BMJ Open

Effect of motion control versus neutral walking footwear on pain associated with lateral tibiofemoral joint osteoarthritis: a comparative effectiveness randomized clinical trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061627
Article Type:	Original research
Date Submitted by the Author:	03-Feb-2022
Complete List of Authors:	Paterson, Kade; University of Melbourne Department of Physiotherapy, Bennell, Kim; University of Melbourne, CHESM Metcalf, Ben; The University of Melbourne Campbell, P; University of Melbourne McManus, Fiona; University of Melbourne Lamb, Karen; The University of Melbourne - Parkville Campus, School of Population and Global Health Hinman, Rana; University of Melbourne,
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

Effect of motion control versus neutral walking footwear on pain associated with lateral tibiofemoral joint osteoarthritis: a comparative effectiveness randomized clinical trial.

AUTHORS: Kade L Paterson PhD[1*], Kim L Bennell PhD[1], Ben R. Metcalf BSc (Hons)[1], Penny K Campbell BAppSci[1], Fiona McManus MBiostat[2], Karen E Lamb PhD[2,3] & Rana S Hinman PhD[1]

*Corresponding author

AFFILIATIONS: [1] Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Melbourne, Australia

[2] Biostatistics Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

[3] Methods and Implementation Support for Clinical Health research platform, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville , AU

CORRESPONDING AUTHOR: Kade Paterson, Centre for Health Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, University of Melbourne, Victoria, Australia 3010. ph: +61 3 8344 0425, fax: +61 3 8344 4188, kade.paterson@unimelb.edu.au

Word count: 3,761

Running title: Footwear for lateral knee OA

ABSTRACT

Objective To determine if motion control walking shoes are superior to neutral walking shoes for reducing knee pain on walking in people with lateral knee osteoarthritis (OA).

Design Participant- and assessor-blinded, comparative effectiveness, superiority randomized controlled trial (RCT).

Setting Melbourne, Australia

Participants People with symptomatic radiographic lateral tibiofemoral OA from the community and our volunteer database.

Interventions Participants were randomized to receive either motion control or neutral shoes and advised to wear them ≥6 hours/day over 6 months.

Outcome measures Primary outcome was change in average knee pain on walking over the previous week (11-point numerical rating scale (NRS, 0-10)) at 6 months. Secondary outcomes included other measures of knee pain, physical function, quality of life, participant-perceived change in pain and function, and physical activity.

Results We planned to recruit 110 participants (55 per arm) but ceased recruitment at 40 (n=18 motion control shoes, n=22 neutral shoes) due to COVID-19-related impacts. All 40 participants completed 6-month outcomes. There was no evidence that motion control shoes were superior to neutral shoes for the primary outcome of pain (mean between-group difference 0.4 NRS units (95% CI -1.0 to 1.7)), nor for any secondary outcome. The number of participants experiencing any adverse events was similar between groups (motion control shoes n=5 (28%), neutral shoes n=4 (18.2%)) and were minor.

Conclusion Motion control shoes were not superior to neutral shoes for improving knee pain on walking in symptomatic radiographic lateral tibiofemoral joint OA. Further research is

needed to identify effective treatments in this important but under-researched knee OA subgroup.

Trial Registration: Prospectively registered with the Australian New Zealand Clinical Trials Registry reference: ACTRN12618001864213

Key words: osteoarthritis, OA, knee, tibiofemoral, footwear, shoes, clinical trial, RCT, biomechanics, pain

Strengths and limitations

- This is the first clinical trial to assess the effect of any type of footwear on pain in people with symptomatic radiographic lateral knee osteoarthritis.
- Our trial found compared the effects of commercially available motion control shoes and neutral walking shoes on walking knee pain in people with predominantly lateral knee OA.
- We were unable to recruit out intended sample size due to extended COVID-19-related lockdowns.

Knee osteoarthritis (OA) is a common and painful condition and a leading cause of global disability (1). The disease is chronic and has no cure, thus people with knee OA have little choice but to self-manage their condition. Accordingly, advice about self-management is the cornerstone of conservative treatment, along with exercise and weight control (2, 3). As abnormal biomechanics are central to OA disease pathogenesis (4, 5), clinical guidelines advocate that clinicians provide advice on "appropriate" footwear as part of core treatment for knee OA (2, 6). However, there is scant evidence from clinical trials to guide footwear choice. Due to the lack of robust clinical trials in this area, international OA organizations and the American Academy of Orthopaedic Surgeons have called for footwear trials as an OA research priority (2, 6, 7).

To date, all clinical trials on footwear for knee OA have targeted people with medial knee OA, likely because the medial tibiofemoral (TF) compartment is affected by OA more often than the lateral compartment (8). However, 10-55% of knee OA patients have radiographic OA changes in the lateral TF joint (8-12), and there is evidence that co-existing lateral TF OA is associated with worse knee pain in people with mixed compartmental OA (13). Importantly, in people with medial knee OA, the aim of biomechanical interventions is to shift joint force distribution from the medial to the lateral TF compartment. However, the aim in people with lateral knee OA is to shift forces from the lateral to the medial TF compartment. Compared to medial tibiofemoral OA, there is scant research evaluating non-surgical treatments for people with lateral tibiofemoral OA. In particular, clinical trials that evaluate biomechanical interventions specifically designed to target the unique biomechanical needs of this lateral TF OA subgroup are urgently needed.

Biomechanical studies have shown that footwear with midsoles that are laterally stiff redistribute knee loads away from the medial towards the lateral TF compartment in people with medial knee OA (14). Conversely, footwear with medially stiff midsoles, such as "motion control" shoes, shift knee loads towards the medial TF compartment (15, 16), likely with concomitant reductions in lateral TF compartment load. Thus, it is possible that motion control footwear may improve symptoms in people with lateral knee OA. Although no randomized controlled trial (RCT) has assessed the effects of motion control shoes on symptoms in people with lateral compartment knee OA, there is some indirect clinical research to suggest that they may be effective. A small study of 30 women with symptomatic radiographic lateral knee OA and bilateral knee valgus deformity found that wearing medially wedged insoles (which have similar biomechanical effects on lateral TF joint loads to motion control shoes (17)) for 3-6 hours/day resulted in greater improvements in pain and other symptoms over 8 weeks, compared to wearing flat insoles (18). Consequently, further research assessing the effects of motion control footwear in people with lateral knee OA is warranted to help inform footwear recommendations in international OA clinical guidelines, and to guide clinical practice, for this important but under-researched OA subgroup.

This study aimed to assess the effectiveness of motion control shoes for improving symptoms in people with lateral knee OA. We hypothesized that wearing motion control shoes would lead to greater reductions in walking knee pain, compared to wearing neutral walking shoes, over 6 months.

PATIENTS AND METHODS

Design

This was a 2-arm, participant- and assessor-blinded, pragmatic, comparative effectiveness, superiority RCT. It was prospectively registered (Australian New Zealand Clinical Trials Registry ACTRN12618001864213) and the protocol is published (19). The study was approved by the University of Melbourne human research ethics committee and participants provided informed consent.

Participants

Community-dwelling participants (Melbourne, Australia) were recruited using advertisements, including targeted invitations to participants on our research volunteer database who had known radiographically diagnosed lateral knee OA. Participants were eligible if they were aged ≥50 years; reported average knee pain on walking over the previous week ≥4 on an 11-point numeric rating scale (NRS); had mild, moderate or severe radiographic knee OA (Kellgren & Lawrence (KL) Grade 2-4) (20); and had a grade of lateral TF joint space narrowing that was greater than medial, determined using a radiographic atlas (21) (where grade 0=no narrowing, 1=mild narrowing, 2=moderate narrowing, 3=severe narrowing). Participants were excluded if they reported knee pain for <3 months; had recent (past 6 months) or planned (next 6 months) knee surgery; or currently used foot orthoses, ankle/knee braces, customized shoes or other shoes worn regularly that would restrict their ability to wear the allocated study shoes for a minimum of 6 hours per day (e.g. work boots). For participants with bilaterally eligible knees, the most painful was deemed the study knee. Full exclusion criteria are in the published protocol (19).

Randomisation and masking

Participants were randomized in a 1:1 ratio. The randomisation schedule was prepared by a biostatistician with permuted block sizes of 6 to 12 and stratified by KL grades 2, 3 or 4. Allocation was concealed using password-protected software (REDCap™) and was revealed by a researcher not involved in recruitment or outcome assessment. Participants were blinded and informed only that the trial was comparing the effects of two types of commercially available walking shoes on knee OA symptoms. We did not disclose the hypothesis or the specific footwear styles/characteristics (i.e. motion control and neutral shoes) under investigation. As participants were blinded, and primary and secondary outcomes were self-reported, this trial was also assessor-blinded. The biostatisticians were blinded for all analyses.

Interventions

Motion control shoes

Black ASICS Gel-Kayano 25 shoes were chosen as the motion control shoes (Appendix Figure 1). These shoes have a dual density midsole which is stiffer medially compared to laterally, a feature that has previously been shown to shift knee loads towards the medial TF compartment (15, 16).

Neutral shoes

Black ASICS Gel-Nimbus 20 were the neutral comparator shoe (Appendix Figure 1). These shoes have a uniformly stiff midsole and are visually similar to the motion control shoes. They are also similar on other key features including midsole foam and gel cushioning systems, an engineered mesh upper, shoe mass, and rearfoot, forefoot and heel drop heights.

Participants were fitted with their allocated shoes by a study researcher (BM). Participants were advised to commence wearing their allocated shoes for two hours on the first day, and to

increase wear time by two hours/day until they were wearing them as much as possible, at a minimum of 6 hours/day, over 6 months.

Outcome measures

Participants completed baseline questionnaires on paper or electronically at the Department of Physiotherapy gait laboratory, The University of Melbourne. The 6-month follow-up questionnaire was completed either on paper or electronically at home.

The primary outcome was 6-month change in average knee pain on walking in the last week, assessed using an 11-point NRS with terminal descriptors of 'no pain' (score=0) and 'worst pain possible' (score=10). This measure has strong clinimetric properties (22), is recommended for knee OA clinical trials (23), and has a minimal clinically important difference (MCID) of 1.8 units (24).

Secondary outcomes included changes in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of i) physical function, ii) pain, iii) sport and recreation, iv) knee-related quality of life, and v) patellofemoral pain and OA (25). Scores for each subscale were transformed to provide an overall value that ranged from 0 to 100 (where higher scores indicate better symptoms and function). Additional secondary outcomes included changes in quality of life, measured using the Assessment of Quality of Life 6D instrument (26) (scored between -0.04 and 1.00, higher scores indicate better quality of life); and physical activity over the previous week, measured using the Physical Activity Scale for the Elderly (PASE) (27) (scored from 0 to over 400, higher scores indicate higher activity). We also assessed patient-perceived global rating of change in i) pain and ii) function at 6 months, each measured using 7-point

Likert scales (terminal descriptors of 'much worse' to 'much better' (28). Participants reporting they were 'moderately better' or 'much better' were classified as improved.

Descriptive measures included height, body mass and body mass index; age; gender; knee OA symptom duration; radiographic disease severity (using the KL scale (20)); anatomical knee alignment (measured in degrees from the knee x-ray (29)); employment status; treatment expectation (using a 5-point ordinal scale (anchors of "no effect at all" to "complete recovery"); self-efficacy (using the Arthritis Self Efficacy Scale (30)); cointervention use via a custom table (also assessed at 6 months); foot posture (using the Foot Posture Index (31) (scores range from -12 to +12, higher score indicates a more pronated foot posture), Foot Mobility Magnitude (32) (in mm, higher values indicate greater mobility) and navicular drop (33) (in mm, higher values indicate greater drop); and the motion control feature score of the participant's usual (most commonly worn) pair of shoes (using the Footwear Assessment Tool (15), scored 0 to 11, higher scores indicate more motion control features).

We assessed adherence to allocated footwear using our successful strategies employed in prior footwear RCTs (34, 35). Participants recorded how much they wore their allocated shoes (hours/day) for 7 consecutive days, for one week of every month, in log books. Those who averaged ≥6hrs/day over 6 months were classified as 'adherent'. At 6 months, participants also rated their overall level of adherence with wearing their allocated shoes ≥6 hours per day using an 11-point NRS (terminal descriptors of 'shoes not worn at all' and 'shoes worn completely as instructed') and indicated whether they stopped wearing the shoes during the study (Yes or No). Participants who responded 'Yes' described when and why they stopped wearing their study shoes. Finally, adverse events (any problem experienced in the study knee or elsewhere

in the body because of wearing the study shoes) were self-reported by participants at 6 months using a custom table.

Statistical analysis

We aimed *a priori* to detect a between-group difference in change in walking pain (the primary outcome) of 1.8 units (the MCID) (24). We assumed a between-participant standard deviation of 2.7 and a baseline to 6-month correlation of 0.21 (34, 35). Using analysis of covariance (ANCOVA) adjusted for baseline score, we needed 46 participants per arm to achieve 90% power to detect the MCID in change in walking knee pain. Allowing for 15% attrition, we aimed to recruit 55 people per arm (n=110 in total). However, due to ongoing COVID-19 restrictions in Melbourne (Australia) halting trial recruitment for a prolonged period of time and grant funding running out, recruitment was ceased with a final sample size of 40. Using ANCOVA adjusted for baseline score, we have 57.8% power to detect the MCID in change in walking knee pain (baseline minus 6 months) with the final sample size of 40 participants (assuming 20 participants per arm).

Main comparative analyses between groups were performed using intention-to-treat. As no primary outcome data were missing from enrolled participants, multiple imputation was not applied, and all analyses were performed on complete case data. Separate linear regression models were fit for each continuous outcome, including the primary outcome of walking knee pain, with treatment group, the outcome at baseline, and the stratifying variable (KL grade) as covariates. Results were calculated as the estimated mean (95% confidence interval (CI)) difference in change (baseline minus 6 months) between groups. Regression assumptions of linearity and homoscedasticity were assessed using standard diagnostic plots. A sensitivity analysis estimated treatment effects on the primary outcome assuming full adherence to shoe

wear (classified as average of ≥6 hours/day for 6 months, based on logbook data), using an instrumental variables approach (36). Improvement based on global change scores and the achievement of the MCID in improvement in walking knee pain (1.8 NRS units) were each compared between groups separately using logistic regression, adjusted for the stratifying variable (KL grade), with results reported as risk ratios and risk differences.

To assess whether the effect of shoe group on the primary outcome was moderated by KL grade, a linear regression model was fit for the primary outcome, with the outcome at baseline, treatment group, and KL grade as covariates, including an interaction between treatment group and KL grade. To assess whether the effect of shoe group on the primary outcome was moderated by i) Foot Posture Index score, ii) knee alignment or iii) KOOS patellofemoral pain and OA, separate linear regression models were fit for the primary outcome for each potential moderator, with the outcome at baseline, treatment group, the relevant potential moderator and KL grade, as covariates, including an interaction between treatment group and the potential moderator. Statistical analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, TX, USA). The *a priori* statistical analysis plan is in the appendix.

Patient and public involvement

Patients and the public were not involved in the design, conduct and dissemination of this research.

RESULTS

Sample characteristics

Participant flow through the study is shown in Figure 1. Between 29 November 2018 and 24 March 2020, we screened 261 people and enrolled 40 participants, predominantly recruited

through targeted invitations to people with lateral knee OA in our research database (37 enrolees (from 65 screened) versus 3 recruited (from 196 screened) via advertising in the community). Due to COVID-19 causing extended lockdowns in Melbourne, Australia (totalling 23 weeks between March 30 and May 12, 2020, and between July 8 and October 27, 2020) and suspension of on-campus research activities, recruitment was postponed on 24 March 2020. Recruitment resumed on 13 June 2020 and by 12 November 2020 we had screened a further 10 participants without any further enrolment. The study was terminated early as it was deemed unfeasible to continue given the considerable number of participants still left to recruit, ongoing uncertainty regarding COVID-19 restrictions, poor community recruitment rates (no further recruitment possible from our volunteer database) and exhaustion of funding. At the 6-month follow-up, all 40 (100%) enrolled participants had completed the primary outcome.

Participant characteristics were comparable between groups at baseline (Table 1) except that a greater proportion of people in the neutral shoe group had a neutral foot posture (motion control 17% vs neutral 36%) and more people in the motion control group had a pronated foot posture (motion control 83% vs neutral 59%). Participant's own usual footwear were similar across groups with respect to motion control features (Table 1, Appendix Table 1), suggesting that on average, people wore shoes with moderate amounts of motion control features. Treatment expectations were generally similar across groups pre-randomization and following shoe allocation (Table 1).

Table 1. Baseline characteristics of participants by group, reported as mean (standard deviation) unless otherwise stated.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Age (years)	64.6 (7.2)	64.2 (7.2)
Gender		
Female, n (%)	11 (61)	13 (59)
Male, n (%)	7 (39)	9 (41)
Symptom duration (years)	11.6 (7.8)	11.1 (8.0)
Height (m)	1.7 (0.1)	1.7 (0.1)
Body mass (kg), median (IQR)	89 (75-95)	89 (81-106)
Body mass index (kg/m^2), median (IQR)	31.4 (27.6-35.4)	31.2 (27.8-33.9)
Unilateral knee OA symptoms, n (%)	3 (17)	7 (32)
Radiographic disease severity, n (%)[a]		
Grade 2 (mild)	2 (11)	3 (14)
Grade 3 (moderate)	8 (44)	10 (45)
Grade 4 (severe)	8 (44)	9 (41)
Radiographic knee alignment (degrees)[b]	188.7 (6.3)	188.1 (5.5)
Foot Posture Index classification, n (%)[c]		
Supinated	0 (0)	1 (5)
Neutral	3 (17)	8 (36)
Pronated	15 (83)	13 (59)
Foot Mobility Magnitude (mm)[d]	7.7 (3.5)	7.7 (2.5)
Navicular drop (mm)[d]	6.5 (4.4)	6.3 (3.0)
Currently employed, n (%)	10 (56)	11 (50)
Current drug/supplement use, n (%)[e]	15 (83)	18 (82)
Paracetamol combinations	11 (61)	15 (68)
Non-steroidal anti-inflammatories	8 (44)	10 (45)
Topical anti-inflammatories	8 (44)	4 (18)
Oral corticosteroids	0 (0)	0 (0)
Oral opioids	0 (0)	0 (0)
Arthritis Self Efficacy Scale[f]	6.4 (2.1)	6.3 (1.5)
Co-interventions used in the last 6 months, n (%)		
Land-based exercise	12 (67)	13 (59)
Heat/cold treatment	11 (61)	7 (32)
Massage	8 (44)	11 (50)
Knee braces	8 (44)	8 (36)
Manual therapy	3 (17)	8 (36)
Orthotics/arch supports	2 (11)	2 (9)
Hydrotherapy	3 (17)	4 (18)
Usual shoes overall motion control feature score, mean (SD)[g]	6.2 (3.2)	6.4 (2.7)
Expectation of treatment – before randomisation, n (%)		
No change	0 (0)	0 (0)
Mild improvement	2 (11)	3 (14)
Moderate improvement	10 (56)	16 (73)
Large improvement	6 (33)	3 (14)
Complete recovery	0 (0)	0 (0)

	Motion control shoes (n=18)	Neutral shoes (n=22)
Expectation of treatment – after shoe allocation, n (%)		
No change	0 (0)	0 (0)
Mild improvement	1 (6)	2 (9)
Moderate improvement	12 (67)	13 (59)
Large improvement	5 (28)	6 (27)
Complete recovery	0 (0)	1 (5)

[a] Using the Kellgren & Lawrence grading system;
[b] Measured as anatomical axis from standing radiograph with 180° indicating neutral alignment, <180°, varus alignment, and >180°, valgus alignment.
[c] Scored from -12 to 12; scores <0 indicated supinated foot posture, 0-5 neutral foot posture, and >5 pronated foot posture;
[d] Higher values indicate greater mobility/drop;
[e] Defined as at least once per week in the last 6 months;
[f] Scores range 1 to 10, higher scores indicate higher self-efficacy;
[g] Measured using the Footwear Assessment Tool; scores range 0-11, with higher scores indicating more motion control features.
IQR = interquartile range (25^{th} – 75^{th} percentile); OA = osteoarthritis.

Adherence and adverse events

Mean (SD) allocated shoe wear was 7.0 (3.4) hours/day with motion control shoes and 8.0 (2.4) hours/day with neutral shoes (Appendix Table 2). Ten participants (56%) were classified as adherent over six months with motion control shoes, compared to 19 (86%) participants with neutral shoes. A similar number of participants in each footwear group reported adverse events (n=5 (28%) with motion control shoes, n=4 (18%) with neutral shoes), mostly knee pain (Table 2). Cointervention use was similar between groups at baseline (Table 1) and follow-up (Table 2). One participant (6%) ceased wearing their motion control shoes due to a fractured ankle that was unrelated to the footwear (Appendix Table 3).

Table 2. Adverse events and co-interventions at follow up according to group, presented as number (%) of participants.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Participants reporting any adverse event(s):	5 (28)	4 (18)
Knee pain	3 (17)	2 (9)
Ankle/foot pain	2 (11)	1 (5)
Blisters	0 (0)	1 (5)
Pain in other areas	2 (11)	1 (5)
Count of adverse events:		
0	13 (72)	18 (82)
1	3 (17)	3 (14)
2	2 (11)	1 (5)
Current drug/supplement use[a]:	16 (89)	15 (68)
Analgesia (paracetamol combinations)	13 (72)	11 (50)
Non-steroidal anti-inflammatories	11 (61)	12 (55)
Topical anti-inflammatories	8 (44)	5 (23)
Oral corticosteroids	0 (0)	1 (5)
Oral opioids	0 (0)	1 (5)
Co-interventions used in the last 6 months:		
Land based exercise	13 (72)	11 (50)
Heat/cold treatment	8 (44)	7 (32)
Massage	6 (33)	8 (36)
Knee braces	2 (11)	5 (23)
Manual therapy	4 (22)	4 (18)
Orthotics/arch supports	4 (22)	0 (0)
Hydrotherapy	3 (17)	4 (18)

[a] Defined as at least once per week in the last 6 months.

Primary outcome

Tables 3 summarizes the primary outcome across time by group and Table 4 presents the change in the primary outcome within and between groups. There was no evidence of a between-group difference in change in walking knee pain at 6 months (mean difference 0.4 NRS units (95% CI -1.0 to 1.7), p=0.60) (Table 4). Sensitivity analyses found similar results when assuming full adherence (Appendix Table 4).

Table 3. Mean (SD) scores on continuous outcome measures across time, by shoe group.

	Baseline		6 months	
	Motion control shoes (n=18)	**Neutral shoes (n=22)**	**Motion control shoes (n=18)**	**Neutral shoes (n=22)**
Primary outcome				
Average knee pain on walking (NRS)	5.7 (1.1)	5.4 (1.0)	4.3 (2.2)	3.7 (2.2)
Secondary outcomes				
KOOS sub-scales:				
i) Physical function	61.0 (16.0)	63.0 (14.7)	71.2 (15.4)	71.0 (14.3)
ii) Pain	52.5 (11.3)	55.1 (12.8)	63.0 (14.3)	64.1 (12.1)
iii) Sport and recreation	24.7 (18.3)	28.0 (22.9)	31.1 (24.6)	39.3 (16.4)
iv) Knee-related quality-of-life	32.6 (13.0)	34.1 (14.3)	37.5 (18.8)	44.3 (17.3)
v) Patellofemoral pain and OA	33.2 (16.1)	33.5 (15.3)	40.2 (20.7)	44.1 (15.6)
Quality of life (AQoL-6D)	0.80 (0.10)	0.76 (0.10)	0.81 (0.10)	0.78 (0.12)
Physical Activity Scale for the Elderly (PASE)	186.5 (78.5)	177.9 (91.8)	177.0 (84.1)	202.5 (89.4)

AQoL = Assessment of Quality of Life instrument (-0.04 to 1.0; higher scores indicate better quality of life); KOOS = Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicating worse pain/symptoms/function/quality-of-life); NRS = numerical rating scale (0-10; higher scores indicate worse pain); OA = osteoarthritis; PASE = Physical Activity Scale for the Elderly (0 to over 400, with higher scores indicating higher physical activity); SD = standard deviation.

Table 4: Mean change within groups, and difference[a] in change between groups for continuous outcomes, using complete case data.

	Mean (SD) change within groups Baseline – 6 months		Difference in change between groups[a] Baseline to 6 months	
	Motion control shoes (n=18)	Neutral shoes (n=22)	Mean difference (95% CI)	P-value
Primary outcome				
Knee pain on walking (NRS)[b]	1.4 (2.1)	1.7 (2.1)	0.4 (-1.0, 1.7)	0.60
Secondary outcomes				
KOOS sub-scales[c]:				
i) Physical function	-10.2 (14.5)	-8.0 (11.4)	1.6 (-5.8, 8.9)	0.67
ii) Pain	-10.5 (14.8)	-9.1 (15.3)	-0.4 (-8.6, 7.8)	0.92
iii) Sport and recreation	-6.4 (27.1)	-11.4 (25.9)	-7.8 (-20.8, 5.3)	0.24
iv) Knee-related quality-of-life	-4.9 (18.1)	-10.2 (17.1)	-6.1 (-16.8, 4.5)	0.26
v) Patellofemoral pain and OA	-6.9 (21.0)	-10.6 (15.0)	-3.9 (-14.4, 6.6)	0.47
Quality of life (AQoL-6D)[c]	-0.01 (0.13)	-0.02 (0.06)	0.00 (-0.05, 0.06)	0.90
Physical activity (PASE)[c]	9.5 (85.7)	-24.6 (51.5)	-32.2 (-73.1, 8.7)	0.12

[a] Difference is adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade).

[b] For change within groups, positive changes indicate improvement. For difference in change between groups, negative differences favour motion control shoes.

[c] For change within groups, negative changes indicate improvement. For difference in change between groups, positive differences favour motion control shoes.

AQoL = Assessment of Quality of Life instrument (-0.04 to 1.0; higher scores indicate better quality of life); CI = confidence intervals; KOOS = Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicating worse pain/symptoms/function/quality-of-life); NRS = numerical rating scale (0-10; higher scores indicate worse pain); OA = osteoarthritis; PASE = Physical Activity Scale for the Elderly (0 to over 400, with higher scores indicating higher physical activity); SD = standard deviation.

Secondary outcomes

Table 3 summarizes continuous secondary outcomes across time by group and Table 4 presents change in continuous secondary outcomes within and between groups. There was no evidence that motion control shoes were superior to neutral shoes for any continuous secondary outcome. Similar proportions (considering our small sample size) of participants reported global

improvement across groups (Table 5), with no significant difference between groups in the relative risk of improvement in pain (1.36, 95% CI 0.61 to 3.01, p=0.45) or function (1.43, 95% CI 0.50 to 4.10, p=0.50). The number of participants achieving the MCID of 1.8 NRS units in pain, and the relative risk of achieving the MCID, was also similar between groups (1.28, 95% CI 0.74 to 2.24, p=0.38) (Table 5).

Table 5: Number (percentage) of participants reporting global improvement or achieving an improvement of 1.8 NRS units in the primary outcome (change in knee pain on walking (baseline minus 6 months)), and relative risks[a] and risk differences[a].

	Motion control shoes (n=18)	Neutral shoes (n=22)	Relative risk (95% CI)[b]	P-value	Risk difference (95% CI)[c]	P-value
Improved pain[d]	6/18 (33)	10/22 (46)	1.36 (0.61, 3.01)	0.45	0.12 (-0.18, 0.42)	0.44
Improved function[d]	4/18 (22)	7/22 (32)	1.43 (0.50, 4.10)	0.50	0.10 (-0.18, 0.37)	0.49
Improvement ≥1.8 NRS units[e]	9/18 (50)	14/22 (64)	1.28 (0.74, 2.24)	0.38	0.14 (-0.16, 0.44)	0.36

[a] Relative risk and risk difference adjusted for radiographic severity (Kellgren & Lawrence Grade).
[b] Relative risks <1 favour motion control shoe group.
[c] Risk differences <0 favour motion control shoe group.
[d] Rated using 7-point scales with terminal descriptors of 'much worse' to 'much better', with participants indicating 'moderately better' or 'much better' classified as improved.
[e] Improvement ≥1.8 NRS units chosen as this is the minimum clinically important difference in the primary outcome, change in knee pain on walking (baseline – 6 months).
CI = confidence intervals; NRS = numerical rating scale.

Subgroup analyses

The effect of allocated shoe group on the primary outcome of walking knee pain was not found to be moderated by any of the pre-specified variables of radiographic disease severity, Foot Posture Index, radiographic knee alignment or KOOS patellofemoral pain and OA subscale score (Appendix Tables 5 and 6).

DISCUSSION

This RCT found that motion control shoes were not superior at reducing knee pain on walking than neutral shoes in people with lateral knee OA. Average within group changes failed to demonstrate clinically-meaningful improvements in knee pain for either footwear group. Motion control shoes were not superior to neutral shoes for any secondary outcome, and a

similar proportion of participants in each group reported global improvements in pain (motion control 33% vs neutral 46%) and function (motion control 22% vs neutral 32%) and achieved the MCID in NRS walking pain (motion control 50% vs neutral 64%). However, we had reduced power (57.8%) to detect the MCID in between-group difference in change in our primary outcome as we did not reach our intended sample size, which may explain our findings. Albeit, the observed effect estimate was well below what is considered clinically meaningful, and the MCID was not contained within the 95% confidence intervals. These findings provide preliminary evidence to suggest motion control shoes may not be beneficial at reducing symptoms associated with predominantly lateral knee OA compared with neutral shoes. However, adequately-powered clinical trials are required to confirm our results.

Although no previous clinical trial has investigated the effects of footwear in people with lateral knee OA, our findings are not consistent with the only other similar trial conducted, which evaluated shoe insoles over 8 weeks. In a previous RCT with a smaller sample size than ours (n=30), medially wedged insoles, but not flat neutral insoles, significantly reduced knee pain with movement (mean (SD) baseline and 8 weeks values for medial wedges: 8.1 (1.5) to 4.2 (2.4); flat insoles: 6.9 (2.6) to 6.4 (2.7)) and at rest (medial wedges: 5.1 (2.3) to 2.7 (2.4); flat insoles: 3.3 (2.2) to 3.1 (2.5)) in women with lateral knee OA (18). However, average between-group differences were not reported in that study, thus it is possible that no significant between group differences were observed. Although adherence rates were not reported in that study, the different outcomes may also be due to the lower proportion of participants being classified as adherent wearing motion control shoes (56%) compared to neutral walking shoes (86%) in our study. To our knowledge, no study has investigated the symptomatic effects of knee bracing or any other biomechanical intervention in people with lateral TF joint OA.

Biomechanical research has demonstrated that motion control shoes (16), medially wedged insoles (37) and medial arch supports (38) redistribute knee joint loading toward the medial TF compartment, likely unloading the lateral TF compartment. The lack of symptomatic benefit with motion control shoes in our study could suggest that these shoes are not effective at unloading the lateral TF compartment, that joint load reductions are not enough to result in clinical meaningful reductions in pain, and/or that relationships between lateral TF joint loads and pain are not strong. Although there has been no research evaluating the relationship between lateral tibiofemoral joint loads and severity of knee pain in people with lateral tibiofemoral OA, previous research by us and others in medial compartment knee OA has shown limited, and at times conflicting, associations between knee pain and medial TF joint loads (39, 40). Thus it is perhaps not surprising that our previous RCT which tested footwear designed specifically to reduce medial TF loads found that they were not superior to conventional walking shoes at reducing walking knee pain in people with medial knee OA (34). Further research is needed to investigate associations between lateral TJ joint loads and knee pain severity in people with lateral knee OA, and whether interventions that produce larger reductions in knee load (for example, high tibial osteotomy and knee bracing) can effectively reduce knee pain in this population.

We failed to reach our intended sample size of 110 participants due to slow recruitment rates, impacting feasibility to complete the trial before funding was exhausted. This was largely because on-campus research was suspended at our university during 23 weeks of COVID-19-related lockdowns in 2020 in Australia. Nonetheless, it is worth highlighting that our recruitment rate prior to trial suspension was very slow (2.5 participants enrolled per month) compared to our previous footwear trials in people with medial tibiofemoral OA (which enrolled 5.9-7.5 participants per month (34, 35)). The much slower recruitment rate in the

current study reflects the lower prevalence of lateral (15%) compared to medial (27%) tibiofemoral OA in the community (41). It is also worth noting that, when recruiting people with lateral tibiofemoral OA from the community, x-ray screening costs can be substantial given that 58% of people recruited from community sources were excluded on the basis of not having a grade of lateral TF joint space narrowing that was greater than medial. In the present study, our most successful recruitment strategy was recruiting from our research database of volunteers, which included participants who had already undergone x-rays for our prior trials and were known to have lateral tibiofemoral OA. In fact, 93% (37/40 participants) of our final sample were recruited this way (Figure 1), and our recruitment of only 3 participants from the 206 people screened from the community resulted in a recruitment rate of only 1.46% from this source. Thus, to recruit the final 70 participants from the community would have required screening an additional 1,522 participants. Future studies should take these recruitment rates into consideration when planning clinical trials in people with predominantly lateral knee OA.

Despite our small sample size, our study is the first to assess any type of footwear for people with predominantly lateral knee OA. Our findings will be important for researchers undertaking meta-analyses of biomechanical interventions for knee OA (42), and in particular, will yield unique data to evaluate efficacy of interventions in the under-researched subgroup of people with lateral tibiofemoral OA. Thus, our findings also have the potential to influence knee OA clinical guidelines, most of which advocate footwear use on the basis of expert opinion alone due to the dearth of footwear RCTs in knee OA (2, 6). Other strengths include our robust RCT design and use of outcome measures recommended for knee OA clinical trials, blinded participants and assessors, excellent retention, and the inclusion of sensitivity and moderator analyses. There were also some limitations, the principal one being that our sample size was smaller than planned. As such, our trial had reduced statistical power to detect between-group

differences. We evaluated a single motion control shoe model, thus our findings cannot be generalized to other motion control shoes. Similarly, the addition of medial wedges or arch support to the motion control shoes may exert greater symptomatic benefits than motion control shoes alone.

In conclusion, motion control shoes were not superior to neutral walking shoes for reducing walking knee pain in people with symptomatic lateral tibiofemoral joint OA. Given the limited clinical trial evidence in people with lateral knee OA, further research is needed to confirm the findings and to identify effective treatments for this important but under-researched subgroup of knee OA patients.

Footnotes

Data sharing statement: Data that support findings of this study are available from the corresponding author upon reasonable request.

Ethics statements:

Patient consent for publication: Consent obtained directly from patient(s)

Ethics approval: This study involves human participants, was approved by University of Melbourne Human Research Ethics Committee and registered with the Australian New Zealand Clinical Trials Registry (date registered 15 November 2018) and complied with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Contributors: KLP and RSH conceived the idea for the study and KLP led the trial. KLP and RSH designed the trial protocol with input from KLB, BM, PK, FM, and KL. FM and KL

formulated and were responsible for the statistical analysis plan and conducted the statistical analyses. KLP drafted the manuscript and all authors provided input and approved the final version.

Funding statement: This study was funded by the National Health and Medical Research Council (Project Grant #1124418). KLP is supported by a National Health & Medical Research Council Emerging Leadership Investigator Grant (#1174229). KLB is supported by a National Health & Medical Research Council Leadership Investigator Grant (#1174431). RSH is supported by a National Health & Medical Research Council Senior Research Fellowship (#1154217).

Competing interests: None

REFERENCES

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018; 392: 1789-858.

2. National Clinical Guideline Centre. Osteoarthritis: Care and management in adults. Clinical guideline CG177. Methods, evidence and recommendations. London; National Institute for Health and Care Excellence 2014.

3. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage 2014; 22: 363-88.

4. Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006; 18: 514-8.

5. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis and Cartilage 2014; 22: 1833-9.

6. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Annals of the Rheumatic Diseases 2013; 72: 1125-35.

7. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty): Published August 31, 2021; 2021 [Accessed October 21, 2021]. Available from: https://www.aaos.org/oak3cpg.

8. Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. Annals of the Rheumatic Diseases 1993; 52: 520-6.

9. Fascingbauer M, Renner L, Waldstein W, Boettner F. Are lateral compartment osteophytes a predictor for lateral cartilage damage in varus osteoarthritic knees?: Data from the Osteoarthritis Initiative. . Bone Jt J 2015; 97B: 1634-9.

10. Cotofana S, Buck R, Wirth W, Roemer F, Duryea J, Nevitt M, et al. Cartilage thickening in early radiographic knee osteoarthritis: a within-person, between-knee comparison. . Arthritis Care Res 2012; 64: 1681-90.

11. Yamabe E, Ueno T, Miyagi R, Watanabe A, Guenzi C, Yoshioka H. Study of surgical indication for knee arthroplasty by cartilage analysis in three compartments using data from Osteoarthritis Initiative (OAI). . BMC Musculoskelet Disord 2013; 14: 194.

12. Nagaosa Y, Lanyon P, Doherty M. Characterisation of size and direction of osteophyte in knee osteoarthritis: a radiographic study. Ann Rheum Dis 2002; 61: 319-24.

13. Iijima H, Aoyama T, Nishitani K, Ito H, Fukutani N, Isho T, et al. Coexisting lateral tibiofemoral osteoarthritis is associated with worse knee pain in patients with mild medial osteoarthritis. Osteoarthritis Cartilage 2017; 25: 1274-81.

14. Bennell KL, Kean CO, Wrigley TV, Hinman RS. Effects of a modified shoe on knee load in people with and without knee osteoarthritis. Arthritis Rheum 2013; 65: 701-9.

15. Paterson KL, Bennell KL, Wrigley TV, Metcalf BR, Kasza J, Hinman RS. Effects of footwear on the knee adduction moment in medial knee osteoarthritis: classification criteria for flat flexible vs stable supportive shoes. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2017; 25: 234-41.

16. Radzimski AO, Mundermann A, Sole G. Effect of footwear on the external knee adduction moment - A systematic review. The Knee 2012; 19: 163-75.

17. Sawada T, Kito N, Yukimune M, Tokuda K, Tanimoto K, Anan M, et al. Biomechanical effects of lateral and medial wedge insoles on unilateral weight bearing. J Phys Ther Sci 2016; 28: 280-5.

18. Rodrigues PT, Ferreira AF, Pereira RMR, Bonfá E, Borba EF, Fuller R. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. Arthritis Care & Research 2008; 59: 603-8.

19. Paterson KL, Bennell KL, Metcalf BR, Campbell PK, Kasza J, Wrigley TV, et al. Footwear for osteoarthritis of the lateral knee: protocol for the FOLK randomised controlled trial. BMC Musculoskeletal Disorders 2020; 21: 247.

20. Kellgren JH, Jeffrey MR, Ball J. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs. Oxford: Blackwell Scientific; 1963.

21. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007; 15: A1-56.

22. Bellamy N. Osteoarthritis clinical trials: candidate variables and clinimetric properties. Journal of Rheumatology 1997; 24: 768-78.

23. Bellamy N. Outcome measurement in osteoarthritis clinical trials. Journal of Rheumatology 1995; 22: 49-51.

24. Bellamy N, Carette S, Ford PM, Kean WF, le Riche NG, Lussier A, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials--results of a consensus development (Delphi) exercise. The Journal of rheumatology 1992; 19: 451-7.

25. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. Journal of Orthopaedic & Sports Physical Therapy 1998; 28: 88-96.

26. Osborne RH, Hawthorne G, Lew EA, Gray LC. Quality of life assessment in the community-dwelling elderly: validation of the Assessment of Quality of Life (AQoL) Instrument and comparison with the SF-36. Journal of clinical epidemiology 2003; 56: 138-47.

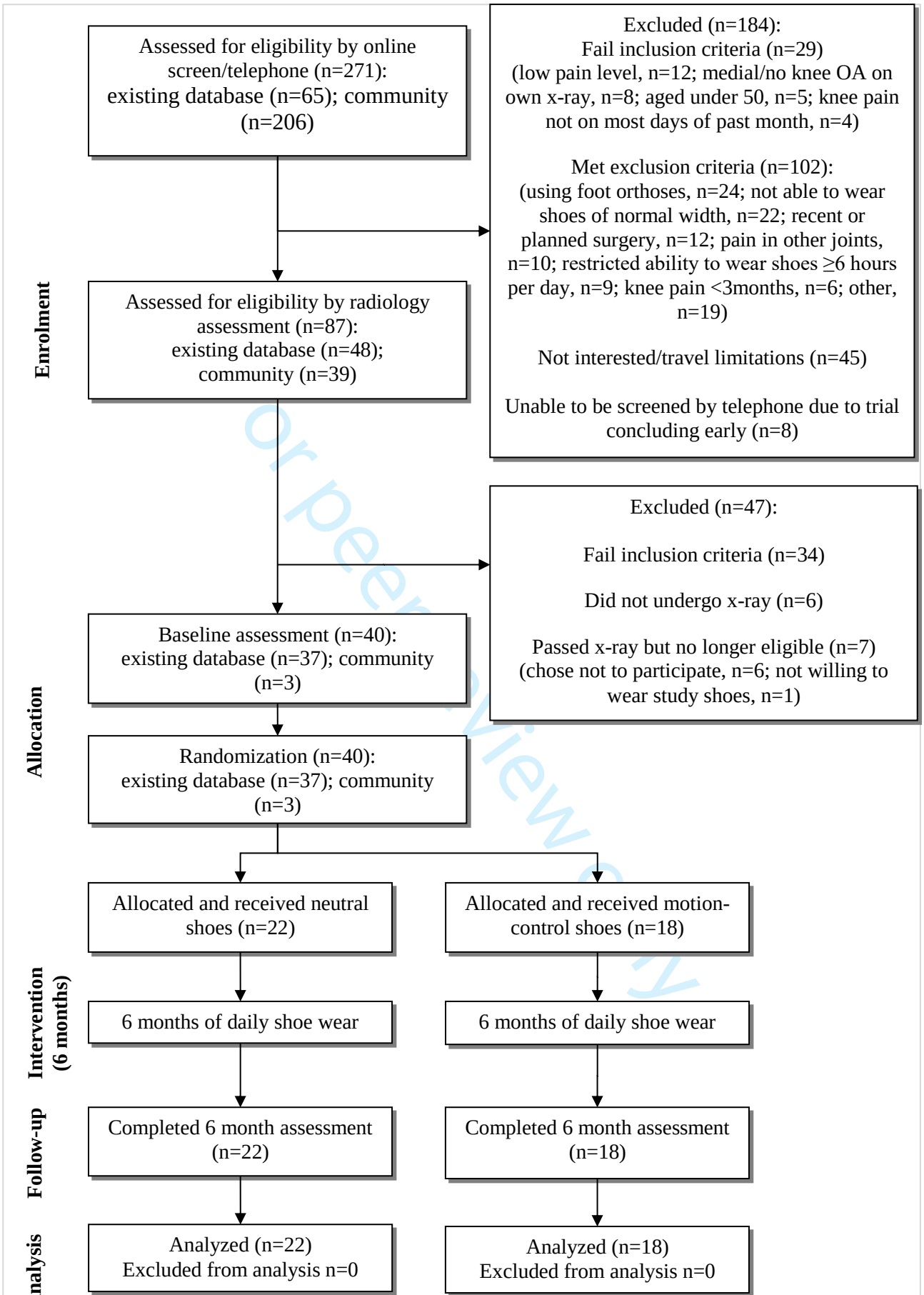
567 27. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger Jr W, Messier SP.
568 Validation of the PASE in older adults with knee pain and physical disability. Medicine and
569 science in sports and exercise 1999; 31: 627-33.
570 28. ten Klooster PM, Drossaers-Bakker KW, Taal E, van de Laar MA. Patient-perceived
571 satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's
572 perspective. Pain 2006; 121: 151-7.
573 29. Hsu R, Himeno S, Coventry M, Chao E. Normal axial alignment of the lower
574 extremity and load-bearing distribution at the knee. Clinical Orthopaedics and Related
575 Research 1990; 255: 215-27.
576 30. Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of
577 a scale to measure perceived self-efficacy in people with arthritis. Arthritis and Rheumatism
578 1989; 32: 37-44.
579 31. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating
580 system for scoring standing foot posture: The Foot Posture Index. Clinical Biomechanics
581 2006; 21: 89-98.
582 32. McPoil T, Vicenzino B, Cornwall M, Collins N, Warren M. Reliability and normative
583 values for the foot mobility magnitude: a composite measure of vertical and medial-lateral
584 mobility of the midfoot. Journal of Foot and Ankle Research 2009; 2: 6.
585 33. Brody DM. Techniques in the evaluation and treatment of the injured runner. The
586 orthopedic clinics of north America 1982; 13: 541.
587 34. Hinman RS, Wrigley TV, Metcalf BR, Campbell PK, Paterson KL, Hunter DJ, et al.
588 Unloading shoes for self-management of knee osteoarthritis: a randomized trial. Annals of
589 internal medicine 2016; 165: 381-9.

590 35. Paterson KL, Bennell KL, Campbell PK, Metcalf BR, Wrigley TV, Kasza J, et al. The
591 effect of flat flexible versus stable supportive shoes on knee osteoarthritis symptoms: a
592 randomized trial. Annals of internal medicine 2021; 174: 462-71.
593 36. Maracy M, Dunn G. Estimating dose-response effects in psychological treatment
594 trials: the role of instrumental variables. Statistical Methods in Medical Research 2011; 20:
595 191-215.
596 37. Schmalz T, Blumentritt S, Drewitz H, Freslier M. The influence of sole wedges on
597 frontal plane kinetics, in isolation and in combination with representative rigid and semi-rigid
598 ankle-foot-orthoses. Clinical Biomechanics 2006; 21: 631-9.
599 38. Franz JR, Dicharry J, Riley PO, Jackson K, Wilder RP, Kerrigan DC. The influence
600 of arch supports on knee torques relevant to knee osteoarthritis. Medicine & Science in
601 Sports & Exercise 2008; 40: 913-7.
602 39. Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction
603 moment during gait in subjects with knee osteoarthritis is more closely correlated with static
604 alignment than radiographic disease severity, toe out angle and pain. Journal of Orthopaedic
605 Research 2002; 20: 101-7.
606 40. Hall M, Bennell KL, Wrigley TV, Metcalf BR, Campbell PK, Kasza J, et al. The knee
607 adduction moment and knee osteoarthritis symptoms: relationships according to radiographic
608 disease severity. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2017;
609 25: 34-41.
610 41. Stoddart JC, Dandridge O, Garner A, Cobb J, van Arkel RJ. The compartmental
611 distribution of knee osteoarthritis – a systematic review and meta-analysis. Osteoarthritis and
612 Cartilage 2021; 29: 445-55.
613 42. Macri EM, Callaghan M, van Middelkoop M, Hattle M, Bierma-Zeinstra SMA.
614 Effects of mechanical interventions in the management of knee osteoarthritis: protocol for an

615 OA Trial Bank systematic review and individual participant data meta-analysis. BMJ Open
616 2021; 11: e043026.

Figures

Figure 1. Flow of participants through the trial.



Appendix Table 1. Motion control features of participants' usual shoes, reported as number (%) unless otherwise stated.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Multiple density midsole	6 (33)	5 (23)
Fixation		
Laces	12 (67)	16 (73)
Straps/buckles	3 (17)	1 (5)
Velcro	1 (6)	1 (5)
None	2 (11)	4 (18)
Heel counter stiffness		
Rigid	7 (39)	13 (59)
Moderate	3 (17)	4 (18)
Minimal	6 (33)	4 (18)
No heel counter	2 (11)	1 (5)
Midfoot sagittal stability		
Rigid	6 (33)	4 (18)
Moderate	1 (6)	2 (9)
Minimal	11 (61)	16 (73)
Midfoot torsional stability		
Rigid	11 (61)	16 (73)
Moderate	4 (22)	3 (14)
Minimal	3 (17)	3 (14)
Overall motion control feature score, mean (SD)[a]	6.2 (3)	6.4 (3)

[a] Measured using the Footwear Assessment Tool; scores range 0 to 11, with higher scores indicating more motion control features.
SD = standard deviation.

Appendix Table 2. Adherence to allocated footwear across groups.

	Motion control shoes[a]	Neutral shoes[b]
Shoe wear in log books (hours/day), mean (SD):		
Month 1	7.1 (2.2)	7.9 (2)
Month 2	7.1 (4.0)	8.5 (3)
Month 3	7.0 (4.3)	7.8 (3)
Month 4	6.6 (3.7)	8.1 (2)
Month 5	7.5 (3.9)	7.4 (3)
Month 6	7.7 (3.9)	8.0 (3)
Overall	7.0 (3.4)	8.0 (2)
Participants classified as adherent[c], n (%):		
Month 1	13 (72)	19 (86)
Month 2	10 (59)	18 (82)
Month 3	11 (61)	18 (82)
Month 4	10 (59)	18 (82)
Month 5	12 (75)	15 (71)
Month 6	12 (80)	18 (86)
Overall[d]	10 (56)	19 (86)
Self-rated adherence with allocated footwear over 6 months (NRS), mean (SD)	7.9 (2.8)	8.5 (1.9)

[a] n=17 for shoe wear and participants classified as adherent at month 2 and month 4; n=16 for shoe wear and participants classified as adherent at month 5; n=15 for shoe wear and participants classified as adherent at month 6; n=18 for all other outcomes.

[b] n=21 for shoe wear and participants classified as adherent at month 5 and month 6; n=22 for all other outcomes.

[c] Adherent defined as an

[d] Overall are participants who

NRS = numerical rating scale, where 0 = shoes not worn at all and 10 = worn completely as instructed; SD = standard deviation.

Appendix Table 3. Reasons for participants to cease wearing shoes over the course of the trial, reported as number (%).

	Motion control shoes (n=18)	Neutral shoes (n=22)
Fractured ankle (unrelated to shoes)	1[a] (6)	0 (0)
Total	1 (6)	0 (0)

[a] Participant ceased wearing shoes in month 2.

Appendix Table 4: Difference[a] in change between groups, for the primary outcome, change in knee pain on walking (baseline 6 months), assuming full adherence[b] (N=40).

	Difference in change between groups Baseline to 6 months	
	Mean difference (95% CI)	**P-value**
Knee pain on walking (NRS)[c]	0.6 (-1.7, 2.9)	0.59

[a] The complier average causal effect difference, adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade).
[b] Full adherence was defined as wearing insoles at least 70% of the time the participant wore shoes.
[c] For difference in change between groups, negative differences favour motion control shoe group.
CI=confidence intervals; NRS=numerical rating scale (0-10; higher scores indicate worse pain).

Appendix Table 5: Results of the moderation analysis for radiographic disease severity (Kellgren & Lawrence Grade) as a potential binary moderator for the primary outcome, change in knee pain on walking, using complete case data.[a]

	Mean (SD) Motion control shoes[b]	Neutral shoes[c]	Neutral shoes – motion control shoes Mean difference[d] (95% CI)	Interaction P-value
Radiographic disease severity				0.70
Grade 2 (mild) or 3 (moderate)	1.50 (2.37)	1.69 (2.46)	0.16 (-1.65, 1.96)	
Grade 4 (severe)	1.38 (1.92)	1.78 (1.72)	0.73 (-1.44, 2.90)	

[a] Presented as the mean scores on the primary outcome, change in average knee pain on walking (baseline – 6 months), in each group in each radiographic disease severity category, as well as in terms of the estimated mean difference in effect between groups (neutral shoes – motion control shoes) on the primary outcome in each radiographic disease severity category, adjusted for the outcome at baseline.
[b] n=10 for Grade 2 or 3; n=13 for Grade 4;
[c] n=8 for Grade 2 or 3; n=9 for Grade 4.
[d] Negative differences favour motion control shoes.
CI=confidence intervals; SD=standard deviation.

Appendix Table 6: Results of the moderation analysis for potential continuous moderators for the primary outcome, change in knee pain on walking, using complete case data[a].

Potential Moderator[b] (taken at baseline)	Motion control shoes Moderator Coeff. (95% CI)	P-value	Neutral shoes Moderator Coeff. (95% CI)	P-value	Difference[c] in coefficients, Neutral shoes – motion control shoes (95% CI)	Interaction P-value
Foot Posture Index[d]	0.09 (-0.29, 0.46)	0.64	0.11 (-0.15, 0.37)	0.41	0.02 (-0.44, 0.48)	0.92
Radiographic knee alignment (degrees)	0.15 (-0.03, 0.34)	0.11	-0.08 (-0.27, 0.12)	0.42	-0.23 (-0.49, 0.03)	0.085
KOOS sub-scale:						
Patellofemoral pain and OA	0.03 (-0.04, 0.10)	0.33	0.06 (-0.01, 0.13)	0.097	0.02 (-0.06, 0.11)	0.58

[a] Presented in terms of the estimated mean effect on the primary outcome, change in average knee pain on walking (baseline 6 months), of a one-unit increase in the potential moderator in each of the motion control shoe group and neutral shoe group, adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade 2, 3 or 4).

[b] n=32 for radiographic knee alignment, n=40 for all other potential moderators.

[c] Negative differences favour motion control shoes.

[d] Scored from -12 to 12; higher scores indicating a more pronated foot posture.

CI=confidence intervals; KOOS = Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicating worse pain/patellofemoral problems); OA = osteoarthritis.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	11
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	13
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 5
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Appendix tables
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Appendix
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effect of motion control versus neutral walking footwear on pain associated with lateral tibiofemoral joint osteoarthritis: a comparative effectiveness randomized clinical trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061627.R1
Article Type:	Original research
Date Submitted by the Author:	14-Aug-2022
Complete List of Authors:	Paterson, Kade; University of Melbourne Department of Physiotherapy, Bennell, Kim; University of Melbourne, CHESM Metcalf, Ben; The University of Melbourne Campbell, P; University of Melbourne McManus, Fiona; University of Melbourne Lamb, Karen; The University of Melbourne - Parkville Campus, School of Population and Global Health Hinman, Rana; University of Melbourne,
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

Effect of motion control versus neutral walking footwear on pain associated with lateral tibiofemoral joint osteoarthritis: a comparative effectiveness randomized clinical trial.

AUTHORS: Kade L Paterson PhD[1*], Kim L Bennell PhD[1], Ben R. Metcalf BSc (Hons)[1], Penny K Campbell BAppSci[1], Fiona McManus MBiostat[2], Karen E Lamb PhD[2,3] & Rana S Hinman PhD[1]

*Corresponding author

AFFILIATIONS: [1] Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Melbourne, Australia

[2] Biostatistics Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

[3] Methods and Implementation Support for Clinical Health research platform, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Australia

CORRESPONDING AUTHOR: Kade Paterson, Centre for Health Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, University of Melbourne, Victoria, Australia 3010. ph: +61 3 8344 0425, fax: +61 3 8344 4188, kade.paterson@unimelb.edu.au

Word count: 3,761

Running title: Footwear for lateral knee OA

ABSTRACT

Objective To determine if motion control walking shoes are superior to neutral walking shoes for reducing knee pain on walking in people with lateral knee osteoarthritis (OA).

Design Participant- and assessor-blinded, comparative effectiveness, superiority randomized controlled trial (RCT).

Setting Melbourne, Australia.

Participants People with symptomatic radiographic lateral tibiofemoral OA from the community and our volunteer database.

Interventions Participants were randomized to receive either motion control or neutral shoes and advised to wear them ≥6 hours/day over 6 months.

Outcome measures Primary outcome was change in average knee pain on walking over the previous week (11-point numerical rating scale (NRS, 0-10)) at 6 months. Secondary outcomes included other measures of knee pain, physical function, quality of life, participant-perceived change in pain and function, and physical activity.

Results We planned to recruit 110 participants (55 per arm) but ceased recruitment at 40 (n=18 motion control shoes, n=22 neutral shoes) due to COVID-19-related impacts. All 40 participants completed 6-month outcomes. There was no evidence that motion control shoes were superior to neutral shoes for the primary outcome of pain (mean between-group difference 0.4 NRS units (95% CI -1.0 to 1.7)), nor for any secondary outcome. The number of participants experiencing any adverse events was similar between groups (motion control shoes n=5 (28%), neutral shoes n=4 (18.2%)) and were minor.

Conclusion Motion control shoes were not superior to neutral shoes for improving knee pain on walking in symptomatic radiographic lateral tibiofemoral joint OA. Further research is

needed to identify effective treatments in this important but under-researched knee OA subgroup.

Trial Registration: Prospectively registered with the Australian New Zealand Clinical Trials Registry reference: ACTRN12618001864213

Key words: osteoarthritis, OA, knee, tibiofemoral, footwear, shoes, clinical trial, RCT, biomechanics, pain

Strengths and limitations

- We used a robust randomized clinical trial design with blinded participants and assessors.
- Our outcomes have strong clinimetric properties and are recommended for knee osteoarthritis clinical trials by international osteoarthritis guidelines.
- We included sensitivity analyses to assess whether our findings changed when assuming full adherence to footwear.
- We did not reach our intended sample size due to COVID-19-related impacts, thus we had reduced power to detect a clinically-relevant between-group difference in our primary outcome.

INTRODUCTION

Knee osteoarthritis (OA) is a common and painful condition and a leading cause of global disability (1). The disease is chronic and has no cure, thus people with knee OA have little choice but to self-manage their condition. Accordingly, advice about self-management is the cornerstone of conservative treatment, along with exercise and weight control (2, 3). As abnormal biomechanics are central to OA disease pathogenesis (4, 5), clinical guidelines advocate that clinicians provide advice on "appropriate" footwear as part of core treatment for knee OA (2, 6). However, there is scant evidence from clinical trials to guide footwear choice. Due to the lack of robust clinical trials in this area, international OA organizations and the American Academy of Orthopaedic Surgeons have called for footwear trials as an OA research priority (2, 6, 7).

To date, all clinical trials on footwear for knee OA have targeted people with medial knee OA, likely because the medial tibiofemoral (TF) compartment is affected by OA more often than the lateral compartment (8). However, 10-55% of knee OA patients have radiographic OA changes in the lateral TF joint (8-12), and there is evidence that co-existing lateral TF OA is associated with worse knee pain in people with mixed compartmental OA (13). Importantly, in people with medial knee OA, the aim of biomechanical interventions is to shift joint force distribution from the medial to the lateral TF compartment. However, the aim in people with lateral knee OA is to shift forces from the lateral to the medial TF compartment. Compared to medial tibiofemoral OA, there is scant research evaluating non-surgical treatments for people with lateral tibiofemoral OA. In particular, clinical trials that evaluate biomechanical interventions specifically designed to target the unique biomechanical needs of this lateral TF OA subgroup are urgently needed.

Biomechanical studies have shown that footwear with midsoles that are laterally stiff redistribute knee loads away from the medial towards the lateral TF compartment in people with medial knee OA (14). Conversely, footwear with medially stiff midsoles, such as "motion control" shoes, shift knee loads towards the medial TF compartment (15, 16), likely with concomitant reductions in lateral TF compartment load. Thus, it is possible that motion control footwear may improve symptoms in people with lateral knee OA. Although no randomized controlled trial (RCT) has assessed the effects of motion control shoes on symptoms in people with lateral compartment knee OA, there is some indirect clinical research to suggest that they may be effective. A small study of 30 women with symptomatic radiographic lateral knee OA and bilateral knee valgus deformity found that wearing medially wedged insoles (which have similar biomechanical effects on lateral TF joint loads to motion control shoes (17)) for 3-6 hours/day resulted in greater improvements in pain and other symptoms over 8 weeks, compared to wearing flat insoles (18). Consequently, further research assessing the effects of motion control footwear in people with lateral knee OA is warranted to help inform footwear recommendations in international OA clinical guidelines, and to guide clinical practice, for this important but under-researched OA subgroup.

This study aimed to assess the effectiveness of motion control shoes for improving symptoms in people with lateral knee OA. We hypothesized that wearing motion control shoes would lead to greater reductions in walking knee pain, compared to wearing neutral walking shoes, over 6 months.

PATIENTS AND METHODS

Design

This was a 2-arm, participant- and assessor-blinded, pragmatic, comparative effectiveness, superiority RCT. It was prospectively registered (Australian New Zealand Clinical Trials Registry ACTRN12618001864213) and the protocol is published (19). The study was approved by the University of Melbourne human research ethics committee (#1852787) and participants provided informed consent.

Participants

Community-dwelling participants (Melbourne, Australia) were recruited using advertisements, including targeted invitations to participants on our research volunteer database who had known radiographically diagnosed lateral knee OA. Participants were eligible if they were aged ≥50 years; reported average knee pain on walking over the previous week ≥4 on an 11-point numeric rating scale (NRS); had mild, moderate or severe radiographic knee OA (Kellgren & Lawrence (KL) Grade 2-4) (20); and had a grade of lateral TF joint space narrowing that was greater than medial, determined using a radiographic atlas (21) (where grade 0=no narrowing, 1=mild narrowing, 2=moderate narrowing, 3=severe narrowing). Participants were excluded if they reported knee pain for <3 months; had recent (past 6 months) or planned (next 6 months) knee surgery; or currently used foot orthoses, ankle/knee braces, customized shoes or other shoes worn regularly that would restrict their ability to wear the allocated study shoes for a minimum of 6 hours per day (e.g. work boots). For participants with bilaterally eligible knees, the most painful was deemed the study knee. Full exclusion criteria are in the published protocol (19).

Randomisation and masking

Participants were randomized in a 1:1 ratio. The randomisation schedule was prepared by a biostatistician with permuted block sizes of 6 to 12 and stratified by KL grades 2, 3 or 4. Allocation was concealed using password-protected software (REDCap™) and was revealed by a researcher not involved in recruitment or outcome assessment. Participants were blinded and informed only that the trial was comparing the effects of two types of commercially available walking shoes on knee OA symptoms. We did not disclose the hypothesis or the specific footwear styles/characteristics (i.e. motion control and neutral shoes) under investigation. As participants were blinded, and primary and secondary outcomes were self-reported, this trial was also assessor-blinded. The biostatisticians were blinded for all analyses.

Interventions

Motion control shoes

Black ASICS Gel-Kayano 25 shoes were chosen as the motion control shoes (Appendix Figure 1). These shoes have a dual density midsole which is stiffer medially compared to laterally, a feature that has previously been shown to shift knee loads towards the medial TF compartment (15, 16).

Neutral shoes

Black ASICS Gel-Nimbus 20 were the neutral comparator shoe (Appendix Figure 1). These shoes have a uniformly stiff midsole and are visually similar to the motion control shoes. They are also similar on other key features including midsole foam and gel cushioning systems, an engineered mesh upper, shoe mass, and rearfoot, forefoot and heel drop heights.

Participants were fitted with their allocated shoes by a study researcher (BM). Participants were advised to commence wearing their allocated shoes for two hours on the first day, and to

increase wear time by two hours/day until they were wearing them as much as possible, at a minimum of 6 hours/day, over 6 months.

Outcome measures

Participants completed baseline questionnaires on paper or electronically at the Department of Physiotherapy gait laboratory, The University of Melbourne. The 6-month follow-up questionnaire was completed either on paper or electronically at home.

The primary outcome was 6-month change in average knee pain on walking in the last week, assessed using an 11-point NRS with terminal descriptors of 'no pain' (score=0) and 'worst pain possible' (score=10). This measure has strong clinometric properties (22), is recommended for knee OA clinical trials (23), and has a minimal clinically important difference (MCID) of 1.8 units (24).

Secondary outcomes included changes in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of i) physical function, ii) pain, iii) sport and recreation, iv) knee-related quality of life, and v) patellofemoral pain and OA (25). Scores for each subscale were transformed to provide an overall value that ranged from 0 to 100 (where higher scores indicate better symptoms and function). Additional secondary outcomes included changes in quality of life, measured using the Assessment of Quality of Life 6D instrument (26) (scored between -0.04 and 1.00, higher scores indicate better quality of life); and physical activity over the previous week, measured using the Physical Activity Scale for the Elderly (PASE) (27) (scored from 0 to over 400, higher scores indicate higher activity). We also assessed patient-perceived global rating of change in i) pain and ii) function at 6 months, each measured using 7-point

Likert scales (terminal descriptors of 'much worse' to 'much better' (28). Participants reporting they were 'moderately better' or 'much better' were classified as improved.

Descriptive measures included height, body mass and body mass index; age; gender; knee OA symptom duration; radiographic disease severity (using the KL scale (20)); anatomical knee alignment (measured in degrees from the knee x-ray (29)); employment status; treatment expectation (using a 5-point ordinal scale (anchors of "no effect at all" to "complete recovery"); self-efficacy (using the Arthritis Self Efficacy Scale (30)); cointervention use via a custom table (also assessed at 6 months); foot posture (using the Foot Posture Index (31) (scores range from -12 to +12, higher score indicates a more pronated foot posture), Foot Mobility Magnitude (32) (in mm, higher values indicate greater mobility) and navicular drop (33) (in mm, higher values indicate greater drop); and the motion control feature score of the participant's usual (most commonly worn) pair of shoes (using the Footwear Assessment Tool (15), scored 0 to 11, higher scores indicate more motion control features).

We assessed adherence to allocated footwear using our successful strategies employed in prior footwear RCTs (34, 35). Participants recorded how much they wore their allocated shoes (hours/day) for 7 consecutive days, for one week of every month, in log books. Those who averaged ≥6hrs/day over 6 months were classified as 'adherent'. At 6 months, participants also rated their overall level of adherence with wearing their allocated shoes ≥6 hours per day using an 11-point NRS (terminal descriptors of 'shoes not worn at all' and 'shoes worn completely as instructed') and indicated whether they stopped wearing the shoes during the study (Yes or No). Participants who responded 'Yes' described when and why they stopped wearing their study shoes. Finally, adverse events (any problem experienced in the study knee or elsewhere

in the body because of wearing the study shoes) were self-reported by participants at 6 months using a custom table.

Statistical analysis

We aimed *a priori* to detect a between-group difference in change in walking pain (the primary outcome) of 1.8 units (the MCID) (24). We assumed a between-participant standard deviation of 2.7 and a baseline to 6-month correlation of 0.21 (34, 35). Using analysis of covariance (ANCOVA) adjusted for baseline score, we needed 46 participants per arm to achieve 90% power to detect the MCID in change in walking knee pain. Allowing for 15% attrition, we aimed to recruit 55 people per arm (n=110 in total). However, due to ongoing COVID-19 restrictions in Melbourne (Australia) halting trial recruitment for a prolonged period of time and grant funding running out, recruitment was ceased with a final sample size of 40. Using ANCOVA adjusted for baseline score, we have 57.8% power to detect the MCID in change in walking knee pain (baseline minus 6 months) with the final sample size of 40 participants (assuming 20 participants per arm).

Main comparative analyses between groups were performed using intention-to-treat. As no primary outcome data were missing from enrolled participants, multiple imputation was not applied, and all analyses were performed on complete case data. Separate linear regression models were fit for each continuous outcome, including the primary outcome of walking knee pain, with treatment group, the outcome at baseline, and the stratifying variable (KL grade) as covariates. Results were calculated as the estimated mean (95% confidence interval (CI)) difference in change (baseline minus 6 months) between groups. Regression assumptions of linearity and homoscedasticity were assessed using standard diagnostic plots. A sensitivity analysis, including all participants as randomized, estimated complier average causal effects,

which are the treatment effects on the primary outcome assuming full adherence to shoe wear (classified as average of ≥6 hours/day for 6 months, based on logbook data), using an instrumental variables approach (where randomization was the instrument for adherence) (36). Two-stage least squares models were fit: first, a model for observed adherence, including terms for randomized group, the outcome at baseline and the stratifying variable (KL grade) and second, a model predicting the primary outcome, given observed adherence. Improvement based on global change scores and the achievement of the MCID in improvement in walking knee pain (1.8 NRS units) were each compared between groups separately using logistic regression, adjusted for the stratifying variable (KL grade), with results reported as risk ratios and risk differences.

To assess whether the effect of shoe group on the primary outcome was moderated by KL grade, a linear regression model was fit for the primary outcome, with the outcome at baseline, treatment group, and KL grade as covariates, including an interaction between treatment group and KL grade. To assess whether the effect of shoe group on the primary outcome was moderated by i) Foot Posture Index score, ii) knee alignment or iii) KOOS patellofemoral pain and OA, separate linear regression models were fit for the primary outcome for each potential moderator, with the outcome at baseline, treatment group, the relevant potential moderator and KL grade, as covariates, including an interaction between treatment group and the potential moderator. Statistical analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, TX, USA). The *a priori* statistical analysis plan is in the appendix.

Patient and public involvement

Patients and the public were not involved in the design, conduct and dissemination of this research.

RESULTS

Sample characteristics

Participant flow through the study is shown in Figure 1. Between 29 November 2018 and 24 March 2020, we screened 261 people and enrolled 40 participants, predominantly recruited through targeted invitations to people with lateral knee OA in our research database (37 enrolees (from 65 screened) versus 3 recruited (from 196 screened) via advertising in the community). Due to COVID-19 causing extended lockdowns in Melbourne, Australia (totalling 23 weeks between March 30 and May 12, 2020, and between July 8 and October 27, 2020) and suspension of on-campus research activities, recruitment was postponed on 24 March 2020. Recruitment resumed on 13 June 2020 and by 12 November 2020 we had screened a further 10 participants without any further enrolment. The study was terminated early as it was deemed unfeasible to continue given the considerable number of participants still left to recruit, ongoing uncertainty regarding COVID-19 restrictions, poor community recruitment rates (no further recruitment possible from our volunteer database) and exhaustion of funding. At the 6-month follow-up, all 40 (100%) enrolled participants had completed the primary outcome.

Participant characteristics were comparable between groups at baseline (Table 1) except that a greater proportion of people in the neutral shoe group had a neutral foot posture (motion control 17% vs neutral 36%) and more people in the motion control group had a pronated foot posture (motion control 83% vs neutral 59%). Participant's own usual footwear were similar across groups with respect to motion control features (Table 1, Appendix Table 1), suggesting that on average, people wore shoes with moderate amounts of motion control features. Treatment

expectations were generally similar across groups pre-randomization and following shoe allocation (Table 1).

Table 1. Baseline characteristics of participants by group, reported as mean (standard deviation) unless otherwise stated.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Age (years)	64.6 (7.2)	64.2 (7.2)
Gender		
Female, n (%)	11 (61)	13 (59)
Male, n (%)	7 (39)	9 (41)
Symptom duration (years)	11.6 (7.8)	11.1 (8.0)
Height (m)	1.7 (0.1)	1.7 (0.1)
Body mass (kg), median (IQR)	89 (75-95)	89 (81-106)
Body mass index (kg/m^2), median (IQR)	31.4 (27.6-35.4)	31.2 (27.8-33.9)
Unilateral knee OA symptoms, n (%)	3 (17)	7 (32)
Radiographic disease severity, n (%)[a]		
Grade 2 (mild)	2 (11)	3 (14)
Grade 3 (moderate)	8 (44)	10 (45)
Grade 4 (severe)	8 (44)	9 (41)
Radiographic knee alignment (degrees)[b]	188.7 (6.3)	188.1 (5.5)
Foot Posture Index classification, n (%)[c]		
Supinated	0 (0)	1 (5)
Neutral	3 (17)	8 (36)
Pronated	15 (83)	13 (59)
Foot Mobility Magnitude (mm)[d]	7.7 (3.5)	7.7 (2.5)
Navicular drop (mm)[d]	6.5 (4.4)	6.3 (3.0)
Currently employed, n (%)	10 (56)	11 (50)
Current drug/supplement use, n (%)[e]	15 (83)	18 (82)
Paracetamol combinations	11 (61)	15 (68)
Non-steroidal anti-inflammatories	8 (44)	10 (45)
Topical anti-inflammatories	8 (44)	4 (18)
Oral corticosteroids	0 (0)	0 (0)
Oral opioids	0 (0)	0 (0)
Arthritis Self Efficacy Scale[f]	6.4 (2.1)	6.3 (1.5)
Co-interventions used in the last 6 months, n (%)		
Land-based exercise	12 (67)	13 (59)
Heat/cold treatment	11 (61)	7 (32)
Massage	8 (44)	11 (50)
Knee braces	8 (44)	8 (36)
Manual therapy	3 (17)	8 (36)
Orthotics/arch supports	2 (11)	2 (9)
Hydrotherapy	3 (17)	4 (18)
Usual shoes overall motion control feature score, mean (SD)[g]	6.2 (3.2)	6.4 (2.7)
Expectation of treatment – before randomisation, n (%)		
No change	0 (0)	0 (0)
Mild improvement	2 (11)	3 (14)
Moderate improvement	10 (56)	16 (73)
Large improvement	6 (33)	3 (14)
Complete recovery	0 (0)	0 (0)

	Motion control shoes (n=18)	Neutral shoes (n=22)
Expectation of treatment – after shoe allocation, n (%)		
No change	0 (0)	0 (0)
Mild improvement	1 (6)	2 (9)
Moderate improvement	12 (67)	13 (59)
Large improvement	5 (28)	6 (27)
Complete recovery	0 (0)	1 (5)

[a] Using the Kellgren & Lawrence grading system;
[b] Measured as anatomical axis from standing radiograph with 180° indicating neutral alignment, <180°, varus alignment, and >180°, valgus alignment.
[c] Scored from -12 to 12; scores <0 indicated supinated foot posture, 0-5 neutral foot posture, and >5 pronated foot posture;
[d] Higher values indicate greater mobility/drop;
[e] Defined as at least once per week in the last 6 months;
[f] Scores range 1 to 10, higher scores indicate higher self-efficacy;
[g] Measured using the Footwear Assessment Tool; scores range 0-11, with higher scores indicating more motion control features.
IQR = interquartile range (25th – 75th percentile); OA = osteoarthritis.

Adherence and adverse events

Mean (SD) allocated shoe wear was 7.0 (3.4) hours/day with motion control shoes and 8.0 (2.4) hours/day with neutral shoes (Appendix Table 2). Ten participants (56%) were classified as adherent over six months with motion control shoes, compared to 19 (86%) participants with neutral shoes. A similar number of participants in each footwear group reported adverse events (n=5 (28%) with motion control shoes, n=4 (18%) with neutral shoes), mostly knee pain (Table 2). Cointervention use was similar between groups at baseline (Table 1) and follow-up (Table 2). One participant (6%) ceased wearing their motion control shoes due to a fractured ankle that was unrelated to the footwear (Appendix Table 3).

Table 2. Adverse events and co-interventions at follow up according to group, presented as number (%) of participants.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Participants reporting any adverse event(s):	5 (28)	4 (18)
Knee pain	3 (17)	2 (9)
Ankle/foot pain	2 (11)	1 (5)
Blisters	0 (0)	1 (5)
Pain in other areas	2 (11)	1 (5)
Count of adverse events:		
0	13 (72)	18 (82)
1	3 (17)	3 (14)
2	2 (11)	1 (5)
Current drug/supplement use[a]:	16 (89)	15 (68)
Analgesia (paracetamol combinations)	13 (72)	11 (50)
Non-steroidal anti-inflammatories	11 (61)	12 (55)
Topical anti-inflammatories	8 (44)	5 (23)
Oral corticosteroids	0 (0)	1 (5)
Oral opioids	0 (0)	1 (5)
Co-interventions used in the last 6 months:		
Land based exercise	13 (72)	11 (50)
Heat/cold treatment	8 (44)	7 (32)
Massage	6 (33)	8 (36)
Knee braces	2 (11)	5 (23)
Manual therapy	4 (22)	4 (18)
Orthotics/arch supports	4 (22)	0 (0)
Hydrotherapy	3 (17)	4 (18)

[a] Defined as at least once per week in the last 6 months.

Primary outcome

Tables 3 summarizes the primary outcome across time by group and presents the change in the primary outcome within and between groups. There was no evidence of a between-group difference in change in walking knee pain at 6 months (mean difference 0.4 NRS units (95% CI -1.0 to 1.7), p=0.60). Sensitivity analyses found similar results when assuming full adherence (Appendix Table 4).

Table 3. Mean (SD) scores on continuous outcome measures across time by shoe group, mean change within groups, and difference[a] in change between groups for continuous outcomes, using complete case data.

	Baseline		6 months		Mean (SD) change within groups: Baseline – 6 months		Difference in change between groups[a]: Baseline to 6 months	
	Motion control shoes (n=18)	Neutral shoes (n=22)	Motion control shoes (n=18)	Neutral shoes (n=22)	Motion control shoes (n=18)	Neutral shoes (n=22)	Mean difference (95% CI)	P-value
Primary outcome								
Average knee pain on walking (NRS)[b]	5.7 (1.1)	5.4 (1.0)	4.3 (2.2)	3.7 (2.2)	1.4 (2.1)	1.7 (2.1)	0.4 (-1.0, 1.7)	0.60
Secondary outcomes								
KOOS sub-scales[c]:								
i) Physical function	61.0 (16.0)	63.0 (14.7)	71.2 (15.4)	71.0 (14.3)	-10.2 (14.5)	-8.0 (11.4)	1.6 (-5.8, 8.9)	0.67
ii) Pain	52.5 (11.3)	55.1 (12.8)	63.0 (14.3)	64.1 (12.1)	-10.5 (14.8)	-9.1 (15.3)	-0.4 (-8.6, 7.8)	0.92
iii) Sport and recreation	24.7 (18.3)	28.0 (22.9)	31.1 (24.6)	39.3 (16.4)	-6.4 (27.1)	-11.4 (25.9)	-7.8 (-20.8, 5.3)	0.24
iv) Knee-related quality-of-life	32.6 (13.0)	34.1 (14.3)	37.5 (18.8)	44.3 (17.3)	-4.9 (18.1)	-10.2 (17.1)	-6.1 (-16.8, 4.5)	0.26
v) Patellofemoral pain and OA	33.2 (16.1)	33.5 (15.3)	40.2 (20.7)	44.1 (15.6)	-6.9 (21.0)	-10.6 (15.0)	-3.9 (-14.4, 6.6)	0.47
Quality of life (AQoL-6D)[c]	0.80 (0.10)	0.76 (0.10)	0.81 (0.10)	0.78 (0.12)	-0.01 (0.13)	-0.02 (0.06)	0.00 (-0.05, 0.06)	0.90
Physical Activity Scale for the Elderly (PASE)[c]	186.5 (78.5)	177.9 (91.8)	177.0 (84.1)	202.5 (89.4)	9.5 (85.7)	-24.6 (51.5)	-32.2 (-73.1, 8.7)	0.12

[a] Difference is adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade).

[b] For change within groups, positive changes indicate improvement. For difference in change between groups, negative differences favour motion control shoes.

[c] For change within groups, negative changes indicate improvement. For difference in change between groups, positive differences favour motion control shoes.

AQoL = Assessment of Quality of Life instrument (-0.04 to 1.0; higher scores indicate better quality of life); CI = confidence intervals; KOOS = Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicating worse pain/symptoms/function/quality-of-life); NRS = numerical rating scale (0-10; higher scores indicate worse pain); OA = osteoarthritis; PASE = Physical Activity Scale for the Elderly (0 to over 400, with higher scores indicating higher physical activity); SD = standard deviation.

Secondary outcomes

Table 3 summarizes continuous secondary outcomes across time by group and presents change in continuous secondary outcomes within and between groups. There was no evidence that motion control shoes were superior to neutral shoes for any continuous secondary outcome. Similar proportions (considering our small sample size) of participants reported global improvement across groups (Table 4), with no significant difference between groups in the relative risk of improvement in pain (1.36, 95% CI 0.61 to 3.01, p=0.45) or function (1.43, 95% CI 0.50 to 4.10, p=0.50). The number of participants achieving the MCID of 1.8 NRS units in pain, and the relative risk of achieving the MCID, was also similar between groups (1.28, 95% CI 0.74 to 2.24, p=0.38) (Table 4).

Table 4: Number (percentage) of participants reporting global improvement or achieving an improvement of 1.8 NRS units in the primary outcome (change in knee pain on walking (baseline minus 6 months)), and relative risks[a] and risk differences[a].

	Motion control shoes (n=18)	Neutral shoes (n=22)	Relative risk (95% CI)[b]	P-value	Risk difference (95% CI)[c]	P-value
Improved pain[d]	6/18 (33)	10/22 (46)	1.36 (0.61, 3.01)	0.45	0.12 (-0.18, 0.42)	0.44
Improved function[d]	4/18 (22)	7/22 (32)	1.43 (0.50, 4.10)	0.50	0.10 (-0.18, 0.37)	0.49
Improvement ≥1.8 NRS units[e]	9/18 (50)	14/22 (64)	1.28 (0.74, 2.24)	0.38	0.14 (-0.16, 0.44)	0.36

[a] Relative risk and risk difference adjusted for radiographic severity (Kellgren & Lawrence Grade).
[b] Relative risks <1 favour motion control shoe group.
[c] Risk differences <0 favour motion control shoe group.
[d] Rated using 7-point scales with terminal descriptors of 'much worse' to 'much better', with participants indicating 'moderately better' or 'much better' classified as improved.
[e] Improvement ≥1.8 NRS units chosen as this is the minimum clinically important difference in the primary outcome, change in knee pain on walking (baseline – 6 months).
CI = confidence intervals; NRS = numerical rating scale.

Subgroup analyses

The effect of allocated shoe group on the primary outcome of walking knee pain was not found to be moderated by any of the pre-specified variables of radiographic disease severity, Foot Posture Index, radiographic knee alignment or KOOS patellofemoral pain and OA subscale score (Appendix Tables 5 and 6).

DISCUSSION

This RCT found that motion control shoes were not superior at reducing knee pain on walking than neutral shoes in people with lateral knee OA. Average within group changes failed to demonstrate clinically-meaningful improvements in knee pain for either footwear group. Motion control shoes were not superior to neutral shoes for any secondary outcome, and a

similar proportion of participants in each group reported global improvements in pain (motion control 33% vs neutral 46%) and function (motion control 22% vs neutral 32%) and achieved the MCID in NRS walking pain (motion control 50% vs neutral 64%). However, we had reduced power (57.8%) to detect the MCID in between-group difference in change in our primary outcome as we did not reach our intended sample size, which may explain our findings. Albeit, the observed effect estimate was well below what is considered clinically meaningful, and the MCID was not contained within the 95% confidence intervals. These findings provide preliminary evidence to suggest motion control shoes may not be beneficial at reducing symptoms associated with predominantly lateral knee OA compared with neutral shoes. However, adequately-powered clinical trials are required to confirm our results.

Although no previous clinical trial has investigated the effects of footwear in people with lateral knee OA, our findings are not consistent with the only other similar trial conducted, which evaluated shoe insoles over 8 weeks. In a previous RCT with a smaller sample size than ours (n=30), medially wedged insoles, but not flat neutral insoles, significantly reduced knee pain with movement (mean (SD) baseline and 8 weeks values for medial wedges: 8.1 (1.5) to 4.2 (2.4); flat insoles: 6.9 (2.6) to 6.4 (2.7)) and at rest (medial wedges: 5.1 (2.3) to 2.7 (2.4); flat insoles: 3.3 (2.2) to 3.1 (2.5)) in women with lateral knee OA (18). However, average between-group differences were not reported in that study, thus it is possible that no significant between group differences were observed. Although adherence rates were not reported in that study, the different outcomes may also be due to the lower proportion of participants being classified as adherent wearing motion control shoes (56%) compared to neutral walking shoes (86%) in our study. We did not identify any between-group differences on the primary outcome when assuming full adherence, however these results assumed that participants had to wear motion control shoes for an average of >6 hours/day for 6 months in order to benefit from them. To

our knowledge, no study has investigated the symptomatic effects of knee bracing or any other biomechanical intervention in people with lateral TF joint OA.

Biomechanical research has demonstrated that motion control shoes (16), medially wedged insoles (37) and medial arch supports (38) redistribute knee joint loading toward the medial TF compartment, likely unloading the lateral TF compartment. The lack of symptomatic benefit with motion control shoes in our study could suggest that these shoes are not effective at unloading the lateral TF compartment, that joint load reductions are not enough to result in clinical meaningful reductions in pain, and/or that relationships between lateral TF joint loads and pain are not strong. Although there has been no research evaluating the relationship between lateral tibiofemoral joint loads and severity of knee pain in people with lateral tibiofemoral OA, previous research by us and others in medial compartment knee OA has shown limited, and at times conflicting, associations between knee pain and medial TF joint loads (39, 40). Thus it is perhaps not surprising that our previous RCT which tested footwear designed specifically to reduce medial TF loads found that they were not superior to conventional walking shoes at reducing walking knee pain in people with medial knee OA (34). Further research is needed to investigate associations between lateral TJ joint loads and knee pain severity in people with lateral knee OA, and whether interventions that produce larger reductions in knee load (for example, high tibial osteotomy and knee bracing) can effectively reduce knee pain in this population.

We failed to reach our intended sample size of 110 participants due to slow recruitment rates, impacting feasibility to complete the trial before funding was exhausted. This was largely because on-campus research was suspended at our university during 23 weeks of COVID-19-related lockdowns in 2020 in Australia. Nonetheless, it is worth highlighting that our

recruitment rate prior to trial suspension was very slow (2.5 participants enrolled per month) compared to our previous footwear trials in people with medial tibiofemoral OA (which enrolled 5.9-7.5 participants per month (34, 35)). The much slower recruitment rate in the current study reflects the lower prevalence of lateral (15%) compared to medial (27%) tibiofemoral OA in the community (41). It is also worth noting that, when recruiting people with lateral tibiofemoral OA from the community, x-ray screening costs can be substantial given that 58% of people recruited from community sources were excluded on the basis of not having a grade of lateral TF joint space narrowing that was greater than medial. In the present study, our most successful recruitment strategy was recruiting from our research database of volunteers, which included participants who had already undergone x-rays for our prior trials and were known to have lateral tibiofemoral OA. In fact, 93% (37/40 participants) of our final sample were recruited this way (Figure 1), and our recruitment of only 3 participants from the 206 people screened from the community resulted in a recruitment rate of only 1.46% from this source. Thus, to recruit the final 70 participants from the community would have required screening an additional 1,522 participants. Future studies should take these recruitment rates into consideration when planning clinical trials in people with predominantly lateral knee OA.

Despite our small sample size, our study is the first to assess any type of footwear for people with predominantly lateral knee OA. Our findings will be important for researchers undertaking meta-analyses of biomechanical interventions for knee OA (42), and in particular, will yield unique data to evaluate efficacy of interventions in the under-researched subgroup of people with lateral tibiofemoral OA. Thus, our findings also have the potential to influence knee OA clinical guidelines, most of which advocate footwear use on the basis of expert opinion alone due to the dearth of footwear RCTs in knee OA (2, 6). Other strengths include our robust RCT design and use of outcome measures recommended for knee OA clinical trials, blinded

participants and assessors, excellent retention, and the inclusion of sensitivity and moderator analyses. There were also some limitations, the principal one being that our sample size was smaller than planned. As such, our trial had reduced statistical power to detect between-group differences. We evaluated a single motion control shoe model, thus our findings cannot be generalized to other motion control shoes. Similarly, the addition of medial wedges or arch support to the motion control shoes may exert greater symptomatic benefits than motion control shoes alone.

In conclusion, motion control shoes were not superior to neutral walking shoes for reducing walking knee pain in people with symptomatic lateral tibiofemoral joint OA. Given the limited clinical trial evidence in people with lateral knee OA, further research is needed to confirm the findings and to identify effective treatments for this important but under-researched subgroup of knee OA patients.

Footnotes

Data sharing statement: Data that support findings of this study are available from the corresponding author upon reasonable request.

Ethics statements:

Patient consent for publication: Consent obtained directly from patient(s)

Ethics approval: This study involves human participants, was approved by University of Melbourne Human Research Ethics Committee (#1852787) and registered with the Australian New Zealand Clinical Trials Registry (date registered 15 November 2018) and complied with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

476

477 Contributors: KLP and RSH conceived the idea for the study and KLP led the trial. KLP and
478 RSH designed the trial protocol with input from KLB, BM, PKC, FM, and KL. FM and KL
479 formulated and were responsible for the statistical analysis plan and conducted the statistical
480 analyses. KLP drafted the manuscript and all authors provided input and approved the final
481 version.

482

483 Funding statement: This study was funded by the National Health and Medical Research
484 Council (Project Grant #1124418). KLP is supported by a National Health & Medical
485 Research Council Emerging Leadership Investigator Grant (#1174229). KLB is supported by
486 a National Health & Medical Research Council Leadership Investigator Grant (#1174431).
487 RSH is supported by a National Health & Medical Research Council Senior Research
488 Fellowship (#1154217).

489

490 Competing interests: None

491

REFERENCES

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2018; 392: 1789-858.

2. National Clinical Guideline Centre. Osteoarthritis: Care and management in adults. Clinical guideline CG177. Methods, evidence and recommendations. London; National Institute for Health and Care Excellence 2014.

3. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage 2014; 22: 363-88.

4. Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006; 18: 514-8.

5. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis and Cartilage 2014; 22: 1833-9.

6. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Annals of the Rheumatic Diseases 2013; 72: 1125-35.

7. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty): Published August 31, 2021; 2021 [Accessed October 21, 2021]. Available from: https://www.aaos.org/oak3cpg.

8. Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. Annals of the Rheumatic Diseases 1993; 52: 520-6.

9. Fascingbauer M, Renner L, Waldstein W, Boettner F. Are lateral compartment osteophytes a predictor for lateral cartilage damage in varus osteoarthritic knees?: Data from the Osteoarthritis Initiative. . Bone Jt J 2015; 97B: 1634-9.

10. Cotofana S, Buck R, Wirth W, Roemer F, Duryea J, Nevitt M, et al. Cartilage thickening in early radiographic knee osteoarthritis: a within-person, between-knee comparison. . Arthritis Care Res 2012; 64: 1681-90.

11. Yamabe E, Ueno T, Miyagi R, Watanabe A, Guenzi C, Yoshioka H. Study of surgical indication for knee arthroplasty by cartilage analysis in three compartments using data from Osteoarthritis Initiative (OAI). . BMC Musculoskelet Disord 2013; 14: 194.

12. Nagaosa Y, Lanyon P, Doherty M. Characterisation of size and direction of osteophyte in knee osteoarthritis: a radiographic study. Ann Rheum Dis 2002; 61: 319-24.

13. Iijima H, Aoyama T, Nishitani K, Ito H, Fukutani N, Isho T, et al. Coexisting lateral tibiofemoral osteoarthritis is associated with worse knee pain in patients with mild medial osteoarthritis. Osteoarthritis Cartilage 2017; 25: 1274-81.

14. Bennell KL, Kean CO, Wrigley TV, Hinman RS. Effects of a modified shoe on knee load in people with and without knee osteoarthritis. Arthritis Rheum 2013; 65: 701-9.

15. Paterson KL, Bennell KL, Wrigley TV, Metcalf BR, Kasza J, Hinman RS. Effects of footwear on the knee adduction moment in medial knee osteoarthritis: classification criteria for flat flexible vs stable supportive shoes. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2017; 25: 234-41.

16. Radzimski AO, Mundermann A, Sole G. Effect of footwear on the external knee adduction moment - A systematic review. The Knee 2012; 19: 163-75.

17. Sawada T, Kito N, Yukimune M, Tokuda K, Tanimoto K, Anan M, et al. Biomechanical effects of lateral and medial wedge insoles on unilateral weight bearing. J Phys Ther Sci 2016; 28: 280-5.

18. Rodrigues PT, Ferreira AF, Pereira RMR, Bonfá E, Borba EF, Fuller R. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. Arthritis Care & Research 2008; 59: 603-8.

19. Paterson KL, Bennell KL, Metcalf BR, Campbell PK, Kasza J, Wrigley TV, et al. Footwear for osteoarthritis of the lateral knee: protocol for the FOLK randomised controlled trial. BMC Musculoskeletal Disorders 2020; 21: 247.

20. Kellgren JH, Jeffrey MR, Ball J. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs. Oxford: Blackwell Scientific; 1963.

21. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007; 15: A1-56.

22. Bellamy N. Osteoarthritis clinical trials: candidate variables and clinimetric properties. Journal of Rheumatology 1997; 24: 768-78.

23. Bellamy N. Outcome measurement in osteoarthritis clinical trials. Journal of Rheumatology 1995; 22: 49-51.

24. Bellamy N, Carette S, Ford PM, Kean WF, le Riche NG, Lussier A, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials--results of a consensus development (Delphi) exercise. The Journal of rheumatology 1992; 19: 451-7.

25. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. Journal of Orthopaedic & Sports Physical Therapy 1998; 28: 88-96.

26. Osborne RH, Hawthorne G, Lew EA, Gray LC. Quality of life assessment in the community-dwelling elderly: validation of the Assessment of Quality of Life (AQoL) Instrument and comparison with the SF-36. Journal of clinical epidemiology 2003; 56: 138-47.

27. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger Jr W, Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Medicine and science in sports and exercise 1999; 31: 627-33.

28. ten Klooster PM, Drossaers-Bakker KW, Taal E, van de Laar MA. Patient-perceived satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's perspective. Pain 2006; 121: 151-7.

29. Hsu R, Himeno S, Coventry M, Chao E. Normal axial alignment of the lower extremity and load-bearing distribution at the knee. Clinical Orthopaedics and Related Research 1990; 255: 215-27.

30. Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis and Rheumatism 1989; 32: 37-44.

31. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: The Foot Posture Index. Clinical Biomechanics 2006; 21: 89-98.

32. McPoil T, Vicenzino B, Cornwall M, Collins N, Warren M. Reliability and normative values for the foot mobility magnitude: a composite measure of vertical and medial-lateral mobility of the midfoot. Journal of Foot and Ankle Research 2009; 2: 6.

33. Brody DM. Techniques in the evaluation and treatment of the injured runner. The orthopedic clinics of north America 1982; 13: 541.

34. Hinman RS, Wrigley TV, Metcalf BR, Campbell PK, Paterson KL, Hunter DJ, et al. Unloading shoes for self-management of knee osteoarthritis: a randomized trial. Annals of internal medicine 2016; 165: 381-9.

35. Paterson KL, Bennell KL, Campbell PK, Metcalf BR, Wrigley TV, Kasza J, et al. The effect of flat flexible versus stable supportive shoes on knee osteoarthritis symptoms: a randomized trial. Annals of internal medicine 2021; 174: 462-71.

36. Maracy M, Dunn G. Estimating dose-response effects in psychological treatment trials: the role of instrumental variables. Statistical Methods in Medical Research 2011; 20: 191-215.

37. Schmalz T, Blumentritt S, Drewitz H, Freslier M. The influence of sole wedges on frontal plane kinetics, in isolation and in combination with representative rigid and semi-rigid ankle-foot-orthoses. Clinical Biomechanics 2006; 21: 631-9.

38. Franz JR, Dicharry J, Riley PO, Jackson K, Wilder RP, Kerrigan DC. The influence of arch supports on knee torques relevant to knee osteoarthritis. Medicine & Science in Sports & Exercise 2008; 40: 913-7.

39. Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. Journal of Orthopaedic Research 2002; 20: 101-7.

40. Hall M, Bennell KL, Wrigley TV, Metcalf BR, Campbell PK, Kasza J, et al. The knee adduction moment and knee osteoarthritis symptoms: relationships according to radiographic disease severity. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2017; 25: 34-41.

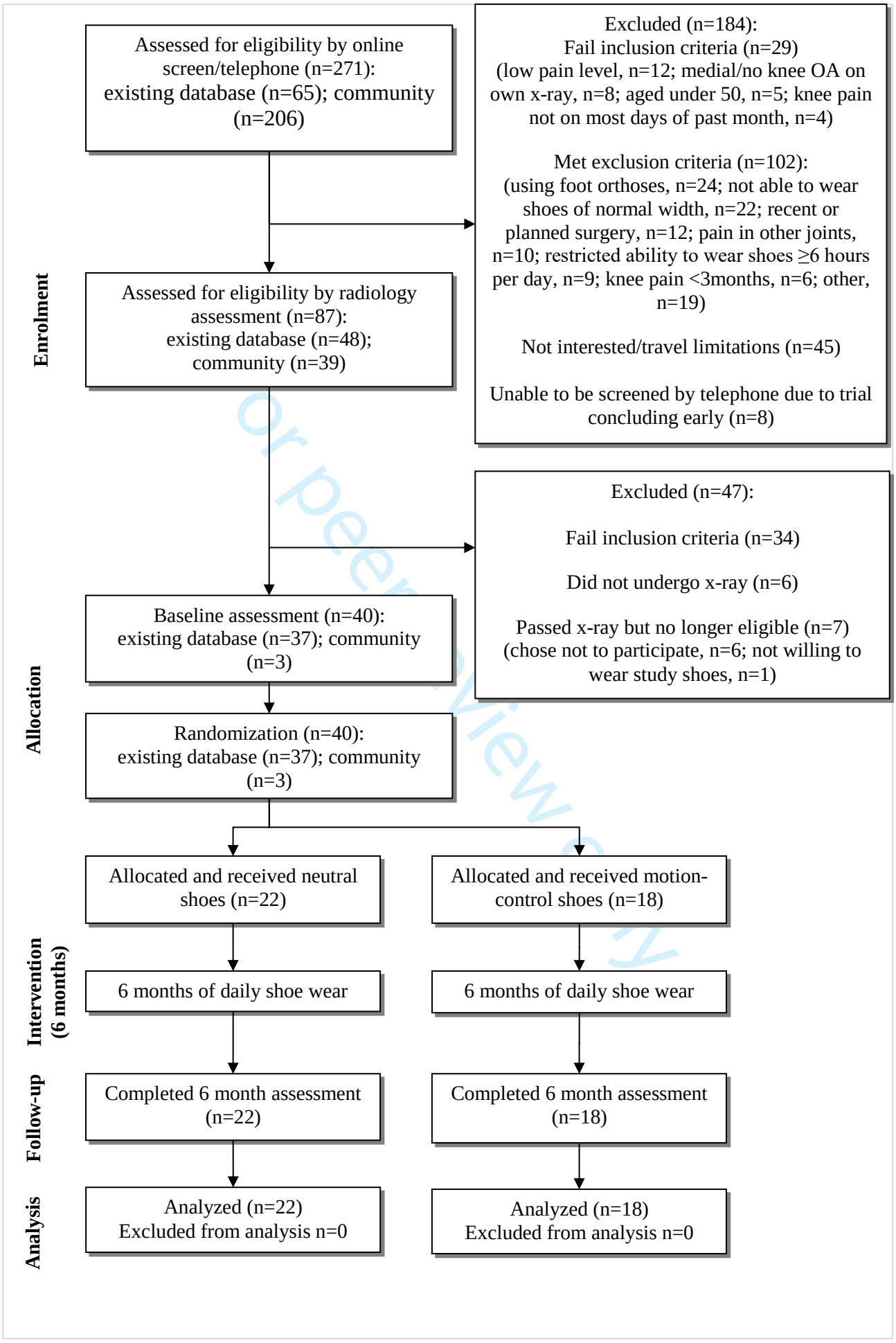
41. Stoddart JC, Dandridge O, Garner A, Cobb J, van Arkel RJ. The compartmental distribution of knee osteoarthritis – a systematic review and meta-analysis. Osteoarthritis and Cartilage 2021; 29: 445-55.

42. Macri EM, Callaghan M, van Middelkoop M, Hattle M, Bierma-Zeinstra SMA. Effects of mechanical interventions in the management of knee osteoarthritis: protocol for an

614 OA Trial Bank systematic review and individual participant data meta-analysis. BMJ Open
615 2021; 11: e043026.

Figures

Figure 1. Flow of participants through the trial.



Appendix Table 1. Motion control features of participants' usual shoes, reported as number (%) unless otherwise stated.

	Motion control shoes (n=18)	Neutral shoes (n=22)
Multiple density midsole	6 (33)	5 (23)
Fixation		
Laces	12 (67)	16 (73)
Straps/buckles	3 (17)	1 (5)
Velcro	1 (6)	1 (5)
None	2 (11)	4 (18)
Heel counter stiffness		
Rigid	7 (39)	13 (59)
Moderate	3 (17)	4 (18)
Minimal	6 (33)	4 (18)
No heel counter	2 (11)	1 (5)
Midfoot sagittal stability		
Rigid	6 (33)	4 (18)
Moderate	1 (6)	2 (9)
Minimal	11 (61)	16 (73)
Midfoot torsional stability		
Rigid	11 (61)	16 (73)
Moderate	4 (22)	3 (14)
Minimal	3 (17)	3 (14)
Overall motion control feature score, mean (SD)[a]	6.2 (3)	6.4 (3)

[a] Measured using the Footwear Assessment Tool; scores range 0 to 11, with higher scores indicating more motion control features.

SD = standard deviation.

Appendix Table 2. Adherence to allocated footwear across groups.

	Motion control shoes[a]	Neutral shoes[b]
Shoe wear in log books (hours/day), mean (SD):		
Month 1	7.1 (2.2)	7.9 (2)
Month 2	7.1 (4.0)	8.5 (3)
Month 3	7.0 (4.3)	7.8 (3)
Month 4	6.6 (3.7)	8.1 (2)
Month 5	7.5 (3.9)	7.4 (3)
Month 6	7.7 (3.9)	8.0 (3)
Overall	7.0 (3.4)	8.0 (2)
Participants classified as adherent[c], n (%):		
Month 1	13 (72)	19 (86)
Month 2	10 (59)	18 (82)
Month 3	11 (61)	18 (82)
Month 4	10 (59)	18 (82)
Month 5	12 (75)	15 (71)
Month 6	12 (80)	18 (86)
Overall[d]	10 (56)	19 (86)
Self-rated adherence with allocated footwear over 6 months (NRS), mean (SD)	7.9 (2.8)	8.5 (1.9)

[a] n=17 for shoe wear and participants classified as adherent at month 2 and month 4; n=16 for shoe wear and participants classified as adherent at month 5; n=15 for shoe wear and participants classified as adherent at month 6; n=18 for all other outcomes.
[b] n=21 for shoe wear and participants classified as adherent at month 5 and month 6; n=22 for all other outcomes.
[c] Adherent defined as an average of ≥ 6 hours/day shoe wear for that month;
[d] Overall are participants who averaged ≥ 6 hours/day shoe wear over 6 months.
NRS = numerical rating scale, where 0 = shoes not worn at all and 10 = worn completely as instructed;
SD = standard deviation.

Appendix Table 3. Reasons for participants to cease wearing shoes over the course of the trial, reported as number (%).

	Motion control shoes (n=18)	Neutral shoes (n=22)
Fractured ankle (unrelated to shoes)	1[a] (6)	0 (0)
Total	1 (6)	0 (0)

[a] Participant ceased wearing shoes in month 2.

Appendix Table 4: Difference[a] in change between groups, for the primary outcome, change in knee pain on walking (baseline – 6 months), assuming full adherence[b] (N=40).

	Difference in change between groups Baseline to 6 months	
	Mean difference (95% CI)	**P-value**
Knee pain on walking (NRS)[c]	0.6 (-1.7, 2.9)	0.59

[a] The complier average causal effect difference, adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade).

[b] The treatment effect on the primary outcome assuming full adherence (where full adherence was defined as an average of ≥ 6 hours/day shoe wear over 6 months) was estimated using an instrumental variables approach (where randomization was the instrument for adherence).[c] For difference in change between groups, negative differences favour motion control shoe group.

CI=confidence intervals; NRS=numerical rating scale (0-10; higher scores indicate worse pain).

Appendix Table 5: Results of the moderation analysis for radiographic disease severity (Kellgren & Lawrence Grade) as a potential binary moderator for the primary outcome, change in knee pain on walking, using complete case data.[a]

	Mean (SD) Motion control shoes[b]	Neutral shoes[c]	Neutral shoes – motion control shoes Mean difference[d] (95% CI)	Interaction P-value
Radiographic disease severity				0.70
Grade 2 (mild) or 3 (moderate)	1.50 (2.37)	1.69 (2.46)	0.16 (-1.65, 1.96)	
Grade 4 (severe)	1.38 (1.92)	1.78 (1.72)	0.73 (-1.44, 2.90)	

[a] Presented as the mean scores on the primary outcome, change in average knee pain on walking (baseline – 6 months), in each group in each radiographic disease severity category, as well as in terms of the estimated mean difference in effect between groups (neutral shoes – motion control shoes) on the primary outcome in each radiographic disease severity category, adjusted for the outcome at baseline.
[b] n=10 for Grade 2 or 3; n=13 for Grade 4;
[c] n=8 for Grade 2 or 3; n=9 for Grade 4.
[d] Negative differences favour motion control shoes.
CI=confidence intervals; SD=standard deviation.

Appendix Table 6: Results of the moderation analysis for potential continuous moderators for the primary outcome, change in knee pain on walking, using complete case data[a].

Potential Moderator[b] (taken at baseline)	Motion control shoes Moderator Coeff. (95% CI)	P-value	Neutral shoes Moderator Coeff. (95% CI)	P-value	Difference[c] in coefficients, Neutral shoes – motion control shoes (95% CI)	Interaction P-value
Foot Posture Index[d]	0.09 (-0.29, 0.46)	0.64	0.11 (-0.15, 0.37)	0.41	0.02 (-0.44, 0.48)	0.92
Radiographic knee alignment (degrees)	0.15 (-0.03, 0.34)	0.11	-0.08 (-0.27, 0.12)	0.42	-0.23 (-0.49, 0.03)	0.085
KOOS sub-scale:						
Patellofemoral pain and OA	0.03 (-0.04, 0.10)	0.33	0.06 (-0.01, 0.13)	0.097	0.02 (-0.06, 0.11)	0.58

[a] Presented in terms of the estimated mean effect on the primary outcome, change in average knee pain on walking (baseline – 6 months), of a one-unit increase in the potential moderator in each of the motion control shoe group and neutral shoe group, adjusted for the outcome at baseline and radiographic severity (Kellgren & Lawrence Grade 2, 3 or 4).
[b] n=32 for radiographic knee alignment, n=40 for all other potential moderators.
[c] Negative differences favour motion control shoes.
[d] Scored from -12 to 12; higher scores indicating a more pronated foot posture.
CI=confidence intervals; KOOS = Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicating worse pain/patellofemoral problems); OA = osteoarthritis.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	11
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	13
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 5
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Appendix tables
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Appendix
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.