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

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ABSTRACT

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

Design Participant-blinded and assessor-blinded, comparative effectiveness, superiority randomised controlled trial.

Setting Melbourne, Australia.

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

Intervention Participants were randomised to receive either motion control or neutral shoes and advised to wear them >6 hours/day over 6 months.

Primary and secondary outcome measures The primary outcome was change in average knee pain on walking over the previous week (11-point Numeric Rating Scale (NRS), 0–10) at 6 months. The 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.

Conclusions Motion control shoes were not superior to neutral shoes in 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 number ACTRN12618001864213.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used a robust randomised 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 and 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 lack of robust clinical trials in this area, international OA organisations 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 patients with knee OA have radiographic OA changes in the lateral TF joint,[8–12] and there is evidence that

coexisting 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 with medial TF OA, there is scant research evaluating non-surgical treatments for people with lateral TF 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 randomised 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 with 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 in improving symptoms in people with lateral knee OA. We hypothesised that wearing motion control shoes would lead to greater reductions in walking knee pain, compared with wearing neutral walking shoes, over 6 months.

PATIENTS AND METHODS

Design

This was a two-arm, participant-blinded and assessor-blinded, pragmatic, comparative effectiveness, superiority RCT. It was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001864213) and the protocol has been published.[19] 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 an average knee pain on walking over the previous week of >4 on an 11-point Numeric Rating Scale (NRS); had mild, moderate or severe radiographic knee OA (Kellgren and Lawrence (KL) grade 2–4)[20]; and had a grade of lateral TF joint space narrowing that was greater than the 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, customised shoes or other shoes worn regularly that would restrict their ability to wear the allocated study shoes for a minimum of 6 hours/day (eg, 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 randomised in a 1:1 ratio. The randomisation schedule was prepared by a biostatistician with permuted block sizes of 6–12 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 (ie, motion control and neutral shoes) under investigation. As participants were blinded and the primary and secondary outcomes were self-reported, this trial was also assessor-blinded. The biostatisticians were blinded to all analyses.

Interventions

Motion control shoes

Black ASICS Gel-Kayano 25 shoes were chosen as the motion control shoes. These shoes have a dual density midsole which is stiffer medially compared with 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 shoes were the neutral comparator shoes. These shoes have a uniformly stiff midsole and are visually similar to the motion control shoes. They are also similar in 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 2 hours on the first day and to increase wear time by 2 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 the 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 the terminal descriptors '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]

The secondary outcomes included changes in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of (1) physical function, (2) pain, (3) sport and recreation, (4) knee-related quality of life, and (5) 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[27] (scored from 0 to over 400; higher scores indicate higher activity). We also assessed patient-perceived global rating of change in (1) pain and (2) function at 6 months, each measured using 7-point Likert scales, with the terminal descriptors '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, with higher scores indicating 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 0–11, with higher scores indicating 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 1 week of every month, on logbooks. Those who averaged >6 hours/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/day using an 11-point NRS (with the terminal descriptors '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 SD 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 a 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 the 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 walking knee pain, with treatment group, outcome at baseline and stratifying variable (KL grade) as covariates. The results were calculated as the estimated mean (95% 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 randomised, estimated the complier average causal effects, which are the treatment effects on the primary outcome, assuming full adherence to shoe wear (classified as an average of >6 hours/day for 6 months, based on logbook data), using an instrumental variables approach (where randomisation was the instrument for adherence).[36] Two-stage least squares models were fit: first, a model for observed adherence, including terms for randomised 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 achievement of the MCID

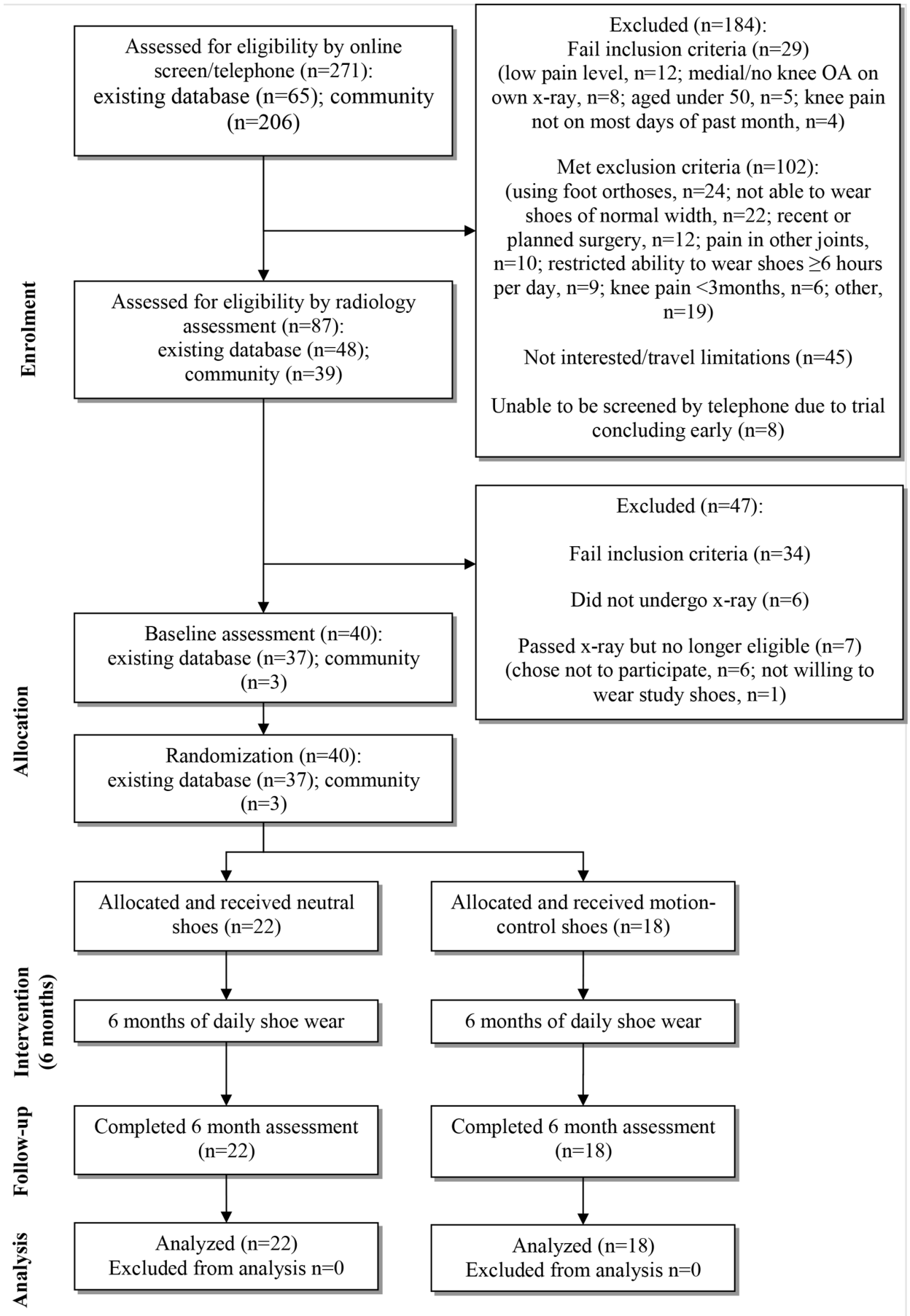

Figure 1 Flow of participants through the trial. OA, osteoarthritis.

Table 1 Baseline characteristics of participants by group

	Motion control shoes (n=18)	Neutral shoes (n=22)
Age (years)	64.6 (7.2)	64.2 (7.2)
Gender, n (%)		
Female	11 (61)	13 (59)
Male	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 osteoarthritis symptoms, n (%)	3 (17)	7 (32)
Radiographic disease severity, n (%)*		
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)†	188.7 (6.3)	188.1 (5.5)
Foot Posture Index classification, n (%)‡		
Supinated	0 (0)	1 (5)
Neutral	3 (17)	8 (36)
Pronated	15 (83)	13 (59)
Foot mobility magnitude (mm)§	7.7 (3.5)	7.7 (2.5)
Navicular drop (mm)§	6.5 (4.4)	6.3 (3.0)
Currently employed, n (%)	10 (56)	11 (50)
Current drug/supplement use, n (%)¶	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**	6.4 (2.1)	6.3 (1.5)
Cointerventions 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)††	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)
Expectation of treatment, after shoe allocation, n (%)		
No change	0 (0)	0 (0)

Continued

Table 1 Continued

	Motion control shoes (n=18)	Neutral shoes (n=22)
Mild improvement	1 (6)	2 (9)
Moderate improvement	12 (67)	13 (59)
Large improvement	5 (28)	6 (27)
Complete recovery	0 (0)	1 (5)

Data reported as mean (SD) unless otherwise stated.
IQR in 25th–75th percentile.
*Using the Kellgren and Lawrence grading system.
†Measured as anatomical axis from standing radiograph, with 180° indicating neutral alignment, <180° varus alignment and >180° valgus alignment.
‡Scored from −12 to 12; scores <0 indicate supinated foot posture, 0–5 neutral foot posture and >5 pronated foot posture.
§Higher values indicate greater mobility/drop.
¶Defined as at least once per week in the last 6 months.
**Scores range 1–10, with higher scores indicating higher self-efficacy.
††Measured using the Footwear Assessment Tool; scores range 0–11, with higher scores indicating more motion control features.

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 (1) Foot Posture Index score, (2) knee alignment or (3) 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, relevant potential moderator and KL grade as covariates, including an interaction between treatment group and the potential moderator. Statistical analyses were performed using Stata V.16.1. The a priori statistical analysis plan is provided in the online supplemental file appendix 2.

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 enrollees (from 65 screened) vs 3 recruited (from 196 screened) via advertising in the community). Due to COVID-19 causing extended lockdowns in Melbourne, Australia (totalling 23 weeks between 30 March and 12 May 2020 and between 8 July and 27 October 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 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%). Participants' own usual footwear were similar across groups with respect to motion control features (table 1 and online supplemental appendix table 1), suggesting that on average people wore shoes with moderate amounts of motion control features. Treatment expectations were generally similar across groups prerandomisation and following shoe allocation (table 1).

Adherence and adverse events

The 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 (online supplemental appendix table 2). Ten participants (56%) were classified as adherent over 6 months with motion control shoes compared with 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 2 Adverse events and cointerventions at follow-up according to group

	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*	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)
Cointerventions 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)

Data presented as number (%) of participants.
*Defined as at least once per week in the last 6 months.

(table 1) and follow-up (table 2). One participant (6%) ceased wearing their motion control shoes due to a fractured ankle which was unrelated to the footwear (online supplemental appendix table 3).

Primary outcome

Table 3 summarises 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 (online supplemental appendix table 4).

Secondary outcomes

Table 3 summarises the 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 were also similar between groups (1.28, 95% CI 0.74 to 2.24, p=0.38) (table 4).

Subgroup analyses

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

DISCUSSION

This RCT found that motion control shoes were not superior to neutral shoes in reducing knee pain on walking in people with lateral knee OA. The average within-group changes failed to demonstrate clinically meaningful improvements in knee pain for either group of footwear. 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 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, although the observed effect estimate was well below what is considered clinically meaningful and the MCID was not contained within the 95% CIs. These findings provide preliminary evidence to suggest motion control shoes may not be beneficial in 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-week values for medial wedges: from 8.1 (1.5) to 4.2 (2.4); flat insoles: from 6.9 (2.6) to 6.4 (2.7)) and at rest (medial wedges: from 5.1 (2.3) to 2.7 (2.4); flat insoles: from 3.3 (2.2) to 3.1 (2.5)) in women with lateral knee OA.[18] However, the average between-group differences were not reported in that study and thus it is possible that no significant between-group differences were observed. Although adherence rates were not

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

	Baseline		6 months		Mean (SD) change within groups: Baseline minus 6 months		Difference in change between groups*: 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)†	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 to 1.7)	0.60
Secondary outcomes								
KOOS subscales‡								
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 to 8.9)	0.67
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 to 7.8)	0.92
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 to 5.3)	0.24
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 to 4.5)	0.26
Patellofemoral pain and osteoarthritis	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 to 6.6)	0.47
Quality of life (AQoL-6D)‡	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 to 0.06)	0.90
PASE‡	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 to 8.7)	0.12

*Difference is adjusted for the outcome at baseline and radiographic severity (Kellgren and Lawrence grade).
†For change within groups, positive changes indicate improvement. For difference in change between groups, negative differences favour the motion control shoes.
‡For change within groups, negative changes indicate improvement. For difference in change between groups, positive differences favour the motion control shoes.
AQoL, Assessment of Quality of Life (–0.04 to 1.0; higher scores indicate better quality of life); KOOS, Knee Injury and Osteoarthritis Outcome Score (0 to 100; lower scores indicate worse pain/symptoms/function/quality of life); NRS, Numeric Rating Scale (0–10; higher scores indicate worse pain); PASE, Physical Activity Scale for the Elderly (0 to over 400; higher scores indicate higher physical activity).

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* and risk differences*

	Motion control shoes (n=18)	Neutral shoes (n=22)	Relative risk (95% CI)†	P value	Risk difference (95% CI)‡	P value
Improved pain§	6/18 (33)	10/22 (46)	1.36 (0.61 to 3.01)	0.45	0.12 (–0.18 to 0.42)	0.44
Improved function§	4/18 (22)	7/22 (32)	1.43 (0.50 to 4.10)	0.50	0.10 (–0.18 to 0.37)	0.49
Improvement >1.8 NRS units¶	9/18 (50)	14/22 (64)	1.28 (0.74 to 2.24)	0.38	0.14 (–0.16 to 0.44)	0.36

*Relative risk and risk difference adjusted for radiographic severity (Kellgren and Lawrence grade).
†Relative risks <1 favour the motion control shoe group.
‡Risk differences <0 favour the motion control shoe group.
§Rated using 7-point scales with the terminal descriptors 'much worse' to 'much better', with participants indicating 'moderately better' or 'much better' classified as improved.
¶Improvement of >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).
NRS, Numeric Rating Scale.

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 with neutral walking shoes (86%) in our study. We did not identify any between-group differences in 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 towards 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 in 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 TF joint loads and severity of knee pain in people with lateral TF OA, previous research by us and others on 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 in reducing walking knee pain in people with medial knee OA.[34] Further research is needed to investigate the associations between lateral TF joint loads and knee pain severity in people with lateral knee OA and whether interventions that produce larger reductions in knee load (eg, 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 with our previous footwear trials in people with medial TF 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 with medial (27%) TF OA in the community.[41] It is also worth noting that, when recruiting people with lateral TF 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 the 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 TF OA. In fact, 93% (37 of 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 1522 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 the efficacy of interventions in the under-researched subgroup of people with lateral TF 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 the 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 and thus our findings cannot be generalised 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 in reducing walking knee pain in people with symptomatic lateral TF 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 patients with knee OA.

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Contributors KLP and RSH conceived the idea for the study. KLP led the trial. KLP and RSH designed the trial protocol, with input from KLB, BM, PKC, FM and KEL. FM and KEL 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. KLP accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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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)		Neutral shoes – motion control shoes	Interaction P-value
	Motion control shoes[b]	Neutral shoes[c]	Mean difference[d] (95% CI)	
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.

Statistical Analysis Plan (SAP)

Footwear for Osteoarthritis of the Lateral Knee: the FOLK Trial

Contents

Paterson KL, *et al. BMJ Open* 2022; 12:e061627. doi: 10.1136/bmjopen-2022-061627

Section 1. Administrative Information

1. Title

Footwear for Osteoarthritis of the Lateral Knee: the FOLK Trial

2. Trial registration

This trial has been prospectively registered by the Australian New Zealand Clinical Trials Registry on 15/11/2018 (reference: ACTRN12618001864213).

3. SAP version

Version: 1.0 Date: 12 July 2021

4. Protocol Version

This document has been written based on information contained in the FOLK study protocol version 1.0 dated 23/10/18. The protocol was published as follows:

Paterson, K. L., Bennell, K. L., Metcalf, B. R., Campbell, P. K., Kasza, J., Wrigley, T. V., & Hinman, R. S. (2020). Footwear for osteoarthritis of the lateral knee: protocol for the FOLK randomised controlled trial. *BMC Musculoskeletal Disorders, 21*(1), 247. doi:10.1186/s12891-020-03275-5.

5. SAP Revisions

Not applicable

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Signature of senior statistician responsible (Ms Fiona McManus): *Date: 28/6/2021*

Signature of chief investigator (Dr Kade Paterson): *Date: 29/2/2021*

Section 2: Introduction

7. Background and rationale

Osteoarthritis (OA) is the leading cause of musculoskeletal pain and disability in Australia and the knee joint is most often affected. Knee OA is extremely debilitating. Pain is dominant, becoming persistent and more limiting as OA progresses. The medial tibiofemoral (TF) compartment is more frequently affected by OA than the lateral compartment.[1] Nonetheless, structural features of lateral TF joint OA occur in 10-55% of cases of knee OA,[1-5] and research has shown that co-existing lateral TF OA is associated with worse knee pain in people with mixed compartmental OA.[6]

Knee OA is a chronic disease with no cure thus people with 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.[7,8] As abnormal biomechanics are central to disease pathogenesis,[9,10] clinical guidelines advocate clinicians provide advice on "appropriate" footwear as part of core treatment for knee OA.[7,11] However, there is scant evidence from clinical trials to guide footwear choice. Unfortunately, all research into footwear for OA has focussed on people with predominantly medial TF OA, and there are no randomised controlled trials (RCTs) evaluating the efficacy of any footwear for people with predominantly TF knee OA. This is a problem given that the biomechanics of people with lateral knee OA differ from those with medial knee OA,[12] and thus any evidence about (in)effectiveness of biomechanical treatments for medial TF OA cannot be directly translated to the lateral compartment.

There is indirect RCT evidence to suggest that "motion control" footwear, which possess medially stiff midsoles and arch support, may be beneficial for people with lateral TF OA. A single small RCT showed improvements in pain and function with medially-wedged foot orthoses compared to neutral insoles in 30 women with predominantly lateral TF OA and bilateral valgus deformity.[13] There have been no RCTs testing the efficacy of motion control shoes on symptoms in people with predominantly lateral TF OA, and there is no evidence to inform clinical guidelines about which type of footwear is best for this important subgroup of patients with knee OA.

8. Objectives

Research hypothesis:

Primary alternative hypothesis: That motion-control walking shoes will lead to significantly greater reductions in knee pain with walking, compared to neutral walking shoes at 6 months.

Secondary alternative hypothesis: That motion-control walking shoes will have significantly greater benefits on other clinical outcomes (physical function, other measures of knee pain, global ratings of change, health-related quality of life, physical activity levels) compared to neutral walking shoes at 6 months.

Study objective:

Primary objective: To determine whether motion-control walking shoes lead to significantly greater reductions in knee pain with walking, compared to neutral walking shoes at 6 months.

Secondary objective: To determine whether motion-control walking shoes will have significantly greater benefits on other clinical outcomes (physical function, other measures of knee pain, global ratings of change, health-related quality of life, physical activity levels) compared to neutral walking shoes at 6 months.

Section 3: Trial Methods

9. Trial design

The FOLK trial is two-arm, superiority, participant- and assessor-blinded RCT. Participants are randomized to either motion-control walking shoes or neutral walking shoes.

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10. Randomisation

The randomisation schedule was prepared by the biostatistician (permuted block sizes 6 to 12) stratified by KL grade (2, 3 or 4). Treatment allocation was using a 1:1 ratio. The schedule was stored on a password-protected website (REDCap) maintained by a researcher not involved in either participant recruitment or administration of primary/secondary outcome measures. Group allocation was revealed by this same researcher after baseline primary/secondary outcomes were completed.

11. Sample size

We originally aimed to detect the minimal clinically important difference (MCID) in the primary outcome (change in severity of knee pain on walking (baseline minus follow up)) between groups (1.8 numerical rating scale (NRS) units). We conservatively assumed a between-subject standard deviation of 2.7 and a baseline to 6-month correlation of 0.21 based on previous similar trials.[14,15] Using analysis of covariance (ANCOVA) adjusted for baseline score, we needed 46 per arm to achieve 90% power to detect the MCID in the primary outcome. Allowing for 15% attrition, we aimed to recruit 55 people per arm in total (n=110).

However, due to COVID-19 restrictions in Melbourne (Australia) halting trial recruitment for a prolonged period of time and grant funding running out, the final total sample size was 40. Using ANCOVA adjusted for baseline score, we have 57.8% power to detect the MCID in change in severity of knee pain on walking (baseline minus follow up) with the final sample size of 40 participants (assuming 20 participants per arm).

12. Framework

This trial uses a superiority hypothesis-testing framework between groups for all outcomes.

13. Statistical interim analyses and stopping guidance

Nil

14. Timing of final analysis

Final analysis will be performed on the final total sample size of 40.

15. Timing of outcome assessments

Table 4.6 in the study protocol document details the timing of outcome assessments, the majority of which occur at baseline and at 6 months post-randomisation.

Section 4: Statistical Principles

16. Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

17. Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

We have one primary outcome (change in knee pain with walking over 6 months). We have several secondary outcomes (physical function, other measures of knee pain, global ratings of change, health-related quality of life, physical activity levels). All secondary outcomes are exploratory and not powered for. We will therefore not adjust for multiple secondary outcomes but instead report all effect sizes, confidence intervals, and p values in order to let readers use their own judgment about the relative weight of the conclusions on the effect of footwear (motion-control walking shoes versus neutral walking shoes) for change in knee pain on walking. This approach aligns with the usage of p-values favoured by the American Statistical Association.[16]

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18. Confidence intervals to be reported
All confidence intervals will be 95% confidence intervals.

19. Adherence and protocol deviations
The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally assigned, regardless of their adherence to their assigned treatments. Any protocol deviations (if they occurred), including errors applying inclusion/exclusion criteria and/or administration of the wrong intervention will be summarised in trial results (patient flow diagram/text) by treatment group. Randomisation errors resulting from these errors will be handled according to recommendations.[17]

Multiple measures of adherence are used in this trial (described in Table 4.6 of the study protocol document) and data from all measures will be reported using means, standard deviations and proportions (number and percentage) as appropriate for each treatment group.

In this study, participants were advised to wear their allocated footwear for at least 6 hours per day. Participants recorded the hours/day they wore their footwear daily for the fourth week of each month in log books. Adherence will be calculated as the average hrs/day spent wearing the study shoes recorded in each of the 6 log books. Participants will be classified as 'adherent' if they wear their footwear for an average of at least 6 hrs/day over 6 months, and all other participants classified as 'non-adherent'.

If a participant does not provide all log books, adherence will be calculated using the available completed log books. If a participant does not provide any log books, non-adherence will be assumed by performing no imputation for the missing adherence variable of average daily wear of allocated footwear.

20. Analysis populations
The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally randomised, regardless of their adherence to their assigned treatments.

Section 5: Trial Population

21. Screening Data
Screening data will be collected and summarized. A CONSORT flow diagram will be created.[18] The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of participants screened, the number of participants recruited, the number of screened participants not recruited, and the reasons for non-recruitment.

22. Eligibility
Trial inclusion and exclusion criteria are described in section 5.2 of the trial protocol document. Reasons for exclusion will be summarized in the CONSORT[18] flow diagram.

23. Recruitment
A CONSORT flow diagram[18] will be used to describe the number of people enrolled, randomised, allocated to each treatment group, lost to follow up (including reasons) and analysed.

24. Withdrawal/follow-up
If a participant withdraws from the study, the nature, timing of and reasons for withdrawal will be described (provided the participant responds to requests for information by the research team). Any data provided up to the point of withdrawal will be analysed in accordance with intention to treat analyses, unless the participant specifically requests to withdraw their data from the study. Losses to follow-up (including reasons)

will be summarised in the CONSORT flow diagram by treatment group.

25. Baseline characteristics

Baseline characteristics will be summarised by treatment group and presented in a table:

- Age
- Gender
- Height, body mass, body mass index
- Radiographic disease severity
- Duration of knee symptoms
- Anatomical knee alignment
- Current employment status
- Expectation of treatment outcome- pre and post randomisation
- Arthritis Self Efficacy Scale
- Co-intervention use
- Current footwear characteristics
- Foot posture index
- Foot mobility magnitude
- Navicular drop

Baseline characteristics will be summarised as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables). Tests of statistical significance will not be undertaken for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

If more than one participant is missing the primary outcome at 6 months, an appendix table will provide summaries of baseline characteristics and baseline levels of primary and secondary outcomes and compare these characteristics between two groups: those participants who provide primary outcomes at 6 months, and those participants who are missing primary outcomes.

Section 6: Analysis

26. Outcome definitions

Primary outcome:

- Change in severity of knee pain on walking: average knee pain intensity on walking in the last week was assessed at baseline and 6 months using an 11-point NRS with terminal descriptors of 'no pain' (score = 0) and 'worst pain possible' (score = 10). Change score at 6 months will be calculated as baseline minus follow-up.

Secondary outcomes:

- Change in overall knee pain (KOOS pain subscale): The pain subscale of the KOOS is scored using nine questions regarding knee pain over the previous week, with Likert response options for each question ranging from none/never (score = 0) to extreme/always (score = 4).[19] Scores are then transformed to provide an overall value that ranges from 0 to 100, with 0 representing extreme knee pain and 100 representing no knee pain. Change scores at 6 months will be calculated as baseline minus follow-up.

- Change in physical function (KOOS physical function subscale): The physical function subscale of the KOOS is used to assess limitations with physical functioning.[19] The subscale contains 17 questions on knee function over the past week, with Likert response options from none (score = 0) to extreme (score = 4). Total score ranges from 0 to 100, with lower scores indicating worse function. Change scores at 6 months will be calculated as baseline minus follow-up.

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- Change in sport and recreation activities (KOOS sport and recreation subscale): The sport and recreation subscale is assessed using five questions on function during sport and recreational activities over the previous week.[19] Likert responses for each question range from none (score = 0) to extreme (score =4). Scores are then transformed to provide an overall value that ranges from 0 to 100, with 0 representing extreme problems with sport and recreation and 100 representing no problems with sports and recreation. Change scores at 6 months will be calculated as baseline minus follow-up.

- Change in knee-related quality of life (KOOS quality of life subscale): This subscale is assessed using four questions on knee-related quality of life experienced in the previous week.[19] There are five Likert response options for each question, ranging from none/never/not at all (score = 0) to extreme/constantly/extremely (score = 4). Scores are then transformed to provide an overall value that ranges from 0 to 100, with 0 representing extreme problems with quality of life and 100 representing no problems with quality of life. Change scores at 6 months will be calculated as baseline minus follow-up.

- Change in patellofemoral pain and OA (KOOS patellofemoral pain and OA subscale): The patellofemoral pain and OA subscale includes 11 questions on knee pain and function experienced in the last week, each with five Likert response options, ranging from none/never/not at all (score = 0) to extreme/always/totally (score = 4).[19] Scores are then transformed to provide an overall value that ranges from 0 to 100, with 0 representing extreme patellofemoral problems and 100 representing no patellofemoral problems. Change scores at 6 months will be calculated as baseline minus follow-up.

- Global improvement at 6 months: Global improvement in i) pain and ii) physical function will each be scored using a 7-point global rating of change Likert scale with response options ranging from “much worse” to “much better” when compared to baseline. Participants indicating they are “moderately better” or “much better” will be classified as improved. All other respondents will be classified as not improved.

- Change in health-related quality of life: The AQoL questionnaire (version AQoL-6D) measures health-related quality of life.[20] This is a 20-item questionnaire and scores range from -0.04 to 1.00 with 1.00 indicating maximum health-related quality of life. Change scores at 6 months will be calculated as baseline minus follow-up.

- Change in physical activity: The Physical Activity Scale for the Elderly was used to assess physical activity over the previous week.[21] This is a 10-item questionnaire which collects responses for the frequency, duration and intensity level of a range of activities typically chosen by older adults. Scores range 0 to >400 with higher scores indicating greater levels of physical activity. Change scores at 6 months will be calculated as baseline minus follow-up.

27. Analysis methods

Primary outcome:

Main comparative analyses between groups will be performed using intention-to-treat. If more than 5% of primary outcomes are missing, multiple imputation will be applied. For the primary hypothesis, differences in mean change in pain (baseline minus follow-up) will be compared between groups using linear regression modelling adjusted for the primary outcome at baseline and the stratifying variable of KL grade (as 3 categories: 2, 3 or 4). Results will be presented as mean differences between groups with 95% confidence intervals, and p-values will also be reported. Complete-case analyses will also be conducted. Standard diagnostic plots will be used to check model assumptions.

Secondary outcomes:

Analyses between groups will be performed using intention-to-treat. For continuous outcomes, analyses will be similar to those for the primary outcomes. Improvement based on global change scores will be compared

between groups using logistic regression, adjusting for the stratifying variable of KL grade (as 3 categories: 2, 3 or 4), with results reported as risk ratios and risk differences. Counts and percentages of participants experiencing improvements will be reported in each treatment group. Improvement based on global change scores and the proportion achieving the MCID in improvement in pain (1.8 NRS units) will each be compared between groups separately using logistic regression, adjusting for the stratifying variable of KL grade (as 3 categories: 2, 3 or 4), with results reported as risk ratios and risk differences. For all between-group comparisons, 95% confidence intervals for comparisons and p-values will be reported. Standard diagnostic plots will be used to check model assumptions.

28. Statistical Methods – adjustment for covariates

For all outcomes, adjustment is as described in the relevant section (Section 27, 29 and 30).

29. Statistical Methods – sensitivity analyses

A sensitivity analysis will estimate treatment effects on the primary outcome assuming full adherence, where full adherence is as defined in Section 19, adjusted for the outcome at baseline and the stratifying variable of KL grade (as three categories: 2, 3 or 4). That is, complier average causal effects will be estimated using an instrumental variables approach (where randomisation is the instrument for adherence). Two-stage least squares models will be fit[22] with complier average causal effects reported with 95% confidence intervals and p-values.

30. Statistical Methods – subgroup analyses

To assess whether the effect of shoe group on the primary outcome of pain is moderated by KL grade, a linear regression model will be fit for the primary outcome with the outcome at baseline, treatment group, and KL grade (as a binary moderator, Grade 4 versus Grade 2 and 3) as covariates, including an interaction between treatment group and KL grade.

To assess whether the effect of shoe group on the primary outcome of pain is moderated by any of FPI score, knee alignment and KOOS PFJ pain and OA, separate linear regression models will be fit for the primary outcome with the outcome at baseline, treatment group, and KL grade (as a binary moderator, Grade 4 versus Grade 2 and 3), as covariates, including an interaction between treatment group and KL grade.

The rationale for the *a priori* choice of treatment effect modifiers is as follows:

- K/L grade- we hypothesise that pain reduction with motion-control shoes (relative to neutral) will be greater in those with more severe radiographic disease severity, based on our prior research that showed that people with more severe radiographic disease had greater pain relief with unloading shoes in a sample of people with medial tibiofemoral OA.[23]
- FPI score- we hypothesise that pain reduction with motion-control shoes (relative to neutral) will be moderated by FPI, given the association between rearfoot eversion and medial-to-lateral knee load distribution.[23]
- Knee alignment- we hypothesise that pain reduction with motion-control shoes (relative to neutral) will be greater in those with more valgus knee alignment, as these people are likely to have greater lateral TF knee loading and thus greater scope for improvement with motion-control shoes.[23]
- KOOS patellofemoral pain and OA subscale score- we hypothesise that pain reduction with motion-control shoes (relative to neutral) will be greater in people with more severe concurrent patellofemoral symptoms, given that medially-posted motion-controlling foot orthoses can alleviate patellofemoral pain.[23]

31. Missing data reporting and assumptions/statistical methods to handle missing data

Baseline characteristics of participants with the primary outcome missing at 6 months will be compared to those of participants with primary outcomes, as outlined in Section 25. If more than 5% of participants have primary outcomes missing at 6 months, multiple imputation will be applied. The number of imputed datasets will be approximately equal to the proportion of participants with missing primary outcomes. Missing baseline

characteristics will be imputed using single mean imputation. Missing outcome values will be imputed separately by treatment group, using chained equations and predictive mean matching, using the five nearest neighbours. Imputation models will include baseline levels of outcomes and baseline characteristics that appear to be different between participants who provide complete follow up data and participants who do not. Initially, imputation models for all outcomes will be chained together, with outcomes broken into subsets if imputation models do not converge. Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes.

To assess the potential impact of the violation of the missing-at-random assumption on conclusions for the primary outcomes, a pattern-mixture approach (as in White et al[24]) will be applied. We will explore the impact of the violation of the missing-at-random assumption if the assumption was violated in both groups, or in one group only.

32. Additional Analyses

Nil

33. Harms

The number (and percentage) of patients experiencing any adverse events will be presented for each treatment group and the nature of the event(s) described. An adverse event is defined as any problem experienced in the study knee or elsewhere in the body because of wearing the study shoes.

34. Statistical Software

Stata v16.1 will be used (StataCorp. 2020. *Stata Statistical Software: Release 16.1*. College Station, TX: StataCorp LLC)

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