Osteoarthritis and Cartilage 26 (2018) 227–235

Osteoarthritis and Cartilage

OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Moderators and mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis: an exploratory analysis of the SHARK randomised controlled trial

K.L. Paterson † *, J. Kasza ‡, K.L. Bennell †, T.V. Wrigley †, B.R. Metcalf †, P.K. Campbell †, D.J. Hunter §, R.S. Hinman †

† Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Melbourne, Australia
‡ Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
§ Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department, Royal North Shore Hospital Australia, Sydney, Australia

ARTICLE INFO

Article history:
Received 24 July 2017
Accepted 1 November 2017

Keywords:
Osteoarthritis
Pain
Moderators
Mediators
Knee adduction moment
Phenotype

SUMMARY

Objective: To investigate moderators and biomechanical mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis (OA).

Methods: Exploratory analysis from 164 participants in a clinical trial comparing unloading (ASICS GEL-Melbourne OA) to conventional walking shoes. The primary outcome was 6-month change in knee pain (11-point numerical rating scale (NRS)). Moderators included baseline peak knee adduction moment (KAM), radiographic severity (Kellgren & Lawrence (KL) scale), body mass, foot posture, neuropathic pain and diffuse knee pain. Mediators included change in peak KAM and KAM impulse.

Results: Radiographic severity was the only moderator to interact with footwear group ($P = 0.02$). Participants with KL = 2 experienced greater pain reductions with conventional compared to unloading shoes (mean difference in change in pain −1.64 units, 95% CI −3.07, −0.21), while unloading shoes tended to result in greater pain reductions than conventional shoes in KL = 3 (0.98, 95% CI −0.44, 2.39) and KL = 4 (0.64, 95% CI −0.64, 1.93). No variable showed any significant mediating effect in the entire cohort. However, there was some evidence that unloading shoes may reduce pain through reductions in peak KAM (indirect effect −0.31, 95% CIs −0.65, 0.03; $P = 0.07$) in people with KL ≥ 3, compared to conventional shoes.

Conclusion: Unloading shoes conferred additional symptomatic benefits over conventional shoes in people with moderate to severe knee OA. There was some evidence effects may be mediated by a reduction in peak KAM. However, we were underpowered for subgroup analyses. These patients may represent a subgroup to which biomechanical interventions designed to reduce the KAM may be more effectively targeted.

Knee osteoarthritis (OA) is a leading cause of joint pain and disability in middle- and older-aged individuals. There are few effective conservative treatments to reduce symptoms and improve function in knee OA, thus weight loss, exercise and other self-management strategies are integral to OA management[1,2]. Footwear is appealing for self-management of the condition, given the critical role joint loading plays in knee OA pathogenesis[3], and the ability of footwear to modify joint loads[4,5]. Accordingly, clinical guidelines recommend "appropriate" footwear for knee OA[1,6]; however, there are few high-quality clinical trials to guide clinical decision-making.

Biomechanical studies show that footwear with midsoles that are stiffer laterally than medially significantly reduce medial knee joint loads in most people with medial knee OA[7,8]. Thus, these "unloading shoes" may also improve pain and function in this group, given the external knee adduction moment (KAM), a proxy

* Address correspondence and reprint requests to: K.L. Paterson, Centre for Health Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, University of Melbourne, Victoria 3010, Australia. Fax: 61-3-8344-4188.

E-mail address: kade.paterson@unimelb.edu.au (K.L. Paterson).

https://doi.org/10.1016/j.joca.2017.11.002
1063-4584/

measure of medial knee load distribution, is associated with knee pain severity and physical dysfunction[9–11]. Our randomised controlled trial (RCT) comparing unloading to conventional walking shoes in 164 people with medial knee OA[12] showed improvements in knee pain and function with both types of shoes after 6 months, consistent with minimum clinically important differences for these outcomes. However, there were no differences in outcomes between footwear groups, supporting the findings of a prior smaller study that evaluated another unloading shoe design[13,14].

Failure of unloading shoes to confer additional symptomatic benefit over conventional shoes may be due to the large variation in the biomechanical response to the intervention amongst individuals with knee OA. Previous research has reported that individual changes in the KAM vary by up to 50% when walking in unloading compared to control shoes, and surprisingly, up to 18% of people experience an increased KAM[7,8]. This suggests that biomechanical interventions are not a "one size fits all" approach but should be targeted to individuals who are most likely to benefit[15,16]. For example, rearfoot motion has been shown to predict which patients "respond" with a KAM reduction to lateral wedge insoles[17].

A useful method for identifying subgroups of "responders" is through analysis of treatment moderators using RCT data. Moderators are patient characteristics measured at baseline, that interact with the treatment to influence clinical outcomes[18], such that those with different levels of the moderator respond differently to the treatment compared to the alternate treatment. Identifying moderators of outcomes from biomechanical interventions may, therefore, help clinicians and researchers to direct treatments to patient subgroups most likely to benefit. In fact, European League Against Rheumatism clinical guidelines have identified moderators of knee OA outcomes as an important research priority to optimise individualised treatment[6]. Similarly, determining the OA subgroups in which biomechanical interventions have the greatest benefit is one of the five key research recommendations from National Institute for Health Care and Excellence[1]. Additionally, the identification of mediators, or the biomechanical mechanisms through which unloading shoes act, and measured as change from pre-to post-intervention, can help explain how unloading shoes influence clinical outcomes. This may help researchers design more effective biomechanical interventions which can then be tested in subsequent clinical trials[18].

Although moderators or mediators of biomechanical treatment in knee OA have not been previously investigated, potential variables may be selected based on prior research and/or the plausibility of hypothesised effects. For instance, peak KAM at baseline and/or radiographic OA severity (which is associated with peak KAM[19]), may moderate therapeutic effects of unloading shoes, given the relationship between peak KAM and knee pain development[9] and severity[10,20]. Thus, it is plausible that people with a higher peak KAM at baseline have greater scope for improvement from a load-reducing intervention than people with a lower peak KAM. Other potential moderators include foot posture, given greater KAM reductions have been observed in people with pronated feet when treated with laterally wedged orthotics[21]; body mass, as it is feasible that patients with a greater body mass may compress the shoe features designed to reduce knee load and render the shoes ineffective; and knee pain characteristics, as people with neuropathic and/or diffuse pain may have more centrally-mediated pain that is less responsive to local biomechanical interventions. The most likely biomechanical mediators of the effects of unloading shoes on knee pain are changes in peak KAM and KAM impulse, as these are the biomechanical characteristics of gait that the shoes are designed to change[7,8] and they are positively correlated with walking knee pain in people with knee OA[10,11].

This aim of this study was to investigate moderators and mediators of effects of unloading shoes on knee pain in people with medial knee OA. We hypothesised that baseline peak KAM, radiographic OA severity, body mass, foot posture and baseline pain characteristics would moderate the difference in change in pain between unloading and conventional shoes. We also hypothesised that the effect of unloading shoes on pain reductions would be mediated by the change in peak KAM and KAM impulse.

Patients and methods

Study population

This is an exploratory analysis of data from 164 participants with medial knee OA who enrolled in a RCT comparing effects of unloading and conventional walking shoes on symptoms[12]. Participants were eligible if they (1) were aged ≥50 years (2) had knee pain on most days of the past month; (3) reported minimum average pain on walking of ≥4 on an 11-point numerical rating scale (NRS, with terminal descriptors of 'no pain' and 'worst pain possible') over the previous week; (4) had radiographic evidence of OA (Kellgren & Lawrence [KL] grade ≥2[22]) and; (5) had radiographic medial tibiofemoral compartment OA (≥grade 1 medial osteophytes AND ≥ grade 1 medial joint space narrowing that was greater than lateral[23]). Exclusion criteria have been published previously[12].

Procedures

Study procedures were approved by the University of Melbourne Human Research Ethics Committee (HREC No. 1239045) and participants provided written informed consent. The procedures and findings from the RCT have been previously published[12,24]. Participants underwent baseline testing at the University of Melbourne, after which they were randomised to receive either unloading or conventional walking shoes. Testing was repeated at a 6-month follow-up visit. Participants were blinded to footwear groups, and because primary and secondary outcomes were participant-reported, assessors are also considered blinded.

Footwear interventions

The unloading shoes were black walking shoes (Gel-Melbourne OA, Asics Oceania, NSW, Australia) with a triple-density midsole that was stiffer laterally compared to medially and had a 5° full-length lateral wedge on the underside of the shoe insole. The conventional shoes were black walking shoes (Gel-Odyssey, Asics Oceania) that were visually similar to the unloading shoes, but did not have the laterally stiff midsole or the lateral wedge. We provided each participant with a pair of their allocated shoes in the appropriate size, with instructions to wear their allocated shoes for a minimum of 4 h each day for 6 months.

Dependent variable

The primary pain outcome in the trial was change in average knee pain on walking over the previous week, measured via a NRS with terminal descriptors of 'no pain' (score = 0) and 'worst pain possible' (score = 10). Participants completed the scale at the baseline and 6-month follow-up visits and we calculated the 6-month change. The trial was powered to detect a minimum clinically important difference in pain of 1.8 units[25].

Selected moderators

We chose moderators based on cross-sectional literature investigating biomechanical effects of unloading shoes and lateral wedge insoles in knee OA and biomechanical plausibility. To be considered a moderator, the variable must be a patient characteristic that was measured at baseline and, ideally, before randomisation[18].

Baseline peak KAM

To calculate peak KAM at baseline, we performed gait analysis while participants walked barefoot at self-selected normal walking speed. Barefoot walking was used to provide a standardised condition for all participants (without unblinding participants to footwear allocation for the RCT). Gait analysis was repeated at 6-months for the mediation analysis (see below). Markers for the Plug-in-Gait model were placed on anatomical landmarks of the lower limbs (Vicon Plug-in-Gait v2, Oxford, UK). Medial knee and ankle markers were added in the static trial to aid determination of axes and joint centers. Marker (120 Hz) and ground reaction force (GRF) (1200 Hz) data were concurrently recorded using a 12-camera Vicon MX system (Oxford, UK) and two force plates (AMTI, Inc., Watertown, MA, USA). External peak KAM during the first half of the stance phase was calculated using standard inverse dynamics in Vicon Nexus 1.85 software (Vicon, Oxford, UK). Peak KAM was expressed in the distal (shank) coordinate system, normalised to body weight times height (Nm/BWxHt%), and averaged over six walking trials. Body segment mass and inertial parameters used for inverse dynamics were calculated from Dempster as tabulated by Winter[26].

Radiographic severity

Participants who did not have their own knee x-ray from the previous 12 months underwent a weight-bearing standardised semi-flexed posteroanterior knee x-ray. Radiographic OA severity was graded using the KL grading scale[22] and categorised as grade 2 (mild), 3 (moderate) or 4 (severe).

Body mass

Body mass was recorded in the laboratory and is reported in kilograms.

Foot posture

Foot posture was measured using the foot posture index (FPI), a valid and reliable tool that scores six features from -2 (more supinated) to $+2$ (more pronated)[27]. These features include talar head palpation, lateral malleolar curvature, calcaneus inversion/eversion, talonavicular bulge, arch congruence and ab/adduction of the forefoot. Total scores range from -12 (highly supinated) to $+12$ (highly pronated).

Likelihood of neuropathic pain

The likelihood of neuropathic pain was scored using the painDETECT questionnaire, a reliable 13-item tool[28]. Final scores range between -1 and 38, with higher scores suggesting an increased likelihood of pain of neuropathic origin[28].

Diffuse knee pain

Participants indicated the location of knee pain on their most symptomatic knee using small crosses on a photographic knee pain map[29], and a tick box for the posterior knee. Pain zone data was collapsed in to five regions (anterior, medial, lateral, posterior and tibia), and diffuse knee pain was considered present if a participant experienced pain in three or more regions[30,31].

Selected mediators

We chose mediators based on the belief that unloading shoes and lateral wedge insoles reduce measures of the KAM[32–34], which in turn reduces knee pain in knee OA. To be considered a mediator, the variable must be expected to change because of the intervention, and therefore, must be measured before and after the intervention is administered. Thus, gait analysis was repeated at the 6-month follow-up visit in the participant's allocated study shoes, and change from barefoot at baseline was investigated for the mediation analysis. Biomechanical mediators were averaged over six walking trials.

Change in peak KAM

The peak external KAM was obtained from the first half of stance and normalised to body weight times height (Nm/BWxHt%).

Change in KAM impulse

The KAM impulse was calculated as the positive integral of the KAM-time curve (i.e., area under the curve), normalised to body weight and height, and reported as Nm·s/BWxHt%. It incorporates both the mean magnitude of the KAM and the time over which it is applied.

Statistical analysis

Stata v14 (Stata Corporation, College Station, TX, USA) was used for analyses. Statistical significance was set at $P \leq 0.05$. Participant characteristics were described using means and standard deviations for continuous variables, or number and percentage for categorical variables.

Moderation analysis

To determine whether the effect of randomised footwear group on walking pain was moderated by the selected baseline characteristics of participants, we included interactions between our chosen moderators and the randomised footwear group in linear regression models for change in walking pain from baseline to 6 months. Regression models were adjusted for baseline levels of pain.

For categorical moderators (KL grade 2–4, and presence/absence of diffuse knee pain), standard interaction terms between these and the footwear group were included in regression models. For the continuous moderators, we included interactions between fractional polynomial terms and footwear group in the regression models using the mfpi function[35].

Mediation analysis

Prior to full mediation analysis, we first selected only the potential mediators that were significantly different between footwear groups, as only these variables may mediate the effect of group on walking pain. These variables were selected by fitting linear regression models for the value of each selected mediator at 6 months, adjusting for the baseline mediator value (because this may be causally related to the 6-month value and hence change), KL grade (because randomisation was stratified by KL grade), and footwear group.

The full mediation analysis for each selected mediator involved fitting two linear models to decompose the “total” effect in to the “direct” and “indirect” effects of footwear group on walking pain (Fig. 1). The first was a linear regression model for walking pain at 6 months, adjusted for footwear group and the selected mediator at 6 months, and for baseline values of KL grade, walking pain and the selected mediator. This model allowed the direct effect of treatment group on the outcome (“C” in Fig. 1), and the effect of the mediator

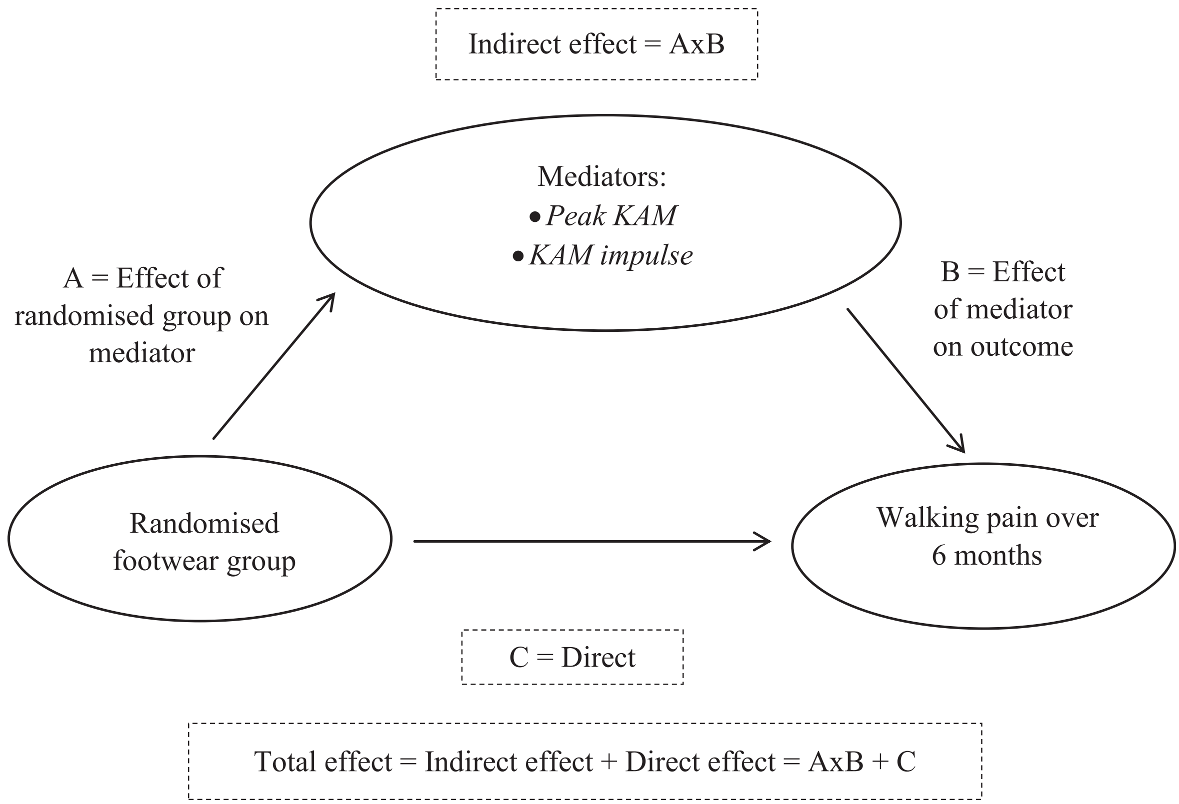

Fig. 1. Illustration of the mediation analysis which decomposes the "total" effect of footwear group on walking pain into the "indirect" effect of footwear group on pain (the effect of the treatment on the outcome that acts through the mediator) and the "direct" effect of footwear group on pain (the effect of the treatment on the outcome that does not act through the mediator). The p value for the indirect pathway needs to be significant for the variable to be considered to have mediated the effect of group on walking pain. KAM, knee adduction moment.

on the outcome ("B" in Fig. 1) to be estimated. The second was a linear regression model for the selected mediator at 6 months, adjusted for footwear group, and baseline values of the mediator, walking pain and KL grade. This model allowed for an estimate of the effect of randomised group on the mediator ("A" in Fig. 1). The indirect effect is obtained by multiplying the estimates of "A" and "B". Models were fit using the paramed command[36], and standard errors were calculated using 1000 bootstrap replications.

Finally, if a potential moderator demonstrated a statistically significant interaction with footwear group, an additional mediation analysis was conducted to determine whether the mechanism by which the unloading shoes (relative to conventional shoes) changed walking pain was dependent on the significant moderator.

Results

Sample characteristics

Descriptive statistics are presented in Table I. Characteristics were similar between the two footwear groups. Participants were generally overweight and reported moderate pain levels on walking.

Moderation analysis

Table II shows the results of the moderation analyses for the categorical variables of KL grade and diffuse pain. Figure 2 displays the relationship between the continuous moderators and the difference in change in walking pain between the footwear groups. Of the potential moderators, only KL grade demonstrated a statistically significant interaction with footwear group ($P = 0.02$). The results suggest that in participants with a KL grade 2, reductions in walking pain over 6 months were greater with conventional shoes compared to unloading shoes, while in those with KL grades $\geq$3, reductions were more likely to be greater with unloading shoes (Table II).

Mediation analysis

Table III presents descriptive statistics for the potential mediators over time by footwear group. The differences between randomised treatment group in the mediators measured at 6-months, adjusted for baseline values of the potential mediator and KL grade are also included. As expected, KAM was elevated at follow-up in both groups because KAM was recorded barefoot at baseline, and in allocated shoes at 6-months, and footwear is known to increase the KAM compared to barefeet[4,37]. However, unloading shoes resulted in a significantly lower peak KAM and KAM impulse at 6 months compared to conventional shoes, and were carried forward to the next stage of analysis.

Results of the mediation analysis are presented in Table IV. As in the primary analysis[12], there was no statistically significant total effect of randomised footwear group on walking pain. However, despite between-group differences in the KAM and KAM impulse, the biomechanical changes did not lead to reductions in walking pain. This suggests that the indirect effect of the unloading shoes acting through these potential mediators was not statistically significant for the group as a whole.

Finally, we also assessed mediation of the moderated effect of randomized shoe group by KL grade, as this was the only moderator

Table I
Descriptive characteristics of participants by group, reported as mean (standard deviation) unless otherwise stated

	Unloading shoes ($n = 83$)	Conventional shoes ($n = 81$)
Baseline characteristics		
Age (years)	65.2 (6.9)	63.3 (7.9)
Male, *n* (%)	41 (49%)	39 (48%)
Height (m)	1.67 (0.10)	1.66 (0.10)
BMI (kg/m^2)	29.7 (3.6)	29.7 (3.7)
Walking pain (0–10)	6.0 (1.6)	5.7 (1.9)
Dependent variable*		
Change in walking pain at 6 months	1.8 (2.9)	1.6 (2.8)
Selected moderators		
Baseline peak KAM (Nm/BWxHt%)†	4.1 (1.2)	4.1 (1.1)
Radiographic disease severity, *n* (%)		
KL grade 2	25 (30%)	24 (30%)
KL grade 3	26 (31%)	26 (32%)
KL grade 4	32 (39%)	31 (38%)
Body mass (kg)	83.3 (14.4)	82.6 (15.2)
FPI score (−12 to +12)	5.0 (3.4)	4.8 (3.6)
PainDETECT score (−1 to 38)	8.1 (5.2)	8.6 (5.6)
Diffuse knee pain present, *n* (%)	36 (43%)	32 (40%)

KL, Kellgren & Lawrence grading system; BMI, body mass index; FPI, foot posture index; KAM, knee adduction moment; NRS, numerical rating scale.
* Where positive scores indicate improved pain at 6 months.
† Recorded during barefoot walking.

Table II
Results of the moderation analysis for categorical moderators

Moderator	Adjusted mean change in walking pain at 6 months (unloading shoes-conventional shoes) (95% CI)	Interaction *P*-value
KL Grade		0.02
2	−1.64 (−3.07, −0.21)	
3	0.98 (−0.44, 2.39)	
4	0.64 (−0.64, 1.93)	
Diffuse knee pain		0.24
Present	0.64 (−0.63, 1.91)	
Absent	−0.35 (−1.42, 0.72)	

CI, confidence intervals; KL, Kellgren & Lawrence.

to interact with footwear group. For this analysis, KL grades 3 and 4 were combined because our moderation analysis showed the relationship between pain and change in KAM with unloading shoes varied between those with more ($KL \geq 3$) and less ($KL = 2$) severe radiographic knee OA. The results suggest some differences in the mechanisms of the unloading shoes, relative to conventional shoes, for the different KL grades (Table V). Specifically, there may be some evidence that unloading shoes reduce walking pain (compared to conventional shoes) by acting through reductions in peak KAM (indirect effect −0.31, 95% CIs −0.65, 0.03; $P = 0.07$) for KL grades ≥3, but not in people with KL grade 2.

Discussion

This is the first study to explore moderators and mediators of effects of a biomechanical intervention for knee OA. Our results suggest that the therapeutic response to unloading and conventional footwear is moderated by radiographic severity of knee OA. In people with KL grades 3 or 4, improvements in walking pain at 6 months were greater in the unloading compared to the conventional shoes, whereas people with KL grade 2 responded more favourably to the conventional shoes. Our results also suggest that the mechanisms by which unloading shoes reduce walking pain are dependent upon radiographic severity. Reductions in peak KAM appeared to mediate the reduction in walking pain with unloading shoes in people with KL grades ≥3, but not KL grade 2. These findings suggest that people with moderate to severe radiographic knee OA may comprise a patient subgroup most likely to benefit from biomechanical interventions designed to reduce the KAM, such as unloading shoes. Conversely, people with mild knee OA appear to benefit more from conventional walking shoes.

Our data suggest that walking pain in people with moderate to severe disease is partially driven by increases in peak KAM, and that other untested mechanisms may be responsible for knee pain in those with mild disease. As our study was not designed to evaluate mechanisms other than KAM parameters, we cannot speculate on the possible reasons explaining why greater reductions in pain were observed with conventional shoes (compared to unloading shoes) in people with mild OA. A previous study reported that KAM reductions with lateral wedges were not associated with change in pain over 3 months[38]. This study included a small sample ($n = 15$), some of whom had KL grade 1 ("doubtful" radiographic OA). Importantly, control group data were not included in the analyses of mediators, and thus the indirect effect of lateral wedges that acted through KAM was not determined, which limits the conclusions that can be drawn from this study regarding mediation. Our previous cross-sectional study showed no relationship between KAM parameters and symptoms at baseline in this cohort with KL grade 2, and that higher KAM impulse was associated with more severe pain in KL grade 3, which supports the current findings[20]. Interestingly, Henriksen *et al.*[39] showed an *inverse* relationship between pain severity and dynamic knee loading in people with KL grades ≤2, such that greater pain severity was associated with *lower* dynamic knee loading. The authors speculated that, rather than abnormalities in knee loading causing pain in people with mild OA, the presence of knee pain leads to gait adaptations that result in reduced dynamic knee loading.

Our mediation analyses provide further evidence that walking pain in people with moderate to severe disease is driven by abnormalities in knee loading more than it is in those with mild disease. When we did not consider the moderating effect of radiographic severity, mediation analyses showed some evidence that the indirect effect of the unloading shoes acting through peak KAM may have suppressed effects of unloading shoes on walking pain ($P = 0.09$; Table IV). However, when we assessed mediation of the moderated effect of randomised shoe group by KL grade, there was some evidence that unloading shoes reduced walking pain via reductions in peak KAM only in those with KL grades ≥3. There was no evidence of this, or of the effects of any other potential mediator, in people with KL grade 2. This suggests that not only does the

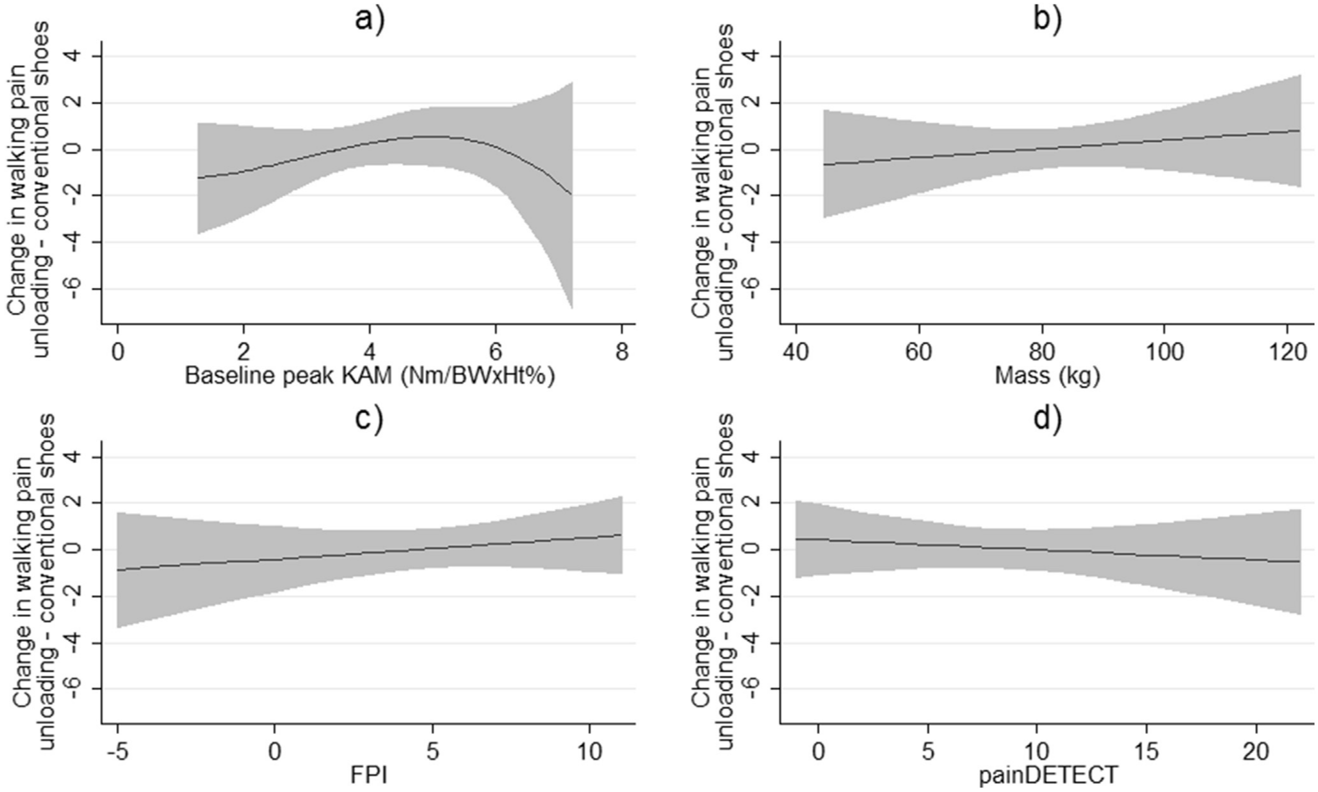

Fig. 2. Interaction between randomised footwear group and a) peak knee adduction moment (KAM), b) mass, c) foot posture index (FPI) and d) likelihood of neuropathic pain (painDETECT score) for walking pain. The solid line indicates the difference between unloading shoes and conventional shoes, with 95% confidence intervals indicated by the shaded area.

Table III
Mean (95% confidence intervals) of potential mediators by randomised footwear group at baseline (barefoot) and 6 months (in allocated shoes), and mean adjusted differences between treatment groups at 6 months, adjusted for baseline mediator value, baseline walking pain, and KL grade

Potential mediators	Baseline*		6 months*		Mean adjusted difference at 6 months† (95% CI)	*P*-value
	Unloading shoes (*n* = 83)	Conventional shoes (*n* = 81)	Unloading shoes (*n* = 68)	Conventional shoes (*n* = 67)		
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		
Peak KAM (Nm/BWxHt%)	4.10 (3.84, 4.36)	4.08 (3.84, 4.33)	4.36 (4.04, 4.67)	4.54 (4.24, 4.83)	−0.28 (−0.50, −0.05)	0.02
KAM impulse (Nm·s/BWxHt%)	1.35 (1.26, 1.45)	1.31 (1.22, 1.39)	1.42 (1.32, 1.52)	1.46 (1.36, 1.57)	−0.10 (−0.16, −0.05)	<0.001

CI, confidence intervals; KAM, knee adduction moment; KL, Kellgren & Lawrence.
* Baseline values recorded during barefoot walking, 6-month values recorded while walking in allocated shoes.
† Determined as unloading shoes minus conventional shoes.

Table IV
Effect estimates (95% confidence intervals) of the total, direct, and indirect effects of randomised footwear group on walking pain at 6 months, for each of the four potential mediators considered for a full mediation analysis

Potential mediators	Total effect		Direct effect		Indirect effect	
	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value
Change in peak KAM (Nm/BWxHt%)	0.04 (−0.79, 0.86)	0.93	−0.20 (−1.06, 0.66)	0.65	0.23 (−0.03, 0.50)	0.09
Change in KAM impulse (Nm·s/BWxHt%)	−0.02 (−0.84, 0.80)	0.97	−0.10 (−1.00, 0.79)	0.82	0.09 (−0.23, 0.40)	0.59

CI, confidence intervals; KAM, knee adduction moment.

effect of the unloading shoes depend on baseline KL grade, but the mechanism by which the unloading shoes work appears to be through altered biomechanics in people with KL grades 3 or 4.

It is important to acknowledge our study was underpowered to assess subgroups effects, and that some of our *P* values were close to, but not less than, our alpha level of 0.05. Thus most of our findings are hypothesis-generating rather than conclusive. However, this is consistent with an exploratory study such as ours. In support, the American Statistical Association recently cautioned against binary conclusions based on a specific threshold[40]. We feel our cautious conclusions are appropriate given ours was a robust and well-designed RCT, with valid and reliable outcome measures.

Table V
Effect estimates (95% confidence intervals) of the total, direct, and indirect effects of randomised footwear group on walking pain at 6 months, for each of the four potential mediators considered for a full mediation analysis, by Kellgren & Lawrence grade

Potential mediators	KL Grade	Total effect		Direct effect		Indirect effect	
		Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value	Effect (95% CI)	*P*-value
Change in peak KAM (Nm/BWxHt%)	2	−1.38 (−2.81, 0.06)	0.06	−1.26 (−2.71, 0.20)	0.09	−0.12 (−0.44, 0.20)	0.47
	3 & 4	0.70 (−0.31, 1.70)	0.18	1.01 (0.01, 2.01)	0.05	−0.31 (−0.65, 0.03)	0.07
Change in KAM impulse (Nm·s/BWxHt%)	2	−1.40 (−2.74, −0.06)	0.04	−1.32 (−2.70, 0.07)	0.06	−0.09 (−0.41, 0.24)	0.60
	3 & 4	0.63 (−0.40, 1.66)	0.23	0.74 (−0.36, 1.85)	0.19	−0.11 (−0.46, 0.24)	0.54

CI, confidence intervals; KAM, knee adduction moment; KL, Kellgren & Lawrence.

Future studies that are appropriately powered to test the effects of unloading shoes on symptoms in people with moderate to severe radiographic disease are needed to validate our preliminary findings and to enable recommendations for clinical practice.

There are some other limitations to this study. There may be other variables that we did not measure at baseline that may moderate or mediate the effects of unloading shoes on knee pain, such as muscle strength and/or rearfoot coronal plane motion. Our use of a skin-based marker model such as Plug-in-Gait may be considered a limitation, however, we implemented several refinements to improve estimation of knee and ankle joint centres and axes. Finally, baseline gait assessment was performed barefoot to provide a standardised condition for all participants, and it is not known whether the unloading shoes increased or decreased KAM relative to participant's own everyday footwear.

Our findings may have important clinical and research implications. This is the first study to suggest that reducing peak KAM with a biomechanical intervention can lead to reductions in walking pain in specific subgroups of knee OA patients. Our data suggest that in people with KL grade $\geq$3, a 1-unit reduction in KAM is associated with a 0.63-unit reduction in NRS walking pain (95% CI 1.35 to −0.09). However, the mean adjusted difference between unloading and conventional shoes in our cohort was only 0.28 KAM units (possibly as high as 0.5 units). Thus unloading shoes in their current form, and used in isolation from other strategies, are unlikely to achieve a 1-unit KAM reduction. Refinements to the design of the unloading shoes tested in this study may be required in order to maximize knee unloading effects. Alternatively, combining unloading shoes with other treatments designed to reduce the KAM (such as unloading knee braces or gait retraining) may also be appropriate. Indeed, given that the minimum clinically meaningful change in pain is approximately 1.8 units, our data suggests that biomechanical interventions should aim to reduce the KAM by amounts even greater than 1-unit, if a clinically meaningful reduction in pain is to occur. Importantly, our findings may also help to explain why previous RCTs investigating unloading shoes and lateral wedge insoles have shown no additional symptomatic benefit over comparators, given all have included patients with mild (KL $\leq$ 2) radiographic disease[12,41–45]. Future RCTs of biomechanical interventions designed to reduce parameters of dynamic knee loading may be best tested in samples of people with moderate to severe radiographic knee OA.

In conclusion, effects of unloading shoes on knee pain are influenced by radiographic severity of knee OA. Unloading shoes conferred additional symptomatic benefits over conventional shoes in people with moderate to severe knee OA, and effects appear to be mediated by a reduction in peak KAM. Conversely, people with mild knee OA responded more favourably to conventional shoes. However, it is important to acknowledge that our study was underpowered for subgroup analyses. Patients with moderate to severe disease may represent a subgroup to which biomechanical interventions designed to reduce the KAM may be more effectively targeted. As this was an exploratory study, the findings need to be confirmed in future clinical trials.

Author contributions

All authors were involved in draughting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Paterson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design

KLP, JK, KLB, TVW, DJH and RSH.

Acquisition of data

KLP, BRM and PKC.

Analysis and interpretation of data

KLP, JK, KLB, TVW, DJH and RSH.

Conflict of interest

RSH, TVW and KLB, and the University of Melbourne received royalties from sales of the Gel Melbourne OA (unloading) shoes from 2012 to 2014. The manufacturer of the unloading shoes played no role in the study design nor had any input into the analysis and interpretation of data from this study.

Funding

The trial was funded by the Australian National Health and Medical Research Council (Project #1044396). RSH is supported by an Australian Research Council Future Fellowship (FT130100175). KLB is supported by a National Health & Medical Research Council Fellowship (#1058440). DJH is supported by a National Health & Medical Research Council Practitioner Fellowship (#1079777).

References

1. National Clinical Guideline Centre. Osteoarthritis: Care and Management in Adults. Clinical Guideline CG177. Methods, Evidence and Recommendations. London: National Institute for Health and Care Excellence; 2014.
2. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, *et al.* OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil 2014;22:363–88.
3. Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006;18:514–8.
4. Radzimski AO, Mündermann A, Sole G. Effect of footwear on the external knee adduction moment — a systematic review. Knee 2012;19:163–75.
5. Shakoor N, Sengupta M, Foucher KC, Wimmer MA, Fogg LF, Block JA. Effects of common footwear on joint loading in osteoarthritis of the knee. Arthritis Care Res 2010;62:917–23.
6. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, *et al.* EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72:1125–35.

7. Bennell KL, Kean CO, Wrigley TV, Hinman RS. Effects of a modified shoe on knee load in people with and those without knee osteoarthritis. Arthritis Rheum 2013;65:701–9.
8. Erhart JC, Mündermann A, Elspas B, Giori NJ, Andriacchi TP. A variable-stiffness shoe lowers the knee adduction moment in subjects with symptoms of medial compartment knee osteoarthritis. J Biomech 2008;41:2720–5.
9. Amin S, Luepongsak N, McGibbon CA, LaValley MP, Krebs DE, Felson DT. Knee adduction moment and development of chronic knee pain in elders. Arthritis Care Res 2004;51:371–6.
10. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 2002;61:617–22.
11. Kito N, Shinkoda K, Yamasaki T, Kanemura N, Anan M, Okanishi N, *et al*. Contribution of knee adduction moment impulse to pain and disability in Japanese women with medial knee osteoarthritis. Clin Biomech 2010;25:914–9.
12. Hinman RS, Wrigley TV, Metcalf BR, Campbell PK, Paterson KL, Hunter DJ, *et al*. Unloading shoes for self-management of knee osteoarthritis: a randomized trial. Ann Intern Med 2016;165: 381–9.
13. Erhart JC, Mündermann A, Elspas B, Giori NJ, Andriacchi TP. Changes in knee adduction moment, pain, and functionality with a variable-stiffness walking shoe after 6 months. J Orthop Res 2010;28:873–9.
14. Erhart-Hledik JC, Elspas B, Giori NJ, Andriacchi TP. Effect of variable-stiffness walking shoes on knee adduction moment, pain, and function in subjects with medial compartment knee osteoarthritis after 1 year. J Orthop Res 2012;30:514–21.
15. Lewinson RT, Stefanyshyn DJ. Unloading shoes for self-management of knee osteoarthritis. Ann Intern Med 2017;166:311–2.
16. Arnold JB. Lateral wedge insoles for people with medial knee osteoarthritis: one size fits all, some or none? Osteoarthr Cartil 2016;24:193–5.
17. Chapman GJ, Parkes MJ, Forsythe L, Felson DT, Jones RK. Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?: an ancillary analysis from the SILK trial. Osteoarthr Cartil 2015;23:1316–22.
18. Kraemer H, Wilson G, Fairburn CG, Agras W. Mediators and moderators of treatment effects in randomized clinical trials. Arch General Psychiatry 2002;59:877–83.
19. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: a systematic review. Knee 2009;16: 303–9.
20. Hall M, Bennell KL, Wrigley TV, Metcalf BR, Campbell PK, Kasza J, *et al*. The knee adduction moment and knee osteoarthritis symptoms: relationships according to radiographic disease severity. Osteoarthr Cartil 2016;24:S448–9.
21. Sawada T, Kito N, Yukimune M, Tokuda K, Tanimoto K, Anan M, *et al*. Biomechanical effects of lateral and medial wedge insoles on unilateral weight bearing. J Phys Ther Sci 2016;28:280–5.
22. Kellgren JH, Jeffrey MR, Ball J. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs, Volume II. Oxford: Blackwell Scientific; 1963.
23. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthr Cartil 2007;15:A1–A56.
24. Hinman R, Wrigley T, Metcalf B, Hunter D, Campbell P, Paterson K, *et al*. Unloading shoes for osteoarthritis of the knee: protocol for the SHARK randomised controlled trial. BMC Musculoskelet Disord 2014;15:48.
25. Bellamy N, Carette S, Ford PM, Kean WF, le Riche NG, Lussier A, *et al*. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials–results of a consensus development (Delphi) exercise. J Rheumatol 1992;19:451–7.
26. Winter DA. Biomechanics and Motor Control of Human Movement. 3rd edn. New York: John Wiley and Sons; 2005.
27. Redmond AC, Crosbie J, Ouvrier RA. Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index. Clin Biomech 2006;21:89–98.
28. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22: 1911–20.
29. Elson DW, Jones S, Caplan N, Stewart S, St Clair Gibson A, Kader DF. The photographic knee pain map: locating knee pain with an instrument developed for diagnostic, communication and research purposes. Knee 2011;18:417–23.
30. Van Ginckel A, Bennell KL, Campbell PK, Kasza J, Wrigley TV, Hunter DJ, *et al*. Associations between changes in knee pain location and clinical symptoms in people with medial knee osteoarthritis using footwear for self-management: an exploratory study. Osteoarthr Cartil 2017;25:1257–64.
31. Van Ginckel A, Bennell KL, Campbell PK, Wrigley TV, Hunter DJ, Hinman RS. Location of knee pain in medial knee osteoarthritis: patterns and associations with self-reported clinical symptoms. Osteoarthr Cartil 2016;24:1135–42.
32. Kean CO, Bennell KL, Wrigley TV, Hinman RS. Modified walking shoes for knee osteoarthritis: mechanisms for reductions in the knee adduction moment. J Biomech 2013;46: 2060–6.
33. Jenkyn TR, Erhart JC, Andriacchi TP. An analysis of the mechanisms for reducing the knee adduction moment during walking using a variable stiffness shoe in subjects with knee osteoarthritis. J Biomech 2011;44:1271–6.
34. Hinman RS, Bowles KA, Metcalf BB, Wrigley TV, Bennell KL. Lateral wedge insoles for medial knee osteoarthritis: effects on lower limb frontal plane biomechanics. Clin Biomech 2012;27: 27–33.
35. Royston P, Sauerbrei W. Two techniques for investigating interactions between treatment and continuous covariates in clinical trials. Stata J 2009;9:230.
36. Emsley R, Liu H. PARAMED: Stata Module to Perform Causal Mediation Analysis Using Parametric Regression Models. URL: http://ideas.repec.org/c/boc/bocode/s457581.html.
37. Paterson KL, Bennell KL, Wrigley TV, Metcalf BR, Kasza J, Hinman RS. Effects of footwear on the knee adduction moment in medial knee osteoarthritis: classification criteria for flat flexible vs stable supportive shoes. Osteoarthr Cartil 2017;25: 234–41.
38. Lewinson RT, Vallerand IA, Collins KH, Wiley JP, Lun VMY, Patel C, *et al*. Reduced knee adduction moments for management of knee osteoarthritis:: a three month phase I/II randomized controlled trial. Gait Posture 2016;50:60–8.
39. Henriksen M, Aaboe J, Bliddal H. The relationship between pain and dynamic knee joint loading in knee osteoarthritis varies with radiographic disease severity. A cross sectional study. Knee 2012;19:392–8.
40. Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. Am Stat 2016;70:129–33.
41. Barrios JA, Crenshaw JR, Royer TD, Davis IS. Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: a one-year prospective controlled trial. Knee 2009;16:136–42.
42. Bennell KL, Bowles K-A, Payne C, Cicuttini F, Williamson E, Forbes A, *et al*. Lateral wedge insoles for medial knee

osteoarthritis: 12 month randomised controlled trial. Br Med J 2011;342.

43. Pham T, Maillefert JF, Hudry C, Kieffert P, Bourgeois P, Lechevalier D, *et al*. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a two-year prospective randomized controlled study. Osteoarthr Cartil 2004;12:46–55.
44. Maillefert JF, Hudry C, Baron G, Kieffert P, Bourgeois P, Lechevalier D, *et al*. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a prospective randomized controlled study. Osteoarthr Cartil 2001;9:738–45.
45. de Campos GC, Rezende MU, Pasqualin T, Frucchi R, Bolliger Neto R. Lateral wedge insole for knee osteoarthritis: randomized clinical trial. Sao Paulo Med J 2015;133:13–9.