4.3
Jones et al. 2014	-0.17	[-0.35, 0.01]	10.5
Jones et al. 2014b	-0.13	[-0.31, 0.05]	10.5
Moyer et al. 2013	-0.02	[-0.20, 0.16]	10.5
Overall	**-0.14**	**[-0.21, -0.07]**	**100**

Test for heterogeneity: Tau² = 0.00; Chi² = 14.44, df = 10 (P = 0.15); I² = 31%

Test for overall effect: Z = 3.84 (P = 0.0001)