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

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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 PhD¹, Ben R. Metcalf BSc (Hons)¹, Penny K Campbell BAppSci¹, Fiona McManus MBiostat², Karen E Lamb PhD^{2,3} & Rana S Hinman PhD¹ *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

2		
3 4	23	ABSTRACT
5 6	24	
7 8 9	25	Objective To determine if motion control walking shoes are superior to neutral walking shoes
10 11	26	for reducing knee pain on walking in people with lateral knee osteoarthritis (OA).
12 13	27	Design Participant- and assessor-blinded, comparative effectiveness, superiority randomized
14 15 16	28	controlled trial (RCT).
17 18	29	Setting Melbourne, Australia
19 20	30	Participants People with symptomatic radiographic lateral tibiofemoral OA from the
21 22	31	community and our volunteer database.
23 24 25	32	Interventions Participants were randomized to receive either motion control or neutral shoes
26 27	33	and advised to wear them ≥ 6 hours/day over 6 months.
28 29	34	Outcome measures Primary outcome was change in average knee pain on walking over the
30 31 32	35	previous week (11-point numerical rating scale (NRS, 0-10)) at 6 months. Secondary outcomes
33 34	36	included other measures of knee pain, physical function, quality of life, participant-perceived
35 36	37	change in pain and function, and physical activity.
37 38	38	Results We planned to recruit 110 participants (55 per arm) but ceased recruitment at 40 (n=18
39 40 41	39	motion control shoes, n=22 neutral shoes) due to COVID-19-related impacts. All 40
42 43	40	participants completed 6-month outcomes. There was no evidence that motion control shoes
44 45	41	were superior to neutral shoes for the primary outcome of pain (mean between-group difference
46 47 48	42	0.4 NRS units (95% CI -1.0 to 1.7)), nor for any secondary outcome. The number of
49 50	43	participants experiencing any adverse events was similar between groups (motion control shoes
51 52	44	n=5 (28%), neutral shoes n=4 (18.2%)) and were minor.
53 54 55	45	Conclusion Motion control shoes were not superior to neutral shoes for improving knee pain
55 56 57 58	46	on walking in symptomatic radiographic lateral tibiofemoral joint OA. Further research is

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Footwear for lateral knee OA

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

55	Strengths and limitations
56	• This is the first clinical trial to assess the effect of any type of footwear on pain in
57	people with symptomatic radiographic lateral knee osteoarthritis.
58	• Our trial found compared the effects of commercially available motion control shoes
59	and neutral walking shoes on walking knee pain in people with predominantly lateral
60	knee OA.
61	• We were unable to recruit out intended sample size due to extended COVID-19-
62	related lockdowns.
63 64	
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	related lockdowns.

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Footwear for lateral knee OA

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.

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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.

106 This study aimed to assess the effectiveness of motion control shoes for improving symptoms 107 in people with lateral knee OA. We hypothesized that wearing motion control shoes would lead 108 to greater reductions in walking knee pain, compared to wearing neutral walking shoes, over 6 109 months.

111 PATIENTS AND METHODS

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112 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.

119 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).

4 134

135 Randomisation and masking

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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 (REDCapTM) 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

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161 increase wear time by two hours/day until they were wearing them as much as possible, at a162 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

185 Likert scales (terminal descriptors of 'much worse' to 'much better' (28). Participants reporting
186 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 Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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

212 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).

38 224

> 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

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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

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Footwear for lateral knee OA

> 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).

	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, $n (\%)^{a}$	5(17)	7 (52)
Grade 2 (mild)	2 (11)	3 (14)
Grade 3 (moderate)	8 (44) 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	0 (0)	1 (7)
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		. (10)
feature score, mean (SD) ^g	6.2 (3.2)	6.4 (2.7)
Expectation of treatment – before	0.2 (0.2)	(2.7)
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)

Recoling characteristics of participants by group, reported as mean (standard 282 Table 1

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Motion control shoes (n=18)Neutral shoes (n=22)Expectation of treatment – after shoe allocation, n (%)Expectation of treatment – after shoe allocation, n (%)No change0 (0)0 (0)Mild improvement1 (6)2 (9) Moderate improvement12 (67)13 (59) Large improvement5 (28)284*Using the Kellgren & Lawrence grading system;5*Measured as anatomical axis from standing radiograph with 180° indicating neutral alignment, 4:80°, varus alignment, and >180°, valgus alignment.7*Scored from -12 to 12; scores <0 indicated supinated foot posture, 0-5 neutral foot posture; and >5 pronated foot posture;289*Higher values indicate greater mobility/drop; 'Scores range 1 to 10, higher scores indicate higher self-efficacy; 'S & 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.297Mean (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 events301(n=5 (28%) with motion control shoes, n=4 (18%) with neutral shoes), mostly knee pain (Table 302312291Adherence and adverse events329adherent 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 even	1			Footw	ear for lateral knee OA
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 ^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. ^f IQR = interquartile range (25th – 75th percentile); OA = osteoarthritis. ^f Mean (SD) allocated shoe wear was 7.0 (3.4) hours/day with motion control shoes and 8.0 (2.4) ^h 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 ^g Ot (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 304). ^g Ot (n=5 (28%) with motion control shoes (Appendix Table 3). 	13	• • •	i	<u> </u>	1 (5)
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 303 2). One participant (6%) ceased wearing their motion control shoes due to a fractured ankle 304 that was unrelated to the footwear (Appendix Table 3). 305 306 	41 42 42	302	2). Cointervention use was similar betwee	en groups at baseline (Table 1) and follow-up (Table
 304 that was unrelated to the footwear (Appendix Table 3). 305 306 	44	303	2). One participant (6%) ceased wearing	their motion control shoes d	ue to a fractured ankle
⁵⁰ ⁵⁰ ⁵¹ 306	16 17	304	that was unrelated to the footwear (Appen	ndix Table 3).	
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5	308	as number (%) of participants.	Motion control shoes	Neutral shoes
6 7			(n=18)	(n=22)
8		Participants reporting any adverse event(s):		4 (18)
9		Knee pain	3 (17)	2 (9)
10		Ankle/foot pain	2(11)	1 (5)
11		Blisters	0 (0)	1 (5)
12 13		Pain in other areas	2 (11)	1 (5)
14		Count of adverse events:		
15		0	13 (72)	18 (82)
16		1	3 (17)	3 (14)
17		2	2(11)	1 (5)
18		Current drug/supplement use ^a :	16 (89)	15 (68)
19 20		Analgesia (paracetamol combinations)	13 (72)	11 (50)
20 21		Non-steroidal anti-inflammatories	11 (61)	12 (55)
22		Topical anti-inflammatories	8 (44)	5 (23)
23		Oral corticosteroids	0(0)	1 (5)
24		Oral opioids	0(0)	1 (5)
25		Co-interventions used in the last 6 months:		
26		Land based exercise	13 (72)	11 (50)
27 28		Heat/cold treatment	8 (44)	7 (32)
28 29		Massage	6 (33)	8 (36)
30		Knee braces	(11)	5 (23)
31		Manual therapy	4 (22)	4 (18)
32		Orthotics/arch supports	4 (22)	0(0)
33		Hydrotherapy	3 (17)	4 (18)
34	309	^a Defined as at least once per week in the las		
35 36	310	r in the second s		
30 37	311	Primary outcome		
38			L	1
39 40	312	Tables 3 summarizes the primary outcome	across time by group an	nd Table 4 presents the
40 41 42	313	change in the primary outcome within and	l between groups. There	was no evidence of a
43 44	314	between-group difference in change in wall	king knee pain at 6 month	ns (mean difference 0.4

Table 2. Adverse events and co-interventions at follow up according to group, presented

р ъ g Ig iitiis 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).

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			Base		U III	onths
			Motion control shoes (n=18)	Neutral shoes (n=22)	Motion control shoes (n=18)	Neutral shoes (n=22)
	Prima	ry outcome				
	Averag (NRS)	e knee pain on walking	5.7 (1.1)	5.4 (1.0)	4.3 (2.2)	3.7 (2.2)
	Second	lary 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	v of life (AQoL-6D)	0.80 (0.10)	0.76 (0.10)	0.81 (0.10)	0.78 (0.12
		al Activity Scale for the (PASE)	186.5 (78.5)	177.9 (91.8)	177.0 (84.1)	202.5 (89.4
322 323 324 325 326 327	higher s the Elde	ng worse pain/symptoms/ cores indicate worse pain erly (0 to over 400, with l deviation.	n); OA = osteoar	thritis; PASE =	= Physical Acti	ivity Scale fo

	continuous outcomes, using	Mean (SD) ch grou Baseline –	ange within ps 6 months	Difference in c between gro Baseline to 6 n	ups ^a
		Motion control shoes (n=18)	Neutral shoes (n=22)	Mean difference (95% CI)	P-val
	Primary outcome				
	Knee pain on walking (NRS) ^b	1.4 (2.1)	1.7 (2.1)	0.4 (-1.0, 1.7)	0
	Secondary outcomes				
	KOOS sub-scales ^c :				
	i) Physical function	-10.2 (14.5)	-8.0 (11.4)	1.6 (-5.8, 8.9)	0
	ii) Pain	- 10.5 (14.8)	-9.1 (15.3)	-0.4 (-8.6, 7.8)	0
	iii) Sport and	-6.4 (27.1)	-11.4 (25.9)	-7.8 (-20.8, 5.3)	0
	recreation iv) Knee-related quality-of-life	-4.9 (18.1)	-10.2 (17.1)	-6.1 (-16.8, 4.5)	0
	v) Patellofemoral pain and OA	-6.9 (21.0)	-10.6 (15.0)	-3.9 (-14.4, 6.6)	0
	Quality of life (AQoL- 6D) ^c	-0.01 (0.13)	-0.02 (0.06)	0.00 (-0.05, 0.06)	0
	Physical activity (PASE) ^c	9.5 (85.7)	-24.6 (51.5)	-32.2 (-73.1, 8.7)	0
330	^a Difference is adjusted for t	the outcome at b	aseline and rac	liographic severity (Kellgre
331 332	Lawrence Grade).	ogitivo ohongog i	ndianta improv	amont For difference	a in ah
333	^b For change within groups, p between groups, negative diff				
334	^c For change within groups, n				e in cha
335	between groups, positive diff				
336	AQoL = Assessment of Qual				
337 338	quality of life); CI = confide Score (0 to 100; lower scores				
339	= numerical rating scale $(0-1)$	•	1 2 1	1 2	
340	= Physical Activity Scale for		1		,
341	physical activity); SD = stand	lard deviation.		-	-
342					
343	Secondary outcomes				
344	Table 3 summarizes continuo	us secondary outc	comes across tin	ne by group and Tabl	e 4 pres
345	change in continuous seconda	ary outcomes with	nin and between	n groups. There was	no evide
346	that motion control shoes were	e superior to neut	ral shoes for any	<i>i</i> continuous seconda	ry outer

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).

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357_		Motion control shoes	onths)), and r Neutral shoes	Relative risk	P-value	Risk difference	
		(n=18)	(n=22)	(95% CI) ^b	I -value	(95% CI) ^c	
	Improved	6/18 (33)	10/22 (46)	1.36	0.45	0.12	
	pain ^d			(0.61, 3.01)		(-0.18, 0.42)	
	Improved	4/18 (22)	7/22 (32)	1.43	0.50	0.10	
	function ^d			(0.50, 4.10)		(-0.18, 0.37)	
	Improvement	9/18 (50)	14/22 (64)	1.28	0.38	0.14	
	≥ 1.8 NRS units ^e			(0.74, 2.24)		(-0.16, 0.44)	
359 360 361 362 363 364	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants ir	ts <1 favour moti rences <0 favou	on control sho ur ith terminal de ately better' or	escriptors of 'mu 'much better' cl	ch worse' t assified as	o 'much better'	"
 358 359 360 361 362 363 364 365 366 367 368 	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants ir ^e Improvement in the primary	ts <1 favour motion rences <0 favour ol shoe group. 7-point scales with indicating 'modera	on control sho ar ith terminal de ately better' or s chosen as th e in knee pain	e group. escriptors of 'mu 'much better' cl s is the minimum on walking (bas	ch worse' t assified as n clinically	o 'much better' improved.	"
 359 360 361 362 363 364 365 366 367 	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants ir ^e Improvement in the primary	ts <1 favour moti- rences <0 favour ol shoe group. 7-point scales with indicating 'modera at \geq 1.8 NRS units y outcome, chang the intervals; NRS	on control sho ar ith terminal de ately better' or s chosen as th e in knee pain	e group. escriptors of 'mu 'much better' cl s is the minimum on walking (bas	ch worse' t assified as n clinically	o 'much better' improved.	, ,
 359 360 361 362 363 364 365 366 367 368 	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants ir ^e Improvement in the primary CI = confident Subgroup an	ts <1 favour moti- rences <0 favour ol shoe group. 7-point scales with indicating 'modera at \geq 1.8 NRS units y outcome, chang the intervals; NRS	on control sho at the terminal defined at the terminal defined the term	e group. escriptors of 'mu 'much better' cl s is the minimus on walking (bas rating scale.	ch worse' t assified as n clinically eline – 6 m	o 'much better improved. important diffe onths).	, 'er
 359 360 361 362 363 364 365 366 367 368 369 370 	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants in ^e Improvement in the primary CI = confiden Subgroup an The effect of a	as <1 favour motion rences <0 favour of shoe group. 7-point scales with adicating 'moderated at \geq 1.8 NRS units y outcome, chang ace intervals; NRS alyses	on control sho at the terminal defined by better' or s chosen as the in knee pain S = numerical	e group. escriptors of 'mu 'much better' cl s is the minimus on walking (bas rating scale.	ch worse' t assified as n clinically eline – 6 m walking kn	o 'much better improved. important diffo onths). ee pain was not	,', er
 359 360 361 362 363 364 365 366 367 368 369 	Grade). ^b Relative risk ^c Risk differ motion contro ^d Rated using participants ir ^e Improvement in the primary CI = confident Subgroup an The effect of a to be moderat	as <1 favour motion rences <0 favour of shoe group. 7-point scales with adicating 'moderand at \geq 1.8 NRS units y outcome, chang the intervals; NRS allyses allocated shoe group	on control sho ar ith terminal de ately better' or s chosen as the e in knee pain S = numerical oup on the print e pre-specified	e group. escriptors of 'mu 'much better' cl s is the minimum on walking (bas rating scale.	ch worse' t assified as n clinically eline – 6 m walking kn diographic c	o 'much better improved. important diffe onths). ee pain was not disease severity	', `er

49 50 375 **DISCUSSION** 51

52 This RCT found that motion control shoes were not superior at reducing knee pain on walking 376 53 54 than neutral shoes in people with lateral knee OA. Average within group changes failed to 377 55 56 378 demonstrate clinically-meaningful improvements in knee pain for either footwear group. 57 58 59 379 Motion control shoes were not superior to neutral shoes for any secondary outcome, and a 60

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Footwear for lateral knee OA

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.

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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-19related 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 Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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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

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1 2		
3 4	455	differences. We evaluated a single motion control shoe model, thus our findings cannot be
5 6 7	456	generalized to other motion control shoes. Similarly, the addition of medial wedges or arch
7 8 9	457	support to the motion control shoes may exert greater symptomatic benefits than motion control
10 11	458	shoes alone.
12 13	459	
14 15 16	460	In conclusion, motion control shoes were not superior to neutral walking shoes for reducing
17 18	461	walking knee pain in people with symptomatic lateral tibiofemoral joint OA. Given the limited
19 20	462	clinical trial evidence in people with lateral knee OA, further research is needed to confirm the
21 22	463	findings and to identify effective treatments for this important but under-researched subgroup
23 24 25	464	of knee OA patients.
26 27	465	
28 29	466	Footnotes
30 31 32	467	Data sharing statement: Data that support findings of this study are available from the
33 34	468	corresponding author upon reasonable request.
35 36	469	
37 38	470	Ethics statements:
39 40 41	471	Patient consent for publication: Consent obtained directly from patient(s)
42 43	472	Ethics approval: This study involves human participants, was approved by University of
44 45	473	Melbourne Human Research Ethics Committee and registered with the Australian New
46 47 48	474	Zealand Clinical Trials Registry (date registered 15 November 2018) and complied with the
49 50	475	Declaration of Helsinki. Participants gave informed consent to participate in the study before
51 52	476	taking part.
53 54 55	477	
56 57	478	Contributors: KLP and RSH conceived the idea for the study and KLP led the trial. KLP and
58 59 60	479	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.

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Fellowship (#1154217).

Competing interests: None

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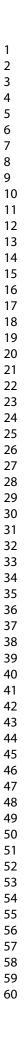
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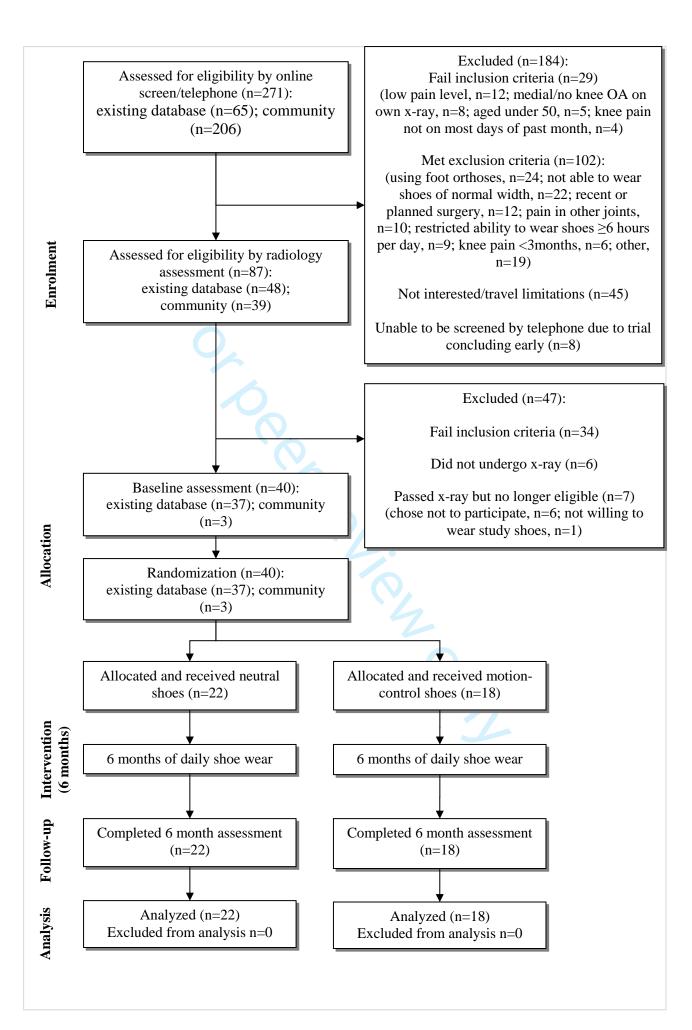
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	Motion control shoes (n=18)	Neutral shoes (n=22)
Multiple density midsole	6 (33)	5 (23)
Fixation		
Laces	12 (67)	16 (73)
Straps/buckles	3 (17)	1 (5)
Velcro	1 (6)	1 (5)
None	2 (11)	4 (18)
Heel counter stiffness		
Rigid	7 (39)	13 (59)
Moderate	3 (17)	4 (18)
Minimal	6 (33)	4 (18)
No heel counter	2 (11)	1 (5)
Midfoot sagittal stability	~ /	X- 7
Rigid	6 (33)	4 (18)
Moderate	1 (6)	2 (9)
Minimal	11 (61)	16 (73)
Midfoot torsional stability		10 (75)
Rigid	11 (61)	16 (73)
Moderate	4 (22)	3 (14)
Minimal	3 (17)	3 (14)
Overall motion control feature score, mean (SD) ^a		6.4 (3)
ndicating more motion control features. SD = standard deviation.		

Overall are participants who $\boxtimes \boxtimes \boxtimes$		Motion control shoes ^a	Neutral shoes ^b
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	Motion control shoes (n=18)	Neutral shoes (n=22)
Fractured ankle (unrelated to shoes)	$1^{a}(6)$	0 (0)
Total ^a Participant ceased wearing shoes in month 2.	1 (6)	0 (0)

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

	Difference in chan Baseline to	
	Mean difference (95% CI)	P-value
Knee pain on walking (NRS) ^c	0.6 (-1.7, 2.9)	0.59

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

^bFull 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).

binary moderator for the primary	U	0 1		/ I
	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

1.69 (2.46)

1.78 (1.72)

1.50 (2.37)

1.38 (1.92)

Annandiv Table 5. Results of the moderation analysis for radiographic disease severity (Kellgren & Lawrence Grade) as a potential

^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 Amotion control shoes) on the primary outcome in each radiographic disease severity category, adjusted for the outcome at baseline.

0.16(-1.65, 1.96)

0.73 (-1.44, 2.90)

^bn=10 for Grade 2 or 3; n=13 for Grade 4;

Grade 2 (mild) or 3 (moderate)

Grade 4 (severe)

^c n=8 for Grade 2 or 3; n=9 for Grade 4.

Certeview only ^d Negative differences favour motion control shoes.

CI=confidence intervals; SD=standard deviation.

Appendix Table 6: Results on walking, using complete		tential continuous moderators	s for the primary outcome, change in knee pain
Potential Moderator ^b	Motion control shoes	Neutral shoes	Difference ^c in coefficients, Interaction

Potential Moderator ^b (taken at baseline)	Moderator Coeff. (95% CI)	P-value	Moderator Coeff. (95% CI)	P-value	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 🖄 months), of a oneunit 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.

^cNegative 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.

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

Section/Topic	ltem 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	2a	Scientific background and explanation of rationale	5
objectives	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	8a	Method used to generate the random allocation sequence	8
generation	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
CONSORT 2010 checklist		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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		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	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
recommended)	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 <u>www.consort-statement.org</u>.

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

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Primary Subject Heading :	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, Clinical trials < THERAPEUTICS





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Footwear for lateral knee OA

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3	Effect of motion control versus neutral walking footwear on pain associated with lateral
4	tibiofemoral joint osteoarthritis: a comparative effectiveness randomized clinical trial.
5	
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21	Word count: 3,761
22	Running title: Footwear for lateral knee OA

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1		Footwear for lateral knee OA
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3 4	23	ABSTRACT
5 6	24	
7 8 9	25	Objective To determine if motion control walking shoes are superior to neutral walking shoes
10 11	26	for reducing knee pain on walking in people with lateral knee osteoarthritis (OA).
12 13	27	Design Participant- and assessor-blinded, comparative effectiveness, superiority randomized
14 15 16	28	controlled trial (RCT).
17 18	29	Setting Melbourne, Australia.
19 20	30	Participants People with symptomatic radiographic lateral tibiofemoral OA from the
21 22 23	31	community and our volunteer database.
23 24 25	32	Interventions Participants were randomized to receive either motion control or neutral shoes
26 27	33	and advised to wear them ≥ 6 hours/day over 6 months.
28 29	34	Outcome measures Primary outcome was change in average knee pain on walking over the
30 31 32	35	previous week (11-point numerical rating scale (NRS, 0-10)) at 6 months. Secondary outcomes
33 34	36	included other measures of knee pain, physical function, quality of life, participant-perceived
35 36	37	change in pain and function, and physical activity.
37 38 39	38	Results We planned to recruit 110 participants (55 per arm) but ceased recruitment at 40 (n=18
40 41	39	motion control shoes, n=22 neutral shoes) due to COVID-19-related impacts. All 40
42 43	40	participants completed 6-month outcomes. There was no evidence that motion control shoes
44 45 46	41	were superior to neutral shoes for the primary outcome of pain (mean between-group difference
47 48	42	0.4 NRS units (95% CI -1.0 to 1.7)), nor for any secondary outcome. The number of
49 50	43	participants experiencing any adverse events was similar between groups (motion control shoes
51 52	44	n=5 (28%), neutral shoes $n=4$ (18.2%)) and were minor.
53 54 55	45	Conclusion Motion control shoes were not superior to neutral shoes for improving knee pain
56 57 58 59 60	46	on walking in symptomatic radiographic lateral tibiofemoral joint OA. Further research is

Footwear for lateral knee OA

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

s00. Key words: osteoarthritis, OA, knee, tibiofemoral, footwear, shoes, clinical trial, RCT,

- biomechanics, pain

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to COVID-19-related impacts, thus we

2		
3 4	55	Strengths and limitations
5 6	56	• We used a robust randomized clinical trial design with blinded participants and
7 8 9	57	assessors.
10 11	58	• Our outcomes have strong clinimetric properties and are recommended for knee
12 13 14	59	osteoarthritis clinical trials by international osteoarthritis guidelines.
15 16	60	• We included sensitivity analyses to assess whether our findings changed when
17 18 10	61	assuming full adherence to footwear.
19 20 21	62	• We did not reach our intended sample size due to COVID-19-related impacts, thus
22 23	63	had reduced power to detect a clinically-relevant between-group difference in our
24 25 26	64	primary outcome.
27 28	65	primary outcome.
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Footwear for lateral knee OA

68 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.

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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.

110 This study aimed to assess the effectiveness of motion control shoes for improving symptoms 111 in people with lateral knee OA. We hypothesized that wearing motion control shoes would lead 112 to greater reductions in walking knee pain, compared to wearing neutral walking shoes, over 6 113 months.

115 PATIENTS AND METHODS

Footwear for lateral knee OA

116 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.

123 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).

139 Randomisation and masking

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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 (REDCapTM) 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

165 increase wear time by two hours/day until they were wearing them as much as possible, at a166 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

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189 Likert scales (terminal descriptors of 'much worse' to 'much better' (28). Participants reporting
190 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,

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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.

260 Patient and public involvement

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

Footwear for lateral knee OA

RESULTS

265 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

2 3 4	287	expectations were generally similar across groups pre-randomization and following shoe
5 6	288	allocation (Table 1).
7 8	289	
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	Motion control shoes	Neutral shoes
Age (years)	(n=18) 64.6 (7.2)	(n=22) 64.2 (7.2)
	04.0 (7.2)	04.2 (7.2)
Gender	11 (61)	12 (50)
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 (81-106)
Body mass index (kg/m ²), med	ian (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 (188.1 (5.5)
Foot Posture Index classification		100.1 (5.5)
		1 (5)
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	$1(\%)^{e}$ 15 (83)	18 (82)
Paracetamol combinations	11 (61)	15 (68)
Non-steroidal anti-inflammat		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 las	St b	
months, n (%)		12 (50)
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 con		
feature score, mean (SD) ^g	6.2 (3.2)	6.4 (2.7)
Expectation of treatment – befo	· · · ·	0.4 (2.7)
randomisation, n (%)	0 (0)	Δ (Δ)
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)

Table 1. Baseline characteristics of participants by group, reported as mean (standard

2							
3			Motion control shoes	Neutral shoes			
4 5			(n=18)	(n=22)			
6		Expectation of treatment – after shoe	9				
7		allocation, n (%)					
8		No change	0 (0)	0 (0)			
9		Mild improvement	1 (6)	2 (9)			
10 11		Moderate improvement	12 (67)	13 (59)			
12		Large improvement	5 (28)	6 (27)			
13		Complete recovery	0 (0)	1 (5)			
14	293	^a Using the Kellgren & Lawrence grad					
15	294	^b Measured as anatomical axis fro		30° indicating neutral			
16 17	295	alignment, <180°, varus alignment, au		5 (10)			
18	296	^c Scored from -12 to 12; scores <0 in	dicated supinated foot posture, 0-	-5 neutral foot posture,			
19	297	and >5 pronated foot posture;	1. / 1				
20	298	^d Higher values indicate greater mobil	5 17				
21	299	^e Defined as at least once per week in					
22 23	300 301	^f Scores range 1 to 10, higher scores in	0	1 with higher george			
23 24	301	^g Measured using the Footwear Ass indicating more motion control featur		i, with higher scores			
25	302	IQR = interquartile range (25th - 75th)					
26	303	iQK – interquartite range (25 – 75	percentine), OA – osteoartinitis.				
27	305	Adherence and adverse events					
28 29	505	Auner ence and auver se events					
29 30 31	306	Mean (SD) allocated shoe wear was 7.	.0(3.4) hours/day with motion con	trol shoes and 8.0 (2.4)			
32 33	307	hours/day with neutral shoes (Appendix Table 2). Ten participants (56%) were classified as					
34 35 26	308	adherent over six months with motion	n control shoes, compared to 19 (86%) participants with			
36 37 38	309	neutral shoes. A similar number of part	rticipants in each footwear group r	reported adverse events			
39 40	310	(n=5 (28%) with motion control shoes	s, n=4 (18%) with neutral shoes), n	nostly knee pain (Table			
41 42	311	2). Cointervention use was similar be	tween groups at baseline (Table 1) and follow-up (Table			
43 44 45	312	2). One participant (6%) ceased wear	ring their motion control shoes d	ue to a fractured ankle			
46 47	313	that was unrelated to the footwear (A)	ppendix Table 3).				
48 49	314						
50 51 52 53 54 55 56 57 58 59 60	315						
00				16			

	Motion control shoes	Neutral shoes
	(n=18)	(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.	
1		

Table 2. Adverse events and co-interventions at follow up according to group, presented

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).

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32	Table 3. Mean (SD) scores on continuous outcome measures across time by shoe group, mean	change within gr	oups, and difference ^a in
32	27 change between groups for continuous outcomes, using complete case data.		
	Moon (SD)	ahanga within	Difference in change

						Mean (SD) ch grou	e	Difference in ch between grou	0
		Base	eline	6 months		Baseline – 6 months		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
Prima	ary outcome								
Avera (NRS)	ge knee pain on walking	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
Secon	dary outcomes								
KOOS	S 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
Qualit	ty 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
2	cal Activity Scale for the y (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.

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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.

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339	Secondary outcomes
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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).

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1 2

3 351 Table 4: Number (percentage) of participants reporting global improvement or achieving 4 352 an improvement of 1.8 NRS units in the primary outcome (change in knee pain on 5 walking (baseline minus 6 months)), and relative risks^a and risk differences^a. 353 6 **Motion control** Neutral Risk 7 P-**Relative risk** 8 shoes shoes **P-value** difference (95% CI)^b value 9 (n=18)(n=22)(95% CI)^c 10 6/18 (33) 10/22 (46) 1.36 0.45 0.12 0.44 Improved 11 12 paind (0.61, 3.01)(-0.18, 0.42)13 14 4/18 (22) 7/22 (32) 1.43 0.50 0.10 0.49 Improved 15 function^d (0.50, 4.10)(-0.18, 0.37)16 17 Improvement 9/18 (50) 14/22 (64) 1.28 0.38 0.14 0.36 18 ≥ 1.8 NRS 19 (0.74, 2.24)(-0.16, 0.44)unitse 20 354 ^a Relative risk and risk difference adjusted for radiographic severity (Kellgren & Lawrence 21 Grade). 22 355 23 356 ^b Relative risks <1 favour motion control shoe group. 24 357 ^c Risk differences <0 favour 25 358 motion control shoe group. 26 359 ^d Rated using 7-point scales with terminal descriptors of 'much worse' to 'much better', with 27 participants indicating 'moderately better' or 'much better' classified as improved. 360 28 ^e Improvement >1.8 NRS units chosen as this is the minimum clinically important difference 361 29 in the primary outcome, change in knee pain on walking (baseline -6 months). 30 362 31 CI = confidence intervals; NRS = numerical rating scale. 363 32 364 33 34 365 **Subgroup analyses** 35 36 37 366 The effect of allocated shoe group on the primary outcome of walking knee pain was not found 38 39 to be moderated by any of the pre-specified variables of radiographic disease severity, Foot 367 40 41 368 Posture Index, radiographic knee alignment or KOOS patellofemoral pain and OA subscale 42 43 369 score (Appendix Tables 5 and 6). 44 45 46 370 47 48 49 371 DISCUSSION 50 51 52 372 This RCT found that motion control shoes were not superior at reducing knee pain on walking 53 54 373 than neutral shoes in people with lateral knee OA. Average within group changes failed to 55 56 demonstrate clinically-meaningful improvements in knee pain for either footwear group. 374 57 58 59 375 Motion control shoes were not superior to neutral shoes for any secondary outcome, and a 60

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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.

, 386

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

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401 our knowledge, no study has investigated the symptomatic effects of knee bracing or any other402 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-19related lockdowns in 2020 in Australia. Nonetheless, it is worth highlighting that our

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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

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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. 22.0

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.

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- 5 6	477	Contributors: KLP and RSH conceived the idea for the study and KLP led the trial. KLP and
7 8	478	RSH designed the trial protocol with input from KLB, BM, PKC, FM, and KL. FM and KL
9 10 11	479	formulated and were responsible for the statistical analysis plan and conducted the statistical
12 13	480	analyses. KLP drafted the manuscript and all authors provided input and approved the final
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Footwear for lateral knee OA

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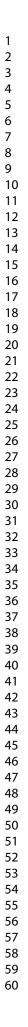
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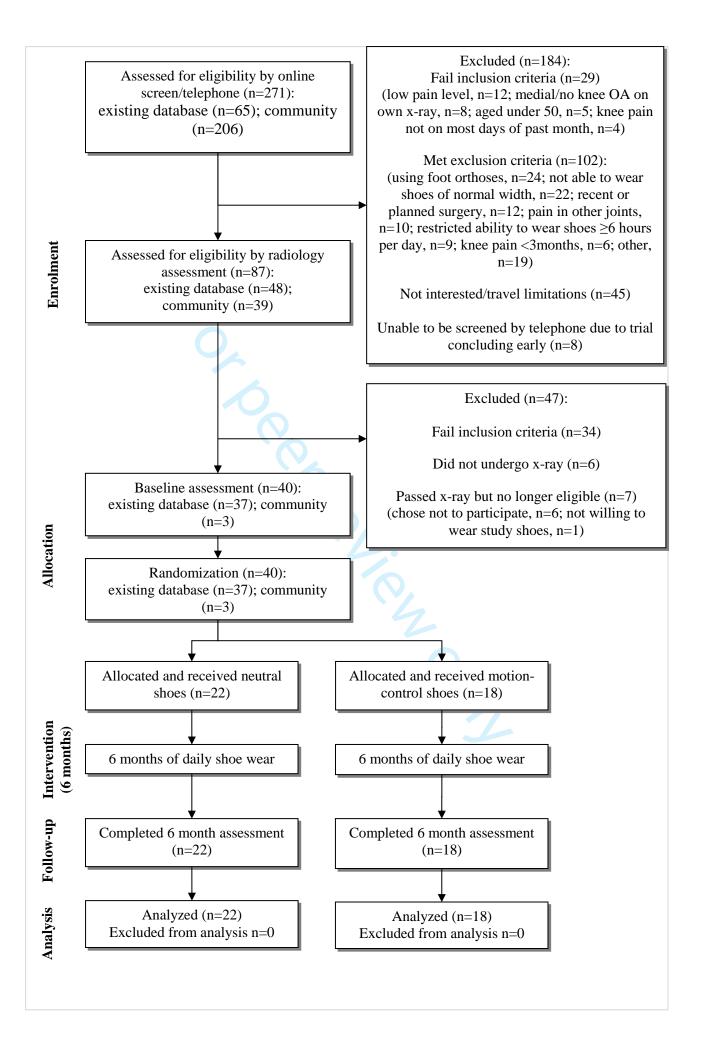
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	Motion control shoes	Neutral shoes
	(n=18)	(n=22)
Multiple density midsole	6 (33)	5 (23)
Fixation		
Laces	12 (67)	16 (73)
Straps/buckles	3 (17)	1 (5)
Velcro	1 (6)	1 (5)
None	2 (11)	4 (18)
Heel counter stiffness		
Rigid	7 (39)	13 (59)
Moderate	3 (17)	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)

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

S indicating more motion control features.

SD = standard deviation.

	Motion control shoes ^a	Neutral shoes
Shoe wear in log books (hours/day), mean (S	D):	
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)
n=17 for shoe wear and participants classified		; n=16 for shoe w
and participants classified as adherent at mont		
dherent at month 6; n=18 for all other outcon		
n=21 for shoe wear and participants classifie		6; n=22 for all other
utcomes.		
Adherent defined as an average of ≥ 6 hours/	day also man for that month.	

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

reported as number (76).		
	Motion control shoes	Neutral shoes
	(n=18)	(n=22)
Fractured ankle (unrelated to shoes)	$1^{a}(6)$	0 (0)
Total	1 (6)	0 (0)

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

^a Participant ceased wearing shoes in month 2.

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

	Difference in chang	e 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 ^c ay sh zation w ces favour n numerical rating 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. each rau... 4; ontrol shoes. 7 deviation.

^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 oneunit 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.

^cNegative 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.

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

Section/Topic	ltem 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	2a	Scientific background and explanation of rationale	5
objectives	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
0	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	8a	Method used to generate the random allocation sequence	8
generation	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
CONSORT 2010 checklist		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	Page

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		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	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	12
diagram is strongly		were analysed for the primary outcome	
recommended)	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	Tables
		by original assigned groups	
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	Appendix
		pre-specified from exploratory	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.

CONSORT 2010 checklist