Osteoarthritis and Cartilage 27 (2019) 1324–1338

Osteoarthritis and Cartilage

Effect of cane use on bone marrow lesion volume in people with medial tibiofemoral knee osteoarthritis: randomized clinical trial

A. Van Ginckel † ‡ *, R.S. Hinman ‡, T.V. Wrigley ‡, D.J. Hunter ‡, C.J. Marshall ‡, J. Duryea ††, L. Melo § ||, M. Simic ¶, J. Kasza #, S.R. Robbins § ||, J.A. Wallis ‡‡, K.L. Bennell ‡

† *Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium*
‡ *Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Parkville, Australia*
§ *Institute of Bone and Joint Research, Kolling Institute, The University of Sydney, Sydney, Australia*
|| *Department of Rheumatology, Royal North Shore Hospital, St Leonards, Australia*
¶ *Discipline of Physiotherapy, Musculoskeletal Research Group, Faculty of Health Sciences, The University of Sydney, Sydney, Australia*
# *Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*
†† *Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA*
‡‡ *Department of Physical Therapy, Eastern Health. Department of Physical Therapy, La Trobe University, Melbourne, Australia*

ARTICLE INFO

Article history:
Received 10 November 2018
Accepted 3 May 2019

Keywords:
Cane
Magnetic resonance imaging
Structure-modification
Bone marrow lesions
Randomized controlled trial
Osteoarthritis
Knee
Biomechanics

SUMMARY

Objective: To evaluate effects of daily cane use for 3 months on medial tibiofemoral bone marrow lesion (BML) volumes in people with medial tibiofemoral osteoarthritis (OA).
Design: In this randomized controlled trial (RCT), 79 participants with medial tibiofemoral OA were randomized to either a cane group (using a cane whenever walking) or control group (not using any gait aid) for 3 months. The cane group received a single training session by a physiotherapist, using a biofeedback cane to teach optimal technique and body weight support and motor learning principles to facilitate retention of learning. The primary outcome was change in total medial tibiofemoral BML volume (per unit bone volume) measured from magnetic resonance imaging (MRI) at 3 months. Secondary outcomes were BML volumes (per unit bone volume) of the medial tibia and femur, and patient-reported outcomes of overall knee pain, knee pain on walking, physical function, perceived global symptom changes and health-related quality of life. MRI analyses were performed by a blinded assessor.
Results: Seventy-eight participants (99%) completed the primary outcome. Mean (standard deviation) daily cane use was 2.3 (1.7) hours over 3 months. No evidence of between-group differences was found for change in total medial tibiofemoral BML volume (mean difference: −0.0010 (95% confidence intervals: −0.0022, 0.0003)). Most secondary outcomes showed minimal differences between groups.
Conclusion: Daily use of a cane during walking for 3 months aiming to reduce knee joint loading did not change medial tibiofemoral BML volumes compared to no use of gait aids.
Clinical trial registration: Australian New Zealand Clinical Trial Registry (ACTRN12614000909628).

Bone marrow lesions (BMLs) have gained interest as structural targets in clinical trials of osteoarthritis (OA).[1,2] They are thought to result from excessive joint stress and have been associated with worsening joint structural damage and symptoms.[1,3–5] Higher medial-to-lateral joint loading during walking is apparent in people with medial tibiofemoral OA compared to controls.[6] There is some evidence that elevated joint loading can increase the risk of cartilage loss and bone marrow lesion (BML) development in medial tibiofemoral compartments.[7,8] Unlike cartilage, changes in BML size are detectable over periods as short as 6–12 weeks, as evident from a 6-week trial of patellofemoral bracing which reduced patellofemoral joint contact stresses and BMLs in people with

* Address correspondence and reprint requests to: A. Van Ginckel, Department of Rehabilitation Sciences, Ghent University, Ghent 9000, BelgiumUniversity Hospital Campus, Building 3B3 office 007, Belgium. Tel.: 32-9-332-53-74.
E-mail addresses: Ans.VanGinckel@UGent.be (A. Van Ginckel), ranash@unimelb.edu.au (R.S. Hinman), timw@unimelb.edu.au (T.V. Wrigley), david.hunter@sydney.edu.au (D.J. Hunter), c.marshall@unimelb.edu.au (C.J. Marshall), jduryea@bwh.harvard.edu (J. Duryea), luciano.melo@sydney.edu.au (L. Melo), milena.simic@sydney.edu.au (M. Simic), jessica.kasza@monash.edu (J. Kasza), sarah.robbins@sydney.edu.au (S.R. Robbins), Jason.wallis@easternhealth.org.au (J.A. Wallis), k.bennell@unimelb.edu.au (K.L. Bennell).

https://doi.org/10.1016/j.joca.2019.05.004
1063-4584/

patellofemoral OA.[1,9] Thus, biomechanical interventions reducing medial tibiofemoral load may facilitate BML resolution in this compartment, thereby reducing structural decline in medial tibiofemoral OA.

Walking canes constitute a simple biomechanical offloading strategy for people with medial tibiofemoral OA.[10] Held in the contralateral hand, walking canes can decrease medial compartmental knee load during walking by up to 17%[10] and may potentially modify joint structure.

This study aimed to investigate whether contralateral cane use can alter joint structure in knee OA. We hypothesized that daily cane walking for 3 months reduces medial tibiofemoral BML volumes compared to no gait aids in people with medial tibiofemoral OA. We also investigated the effects of cane use on clinical symptoms and health-related quality of life.

Methods

Design overview

We conducted a parallel-group randomized controlled trial (RCT) with 1:1 allocation into an intervention and control group, at two sites in Australia (Melbourne, Sydney). The protocol has been published.[11] Recruitment occurred from October 2014 to December 2017, with follow-up completed March 2018. The trial was prospectively registered with the Australian New Zealand Clinical Trial Registry (ACTRN12614000909628), approved by the local Institutional Human Ethics Committees. All participants provided written informed consent.

Study participants

We recruited participants via advertisements, medical practitioners, hospitals and our volunteer databases. Eligibility was ascertained via an online and telephone survey, radiography (KLB) and magnetic resonance imaging (MRI) (AVG).[11] Inclusion criteria were: (i) aged $\geq$50 years; (ii) knee pain on most days of the past month; (iii) radiographic evidence of medial tibiofemoral OA (Kellgren Lawrence (KL) grade $\geq$2 and Osteoarthritis Research Society grade $\geq$1 medial joint space narrowing and greater than lateral)[12–14]; (iv) at least one medial tibiofemoral BML on MRI; (v) willing to use a cane daily for 3 months if allocated to cane group; and (vi) sufficient English language. Exclusion criteria were: (i) imaging contra-indications; (ii) history of knee replacement or osteotomy on either knee; (iii) knee arthroscopy or intra-articular (corticosteroid or hyaluronan) injections in the prior 6 months; (iv) planned hip or knee surgery in subsequent 3 months; (v) current use of potential disease-modifying and/or anti-bone resorption drugs; (vi) current and previous (past 3 months to match intervention duration) use of shoe inserts, knee/ankle braces or customized shoes prescribed by a health professional and inability/unwillingness to cease for trial; (vii) current and previous (past 3 months) cane use; and (viii) other conditions affecting lower limb function or ability to use a cane. The most painful knee was considered the study knee. In cases of bilaterally eligible knees, the right knee was studied.

Randomization and blinding

Participants were randomly assigned in permuted blocks of size 6 to 10 and stratified by site (Melbourne, Sydney), KL grade (grade 2, 3 or 4) and body mass index (BMI) ($\leq$30.4 kg/m^2, $\geq$30.5 kg/m^2). The randomization schedule was prepared and concealed in consecutively numbered, sealed, opaque envelopes by an independent researcher and stored in a central locked location. A researcher not involved in the trial accessed the schedule. BML volume calculations (including the primary outcome) were performed assessor-blinded. The patient-reported measures of symptoms and health-related quality of life were not blinded as participants were aware of group allocation. Statistical analyses were performed by a blinded statistician.

Interventions

The cane group received a single individual training session from a physiotherapist with >10 years of experience in musculoskeletal physiotherapy (CM, LM, SRR) (Appendix 1). This structured 30–45 min session aimed to teach the correct cane gait technique to achieve optimal amount and timing of knee off-loading.[10] In addition to motor learning principles to facilitate retention of learning effects,[11] we utilized a force-feedback cane with on-off vibration biofeedback through the handle (nCounters, Kew, Victoria, Australia; Fig. 1) during the training session, with vibration triggered when a target force window of 10% (+/− 2.5%) of body weight support through the cane was reached when walking. Participants were taught to consistently achieve $\geq$10% of body weight support. This amount was chosen as this is achievable and reduces external medial joint loading parameters comparable to other gait modification strategies for knee OA.[15–17] The physiotherapist monitored cane force in real-time and used a checklist of optimal motion patterns to provide feedback (Appendix 1).[11] Additionally, the session included education about benefits and barriers to cane use to facilitate adherence. Participants were then provided with a generic "swan neck" cane (Fig. 1) fitted to their height[18] and instructed to use it daily whenever walking, for 3 months. The cane group was contacted fortnightly via telephone to remind them to complete/return logbooks and facilitate adherence to cane use by discussing any issues including barriers.

To maximize treatment fidelity, physiotherapists were provided with a manual and 1-day training session in how to teach the correct gait technique and use the biofeedback system. A refresher training session was organised for the physiotherapists halfway through the trial.

The control group was instructed to maintain their regular lifestyle and to not use any gait aids during the study. Both groups were allowed to continue regular medication for knee pain (if any).

Outcomes

The primary outcome was change (baseline to 3 months) in the total medial tibiofemoral BML volume per unit of the articular bone volume (mm^3/mm^3).[11,19] In our laboratory, we attained excellent intra-rater reliability (intra-class correlation coefficient (2,1) of 0.9 (95% confidence interval (CI): 0.8–0.9)) and acceptable precision (Standard Error of Measurement (SEM): 0.0010). Convergent validity of BML volume measurements from MRI has been established in knee OA samples,[20] with normalized BML volumes superior to absolute volumes in reliability and potentially sensitivity to change.[19] We used 3T MRI (Magnetom Trio Tim in Melbourne, Magnetom Verio in Sydney; Siemens Medical Solutions, Erlangen, Germany) implementing a T2-weighted fat-suppressed turbo spin-echo sequence and imaging parameters published previously.[11,21] A trained reader with >8 years of experience in musculoskeletal MRI analysis (AVG) quantified changes in OA-related BML volumes with support from a senior researcher with extensive expertise in MRI and OA (DJH). Scans were blinded to time of scanning and group allocation, and analysed in pairs. BMLs were segmented in custom-written software ((C and IDL (Research Systems, Inc., Boulder, CO)) applying semi-automated methods.[11,20] We excluded intercondylar tibial regions from segmentations as well as differential

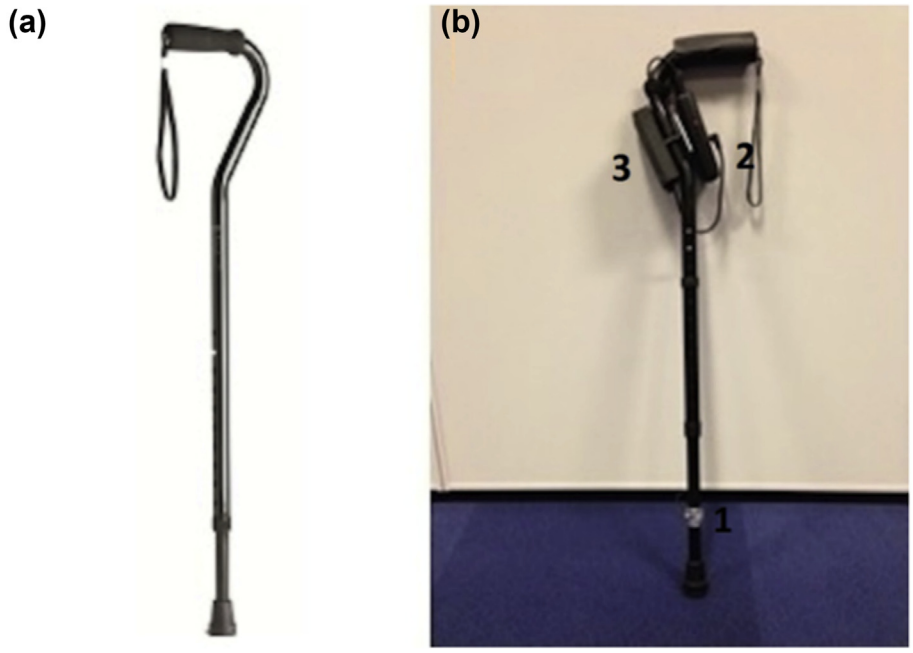

Fig. 1. The study canes: (a) generic swan neck cane and (b) vibration feedback cane used for training in correct technique. 1: embedded uniaxial load cell; 2: vibration feedback unit; 3: data logger.

diagnoses falsely suggestive of OA-related BMLs.[11] Subsequently, based on the MRI Osteoarthritis Knee Score,[21] knee joints were subdivided in medial/lateral tibiofemoral and patellofemoral joint compartments. Absolute BML volumes (mm^3) were calculated for each compartment separately and volumes of medial tibial and femoral BMLs summed for the primary outcome. To normalize BML volumes to bone volume units, absolute BML volumes were divided by end-bone volumes (mm^3) determined from the same MR images via semi-automated slice-by-slice segmentations of bone contours using custom-written software (Matlab, The MathWorks Inc., Natick, MA).[11] (Fig. 2) Quality assurance was performed for pairs showing BML volume changes of ≥50%. This led to 33 cases reviewed and 12 corrected.

Secondary outcomes comprised either baseline to 3 months changes or were collected at 3 months only. These included BML volumes of the medial tibia and medial femur separately, as per the primary outcome; knee pain using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC, Likert version 3.1) pain subscale (scores ranging 0–20, higher scores indicating worse outcomes and minimum clinically important difference (MCID) of ≥18% from baseline)[22]; difficulty with physical functioning using the WOMAC physical function subscale (scores ranging 0 (no dysfunction)-68 (maximum dysfunction) and MCID of 6 non-normalized units)[23]; average overall knee pain and knee pain on walking during the past week, both recorded on separate 11-point numeric rating scales (NRS) with terminal descriptors "0 = no pain" to "10 = worst pain possible" and MCID of 1.8 units[24]; participant-perceived global change in pain, physical function and overall condition, measured on 7-point ordinal scales (with anchors "1 = much worse" to "7 = much better")[25] at 3 months with participants reporting they were moderately better or much better classified as "improved"; health-related quality of life using the Assessment of Quality of Life 6D scale (scores range −0.04 (lowest quality) to 1.00 (highest quality) and MCID of 0.06 units).[26]

Additional measures included participant demographics; physical activity measured as average daily step count over 7 consecutive days in weeks 1 and 12 using waist pedometers (Omron HJ-720ITC, Omron Healthcare, Illinois, USA), and habitual physical activity over the past week at baseline and 3 months evaluated with the Physical Activity Scale for the Elderly questionnaire (scores ranging 0–400, higher scores representing greater physical activity levels).[27] Adherence was measured using logbooks for: i) daily duration of cane use, averaged in hours for each month; ii) amount of cane use whenever walking on an 11-point NRS (anchors "not at all" to "always whenever walking") measured weekly and averaged for each month; and iii) amount of cane use whenever walking over the entire intervention period, using an identical NRS measured at 3 months.

Following cane training, process measures recorded participants' perceived level of difficulty, effort and unnaturalness associated with using the biofeedback cane and usefulness of biofeedback in learning optimal body weight support.[11] Other process measures at 3 months included the perceived level of difficulty, effort and unnaturalness of cane use as well as confidence in correct cane use, likelihood of continuation or recommendation of regular cane use to a friend with a similar condition, using 7 custom-designed 11-point NRSs.[11] Finally, adverse events of cane use (any problem believed by the participant to be caused by cane use and lasting ≥2 days or requiring medication/treatment) were collected in monthly logbooks. Co-interventions were recorded monthly in logbooks and at 3 months by questionnaire.

Statistical analysis and sample size calculation

This trial was powered to detect a 0.6 effect size[1,28] for change in normalized total medial tibiofemoral BML volume (primary outcome). Given cane use has relatively poor uptake among people with OA often because of patient vanity,[29,30] we deemed a moderate-to-large effect size of 0.6 was warranted to advocate cane use.[31] Assuming a correlation between baseline and follow-up measurements of 0.34,[11] with two-tailed $\alpha = 0.05\%$ and 80% power using analysis of covariance controlling for the baseline level of the outcome, 78 participants were required. Allowing for 35% drop-out given reported high cane abandonment rates,[29] we aimed to

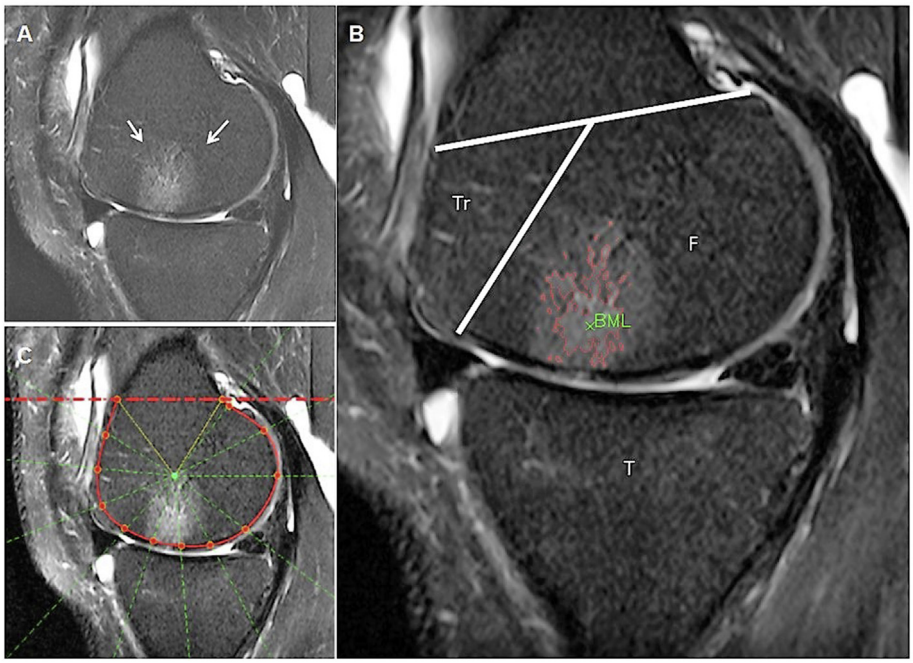

Fig. 2. magnetic resonance imaging (MRI) assessment of bone marrow lesion (BML) volumes. (A) Unsegmented BML (white arrow), (B) Segmented BML (red contour) and depicting the MOAKS subregions (Tr: Trochlear, F: femoral, T:tibial). (C) Bone volume calculation, as per our previously published methods.[11] Figure adapted with permission from Van Ginckel et al.[11].

recruit 120 participants (Stata 12.0, StataCorp, Texas, USA). As only one participant dropped out, we ceased recruitment once the minimum required sample of 78 participants was achieved and performed a complete case analysis.

Data were analyzed by a blinded biostatistician using Stata v15.0 (StataCorp, Texas, USA) with $P < 0.05$ considered significant. Main comparative analyses between groups were performed using intention-to-treat including all available data. Mean changes from baseline in continuous outcomes were compared between groups using linear regression models, adjusted for the stratifying variables, and standardized mean difference (SMD) calculated for the primary outcome. Change in BML volume, relative to the SEM, was also categorized as 'regressing (getting smaller)', 'progressing (getting larger)', or 'stable' (no change, i.e., BML volume at follow-up within ± 0.0010 of BML volume at baseline, per unit of bone volume),[32] and categories compared between groups using multinomial logistic regression models, adjusted for stratifying variables, with "stable" the referent, and results presented as risk ratios (95% CI). Global change outcomes were dichotomized as "moderately" or "much better" relative to all other categories combined and compared between groups using logistic regression models adjusted for the stratification variables. Two participants were incorrectly assigned to the BMI >30.5 kg/m^2 stratum. These two participants were analyzed according to BMI strata as originally assigned as a sensitivity analysis confirmed that use of corrected BMI strata had minimal impact on results. Sensitivity analyses were conducted to estimate dose–response relationships between hypothetical levels of daily hours of cane use and outcomes using a two-stage least squares instrumental variables approach (Appendix 2).[33] Posthoc analyses were also performed to investigate whether symptom laterality (unilateral/bilateral) moderated the effect of cane use on the primary outcome by including an interaction term between group and subgroup variable.

Results

We enrolled 79 participants (Fig. 3). Treatment groups were similar at baseline (Table I, Appendix 3). Participants were on average 66.1 (SD 7.3) years, and classified as obese (average BMI of 30.4 (SD 4.1) kg/m^2). The majority were female (57%, $n = 45$) and had moderate (KL grade 3) radiographic OA (66%, $n = 52$) and bilateral knee symptoms (71%, $n = 56$). With only one drop-out in the control group (due to patellar bone fracture following trauma), retention and completion of primary outcome measurements was excellent ($n = 78$, 99%). Nine participants in the cane group (23%) reported adverse events. These were worse pain in the contralateral non-study knee ($n = 2$) or hip ($n = 1$), worse pain/swelling in study knee or lower limb ($n = 4$), shoulder/neck pain ($n = 2$), back and/or referred pain ($n = 2$), or complaints in elbow or wrists opposite to the cane due to additional load carrying on this side ($n = 1$). The proportion of participants self-reporting medication use or other non-surgical treatments during the trial was similar across groups (Appendix 4). Process measures collected after the initial training session and at 3 months are presented in Appendix 5. The mean (SD) duration of daily cane use over the 3 months was 2.3 (1.7) hours. This slightly declined during the trial with a mean of 2.6 (2.4) hours/day in month 1 (range 0.2–14.6 h), a mean of 2.2 (1.7) hours/day in month 2 (range 0.0–8.8 h) and a mean of 2.0 (1.4) hours/per day in month 3 (range 0.0–5.6 h). Adherence with cane use instructions remained relatively stable throughout with a mean (SD) of 6.7 (2.0) units out of 10 for the trial duration (Appendix 6).

Table II summarizes continuous outcomes at baseline and 3 months across groups. Changes within groups and differences in change between groups are reported in Table III. We did not find evidence of between-group differences in the change in medial tibiofemoral BML volume (mean difference (95% CI) per unit bone volume: −0.0010 (−0.0022, 0.0003), $P = 0.14$). Compared to the

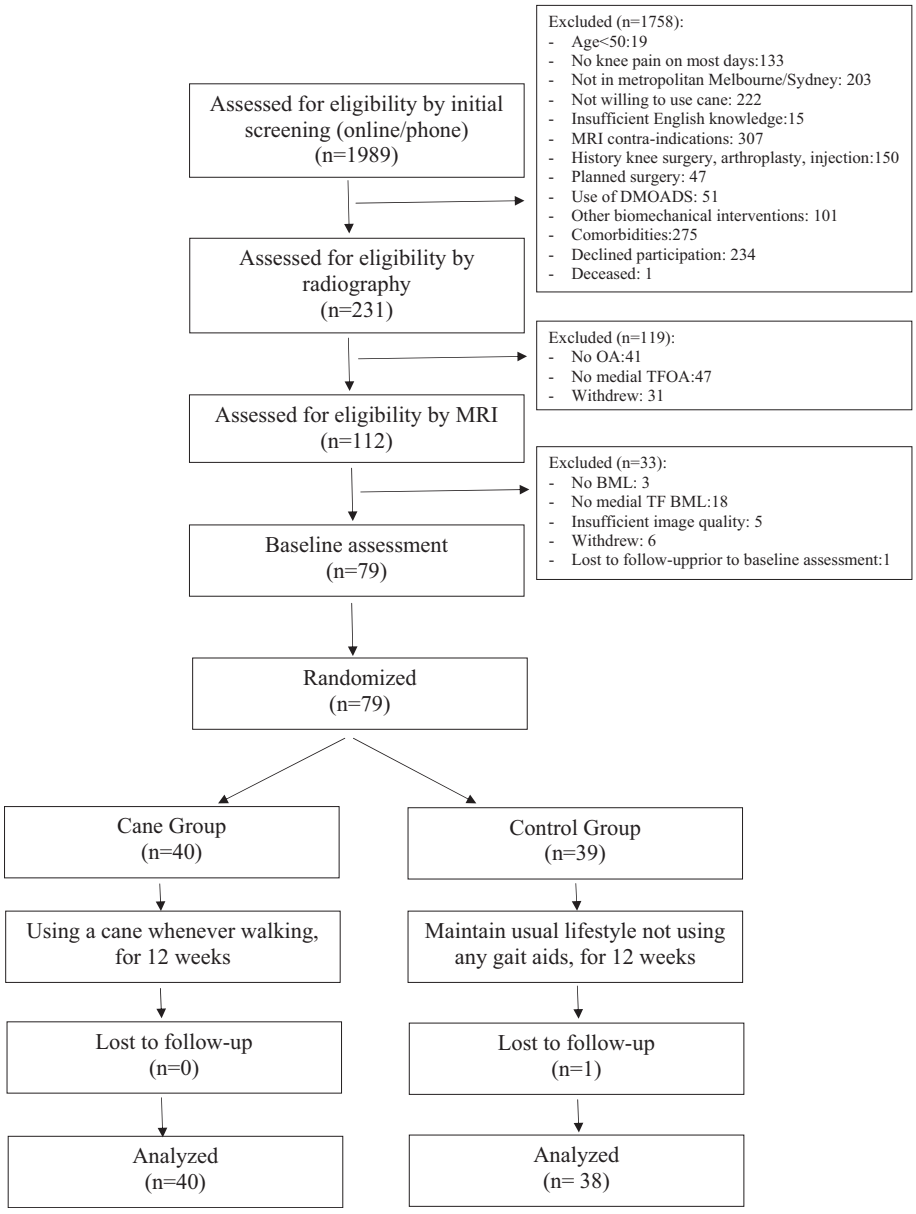

Fig. 3. Study flow diagram. The number of participants analyzed is based on data obtained for the primary outcome. MRI: MRI; DMOADS: disease-modifying and/or anti-bone resorption osteoarthritis drugs; (TF)OA: (tibiofemoral) osteoarthritis; BML: BML.

proportion with stable BMLs, there was no evidence of between-group differences in the proportion showing progression or regression, for any of the BML outcomes (Table IV). Within and between-group changes in absolute BML volumes are presented in Appendix 7, showing no evidence of between-group differences. We found no evidence of between-group differences for any secondary outcome (Table III), except for participant-perceived change in condition (Table V). Compared to controls, the cane group had a greater likelihood of global improvements in knee pain (risk ratio (95% CI): 4.0 (1.2, 12.8), $P = 0.021$) (Table V). We also did not find between-group differences in the changes in PASE scores or step count (Table III). Sensitivity analyses did not suggest evidence of an association between the number of hours of cane use and outcomes among participants who would have used the cane for a specified number of hours (Appendix 2). There was no evidence of differences in change in medial tibiofemoral BML volume at 3 months based on symptom laterality (Appendix 8).

Discussion

In a cohort of people with medial tibiofemoral OA reporting moderate pain and physical dysfunction, 3 months of daily cane use did not reduce BML volumes in the medial tibiofemoral compartment, when compared to not using any gait aids. Using a cane was also not effective in improving most secondary outcomes of clinical symptoms and health-related quality of life.

The effect of cane use on total medial tibiofemoral BML volume was relatively small, attaining an SMD of 0.04 (95% CI: −0.40, 0.49), and highly variable for both normalised and absolute BML volume changes. Except for tibial BMLs, average changes in BML volumes did not exceed the measurement error in either group. Floor effects may have occurred in participants with smaller lesions at baseline thus attenuating treatment benefits. However, tibiofemoral BMLs completely resolved in only 3% of the sample ($n = 2$) limiting

Table I
Baseline characteristics of all participants and by treatment group. Data are presented as mean (SD) unless otherwise stated

Characteristic	All participants ($n = 79$)	Cane Group ($n = 40$)	Control Group ($n = 39$)
Site, *n* (%)			
Melbourne	32 (40)	17 (43)	15 (38)
Sydney	47 (60)	23 (57)	24 (62)
Age, years	66.1 (7.3)	65.0 (6.7)	67.3 (7.7)
Body mass index, kg/m^2	30.4 (4.1)	30.6 (4.1)	30.3 (4.1)
Symptom duration, years	8.4 (9.0)	8.4 (11.2)	8.4 (6.2)
Bilateral symptoms, *n*(%)	56 (71)	27 (68)	29 (74)
Female gender, *n*(%)	45 (57)	27 (68)	18 (46)
Smoking history, *n*(%)	22 (28)	12 (30)	10 (26)
Employment status, *n*(%)			
Employed	39 (49)	20 (50)	19 (49)
Temporarily unable to work	2 (3)	1 (2)	1 (2)
Retired	36 (45)	17 (43)	19 (49)
Home duties	2 (3)	2 (5)	0 (0)
History of knee surgery, *n*(%)	24 (30)	10 (25)	14 (36)
KL Grade, *n*(%)			
2	13 (16)	7 (17)	6 (15)
3	52 (66)	26 (65)	26 (67)
4	14 (18)	7 (18)	7 (18)
OARSI medial JSN Grade, *n*(%)			
0	0 (0)	0 (0)	0 (0)
1	34 (43)	20 (50)	14 (36)
2	36 (46)	16 (40)	20 (51)
3	9 (11)	4 (10)	5 (13)
OARSI lateral JSN Grade, *n*(%)			
0	76 (96)	38 (95)	38 (97)
1	2 (3)	1 (3)	1 (3)
2	1 (1)	1 (3)	0 (0)
3	0 (0)	0 (0)	0 (0)
Treatment with drugs or supplements, *n* (%)[a]			
Anti-inflammatory tablets or capsules	31 (39)	18 (45)	13 (33)
Cox-2 inhibitors	4 (5)	0 (0)	4 (10)
Paracetamol	41 (52)	23 (58)	18 (46)
Paracetamol and codeine combinations	8 (10)	6 (15)	2 (5)
Tramadol	1 (1)	1 (2)	0 (0)
Topical anti-inflammatory gels or creams	23 (29)	12 (30)	11 (28)
Glucosamine or chondroitin	11 (28)	4 (10)	7 (18)
Oral corticosteroids	0 (0)	0 (0)	0 (0)
Topical liniment rubs	17 (22)	8 (20)	9 (23)
Opioid oral Medication	0 (0)	0 (0)	0 (0)
Fish oil/krill oil	20 (25)	8 (20)	12 (31)

KL: Kellgren–Lawrence grade: grade 2 = mild: definite osteophytes and possible joint space narrowing, grade 3 = moderate: moderate multiple osteophytes, definite joint space narrowing and possible bone deformity, grade 4 = severe: large osteophytes, marked joint space narrowing, severe sclerosis and definite bone deformity. OARSI JSN: Osteoarthritis Research Society International Joint Space Narrowing grade: grade 0 = none, grade 1 = mild, grade 2 = moderate, grade 3 = severe.
[a] Ever had this treatment for knee osteoarthritis in the past month prior to entering the study.

potential interference from floor effects. There are several other potential explanations for our lack of treatment effect.

First, the total amount of cane use may have been insufficient. Average cane use approximated 2–3 h per day but with considerable variability (0–14.6 h). Although self-report measures of cane use can be prone to error and bias, we showed no evidence of a dose–response relationship between hypothetical daily hours of cane use and outcomes (Appendix 2). Participants walked on average more than 5,000 steps per day. Yet, it is not clear how many of these steps were undertaken when using the cane. Self-rated adherence to using the cane whenever walking over the trial showed a mean of 6.7 out of 10. Thus, adherence to cane use may have been inadequate to impact BMLs.

A second potential explanation for our lack of cane effects on BMLs is that the amount of offloading through the cane was insufficient to impact joint structure. Participants were taught to offload $\geq$10% body weight support as this is achievable for people with knee OA and yields reductions in joint loading comparable to that of other gait modification techniques.[15–17] We implemented motor learning principles and vibration biofeedback to facilitate learning and retention of adequate joint offloading once biofeedback has ceased.[34] We have shown that a single training session by a physiotherapist using our biofeedback system significantly improved the magnitude and timing of body weight support through the cane.[35] However, whether adequate offloading was achieved throughout the trial is unknown, as we did not measure body weight support through the cane beyond the initial training period. Bilateral knee pain was common in our sample which may also have hampered appropriate offloading. Nonetheless, exploratory analyses did not find evidence of a differential effect of cane use in those with bilateral vs unilateral knee symptoms.

A third explanation relates to the relationship between knee load and structure. Body weight support of $\geq$10% through the cane corresponds to a reduction in the knee adduction moment (an indicator of medial joint load) of approximately 7% or higher.[10] However, we do not know the optimal amount of knee offloading to induce changes in tibiofemoral BML volume changes. Debate exists as to whether abnormal knee loading during walking causes structural disease progression in knee OA.[36] Lack of any such causal relationship may indirectly explain our inability to detect significant BML volume change in this study in spite of reduced knee

Table II
Continuous outcomes at baseline and 3 months, by treatment group. Data are presented as mean (SD)

Outcome	Baseline		3 months	
	Cane Group ($n = 40$)	Control Group ($n = 39$)	Cane Group ($n = 40$)	Control Group ($n = 38$)*
Primary				
Medial tibiofemoral bone marrow lesion volume (per unit bone volume, mm^3/mm^3)	0.0042 (0.0050)	0.0061 (0.0116)	0.0034 (0.0037)	0.0055 (0.0085)
Secondary				
Medial femoral bone marrow lesion volume (per unit bone volume, mm^3/mm^3)	0.0017 (0.0025)	0.0029 (0.0047)	0.0014 (0.0018)	0.0026 (0.0046)
Medial tibial bone marrow lesion volume (per unit bone volume, mm^3/mm^3)	0.0094 (0.0143)	0.0107 (0.0242)	0.0076 (0.0119)	0.0109 (0.0201)
Knee pain (WOMAC)†	7.8 (3.0)	7.7 (3.4)	6.3 (3.4)	5.8 (2.8)
Physical function (WOMAC)‡	24.6 (9.7)	25.3 (12.3)	19.5 (10.0)	20.5 (7.1)
Average overall knee pain (NRS)§	4.8 (2.0)	4.4 (2.3)	4.1 (2.2)	3.6 (2.2)
Average knee pain with walking (NRS)§	5.5 (2.0)	4.9 (2.3)	4.4 (2.3)	4.3 (2.1)
Average knee pain with walking in non-study knee (NRS)§	3.2 (2.4)	2.1 (2.2)	2.3 (2.0)	2.1 (2.4)
Quality of life (AQoL-6D)‖	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.2)
Additional				
Physical activity (PASE)¶	161.5 (70.1)	146.1 (90.0)	175.5 (99.1)	158.4 (73.8)
Average daily step count#	5,079 (2278)	5,856 (3066.0)	5,409 (2773.0)	5,549 (2972.0)

WOMAC: Western Ontarior Mc Masters Universities Osteoarthritis Index physical function subscale; NRS: numeric rating scale; AQoL-6D: Assessment of Quality of Life 6D scale; PASE: Physical Activity Scale for the Elderly; CCMS: Cane Use Cognitive Mediators Scale.
* One participant in the control group dropped out and had all outcomes missing at 3 months.
† Scores range 0–20; with higher scores indicating worse knee pain.
‡ Score range 0–68; with higher scores indicating worse physical function.
§ Score range 0–10; with higher scores indicating worse knee pain.
‖ Scores range −0.04 to 1.00; with higher scores indicating better health-related quality of life.
¶ Scores range 0–400; with higher scores indicating better physical activity levels.
# daily step count averaged over 7 subsequent days, measured at week 1 and week 12.

loading. Finally, the 3 month duration of the intervention may have been too short to detect structural changes from cane use.

There is limited research investigating the structural effect of biomechanical interventions designed to reduce knee load. Our findings agree with our previous clinical trial investigating 12-months use of lateral-wedged shoe insoles.[37] This trial, in a similar population, also showed no treatment effects on tibiofemoral BML severity assessed using a semi-quantitative grading system, and on medial tibial cartilage volume (SMD (95% CI): 0.0 (−0.28, 0.28)).[37] In contrast, patellofemoral bracing in people with patellofemoral OA[1] resulted in significant reductions in patellofemoral BML volumes in the brace compared to non-brace group, after 6 weeks of use (SMD (95% CI): 0.4 (0.03,0.8)). Differences in results may reflect differences in OA sites and the dose of biomechanical effect (e.g., duration, frequency and amount of biomechanical change).

Table III
Mean change (SD) within groups and adjusted mean difference (95% confidence interval (CI)) in change between groups, for continuous outcomes, adjusted for the stratifying variables of site, Kellgren Lawrence (KL) grade and body mass index (BMI) strata

Outcome	Baseline − 3 month change		Difference in change between groups	
	Cane Group ($n = 40$)	Control Group* ($n = 38$)	Mean Difference (95% CI)	*P*-value
Primary				
Medial tibiofemoral bone marrow lesion volume (per unit bone volume, mm^3/mm^3)†	0.0009 (0.0035)	0.0007 (0.0052)	−0.0010 (−0.0022, 0.0003)	0.14
Secondary				
Medial femoral bone marrow lesion volume (per unit bone volume, mm^3/mm^3)†	0.0002 (0.0023)	0.0004 (0.0025)	−0.0002 (−0.0012, 0.0008)	0.68
Medial tibial bone marrow lesion volume (per unit bone volume, mm^3/mm^3)†	0.0018 (0.0088)	0.0001 (0.0119)	−0.0025 (−0.0061, 0.0011)	0.17
Knee pain (WOMAC)†	1.4 (3.9)	1.8 (3.2)	0.6 (−0.7, 1.9)	0.38
Physical function (WOMAC)†	5.1 (11.3)	4.3 (9.5)	−0.7 (−4.1, 2.7)	0.70
Average overall knee pain (NRS)†	0.7 (2.6)	0.8 (2.2)	0.4 (−0.5, 1.3)	0.40
Average knee pain with walking (NRS)†	1.1 (2.8)	0.6 (2.2)	0.0 (−1.0, 0.9)	0.94
Average knee pain with walking in non-study knee (NRS)†	0.9 (1.7)	0.0 (1.5)	−0.5 (−1.2, 0.2)	0.13
Quality of life (AQoL-6D)‡	−0.0 (0.1)	−0.0 (0.1)	0.0 (0.0, 0.0)	0.39
Additional				
Physical activity (PASE)‡	−14.1 (84.5)	−11.0 (63.0)	7.4 (−24.2, 39.0)	0.65
Average daily step count‡	−330 (2010)	362 (1567)	550 (−239, 1339)	0.17

KL grade: Kellgren–Lawrence grade; WOMAC: Western Ontarior Mc Masters Universities Osteoarthritis Index physical function subscale; NRS: numeric rating scale; AQoL-6D: Assessment of Quality of Life 6D scale; PASE: Physical Activity Scale for the Elderly; CCMS: Cane Use Cognitive Mediators Scale.
* One participant in the control group dropped out and had all outcomes missing at 3 months.
† For changes within groups, a positive value indicates improvement (i.e., smaller values at follow-up). For between-group comparisons negative values favour canes.
‡ For changes within groups, a negative value indicates improvement (i.e., greater values at follow-up). For between-group comparisons positive values favour canes.

Table IV
Proportion (n,%) of participants (N) with changes in bone marrow lesion (BML) volumes from baseline measured at 3 months, with risk ratios (95% CI) comparing categories of BML volume change from "stable" between groups

	Cane Group ($n = 40$), n/N (%)	Control Group ($n = 38$), n/N (%)*	Risk Ratio (95% CI)	*P*-value
Medial tibiofemoral bone marrow lesion volume				
Progressing	7/40 (17.5)	12/38 (31.6)	0.4 (0.1, 1.4)	0.17
Stable	19/40 (47.5)	17/38 (44.7)	1 (Ref)	
Regressing	14/40 (35.0)	9/38 (23.7)	1.5 (0.5, 4.4)	0.46
Medial tibial bone marrow lesion volume				
Progressing	7/40 (17.5)	12/38 (31.6)	0.9 (0.1, 1.3)	0.12
Stable	21/40 (52.5)	17/38 (44.7)	1 (Ref)	
Regressing	12/40 (30.0)	9/38 (23.7)	1.1 (0.4, 3.5)	0.82
Medial femoral bone marrow lesion volume				
Progressing	4/40 (10.0)	3/38 (7.9)	1.7 (0.3, 9.0)	0.51
Stable	27/40 (67.5)	30/38 (78.9)	1 (Ref)	
Regressing	9/40 (22.5)	5/38 (13.2)	2.1 (0.6, 7.2)	0.24

Risk Ratio>1 indicates greater risks for bone marrow lesion volumes progressing or regressing, as opposed to stable, in the cane group when compared to the control group.
* One participant in the control group dropped out and had all outcomes missing at 3 months.

Although we did not power the study for secondary outcomes, our results provide little evidence of pain-relieving benefits of cane use over 3 months, as most pain measures showed no difference between groups. While the cane group was more likely to perceive clinical improvements, the CIs around the differences were wide. These results are contrary to those of the only other RCT of cane use in 64 people with knee OA conducted by Jones and colleagues in Brazil[38] that reported significant improvements in pain and exceeding the minimal clinically important difference in physical function.[24] Explanations for the contrasting results are not entirely clear given similarities in clinical characteristics and pain outcomes in the two studies as well as a slightly greater daily cane usage, more intensive cane training, longer intervention duration and more participants in our trial. However, given the studies were set in culturally distinct countries, differences may have existed in patient perceptions and social acceptance towards walking canes. Nonetheless, cane use did not improve quality of life in either study.

The lack of symptom relief in our study may be partly due to a concomitant lack of reduction in BML volumes, given that larger BMLs have been associated with greater pain severity[39,40] and/or the reported weak and inconsistent associations between knee loading and pain severity.[41] Yet, pain perception is a multi-faceted concept and it is somewhat surprising that clinical benefits with cane use were not seen given the well-documented placebo effects in OA[42] and with participants unblinded to the intervention and completing self-reported symptom measures. However, while placebo effects with cane use have not been specifically quantified, they are likely much smaller compared to other OA drug and/or surgical treatments. Participants may have been uncertain about the benefits of canes as there is some degree of stigma and embarrassment attached to cane use.[43] Our process measures (Appendix 5) also showed that participants were somewhat ambivalent about continuing to use the cane after the trial. Indeed, surveys have shown relatively limited uptake of canes by people with knee OA[29,44] and recruitment for our study progressed slowly, especially when compared to our other RCTs of non-drug and/or biomechanical interventions for knee OA.[45,46] Finally, approximately 1 in 5 cane users reported an adverse event which may have tempered symptom improvement or indirectly influenced adherence and/or the amount of force applied to the cane during the trial.

This study has several strengths. It is the first to investigate changes in quantitative tibiofemoral BML volumes following an offloading intervention targeting the medial tibiofemoral compartment for knee OA. We confined the study to participants with at least one BML at baseline to allow scope for change in our primary outcome, and to those with involvement of the medial tibiofemoral compartment to provide a more homogenous sample. We used a quantitative method of assessing BML volume that is considered more sensitive to change than semi-quantitative assessments, particularly in treatments of shorter duration and compared to outcomes of cartilage change.[1,9,19,47] Limitations were that morbidly obese people, who could otherwise benefit from a cane, were excluded due to difficulties associated with MRI coil size. Selection bias as such may have attenuated treatment effects. We did not include objective measurements of the amount of body weight support through the cane and of cane use or the percentage of time spent walking when using a cane nor performed 3-dimensional biomechanical measures to assess whether parameters of medial tibiofemoral load were reduced with cane use. We did not include joint alignment measurements, an important predictor of medial knee joint loading, and thus were unable to study potential moderation of alignment on treatment effects. This RCT was not powered to detect differences in symptoms and we did not measure other clinically-relevant outcomes, such as postural instability or fall risk, that are prevalent in people with knee OA and may benefit from cane use.[48] Last, as our software quantified volumes of newly formed BMLs together with those of existing BMLs, we cannot determine whether cane use differentially affected these.

Table V
Proportion (n,%) of participants (N) reporting global improvements ("moderately better" and "much better") since the start of the trial measured at 3 months with risk ratios (95% CI) adjusted for the stratifying variables of site, KL grade and BMI strata

Outcome	Cane Group ($n = 40$), n/N (%)	Control Group ($n = 38$), n/N (%)	Risk Ratio (95% CI)	*P*-value
Global improvement in knee pain	13/40 (32.5)	3/38 (7.9)	4.0 (1.2, 12.8)	0.021
Global improvement in function	10/40 (25.0)	5/38 (13.2)	1.9 (0.7, 4.8)	0.20
Global improvement overall	12/40 (30.0)	4/38 (10.5)	2.7 (1.0, 7.6)	0.059

KL Grade: Kellgren–Lawrence grade.
Risk Ratio>1 indicates greater risk of improvement in the cane group relative to the control group.
*One participant in the control group dropped out and had all outcomes missing at 3 months.

In people with medial tibiofemoral OA, we showed no evidence of an effect of cane use for approximately 2–3 h per day over 3 months on medial tibiofemoral BML volume changes, compared to not using any gait aids.

Author contributions

All authors have contributed sufficiently and Kim Bennell takes responsibility for the integrity of the work from inception to publication (k.bennell@unimelb.edu.au).

AVG: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, obtaining of funding. RSH: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients. TVW: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support. DJH: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, obtaining funding. CJM: critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support, collection and assembly of data. JD: analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support. LM: critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support, collection and assembly of data. MS: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients. JK: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, statistical expertise, collection and assembly of data. SRR: critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support, collection and assembly of data. JAW: critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, administrative, technical or logistic support. KLB: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, obtaining funding.

Conflict of interest statements

All authors have completed an ICMJE uniform conflicts of interest form.

Role of the funding source

AVG is currently supported by a FWO (Pegasus)[2] EU Marie-Sklodowska Curie Fellowship (EU Horizon 2020, #66501). KLB is supported by a National Health and Medical Research Council Principal Research Fellowship (#1058440). RSH is supported by an Australian Research Council Future Fellowship (FT130100175). DJH is supported by a NHMRC Practitioner Fellowship (#1079777). This study received funding from NHMRC program grants (# 631717,61887) and an Early Career Researcher grant (#602640) from the University of Melbourne. The sponsor of this trial is The University of Melbourne. Neither the funding sources nor the sponsor was involved in the study design, data collection, data analysis, interpretation of the results, or the decision to submit manuscripts.

Appendix 1. Cane training session: (a) components and progression and (b) checklist of technique mastery

(a) Components of the training session and criteria for progression

The training session incorporates motor learning principles of autonomy supportive instructions enhancing the participants' ability to walk correctly and independently with a cane; social comparative feedback; principles of summary, delayed, reduced, positive, or program/parameter feedback; and external feedback. The trainer always demonstrates techniques first and builds in rest as required to avoid worsening of knee pain. The duration of sections is estimated and depends on participants' mastery of skills.(Table b) The total duration is approximately 30–45 min. Demonstration of the basic cane gait technique is in the Video. The detailed qualitative checklist of technique features (cane timing, placement) and movement patterns (trunk, upper limb girdle, hip, and knee) is shown in Table b.

Component	Goal	Key Instructions for Trainers
1. Natural unassisted gait	Clinically observe natural walking pattern.	Duration: 2–3 min Observe natural walking pattern to support training feedback. Focus on step width/length and trunk lean, as these should not be considerably affected by cane use.
2. Instinctive gait with cane	Record/observe undirected understanding of correct cane use before any formal instruction.	Duration: 5 min Observe features needing correction in training. Set cane height and no-vibration feedback. Allow 5 min of practice. Observe technique errors. Focus on use in correct hand, cane placement, and timing and collect cane loading data in the final minute.
3. Education	Address usefulness of a cane for knee OA and stigma, barriers, and benefits to improve participation.	Duration: 5 min Participants watch a slide show in which benefits of cane use will be explained using visuals.
4. Gait technique	Teach 2-point gait pattern without vibration feedback.	Duration: 10–15 min Prompts for instruction: correct hand, cane placement and timing, and trunk position (Video).

(*continued*)

Component	Goal	Key Instructions for Trainers
		Feedback: verbal, tactile, or visual (mirror). • Give feedback after bouts of 3 trials initially and reduce frequency of feedback as appropriate. • Avoid concurrent feedback. • Stress positive achievements and confirm that performance is as good as or better than that of peers, when appropriate. • Give feedback on basic motion patterns first (i.e., timing and cane placement; step width/length and duration stance phase; natural trunk lean). Then, provide parameter feedback (i.e., usual hip extension and knee flexion/extension, natural upper limb girdle motion) (Table b). Criteria for progression: correct technique performance without additional feedback for 3 min. Ensure that basic features are adequately performed.
5. Off-loading technique	Teach participants how to use the cane for off-loading purposes without vibration feedback.	Duration: 5 min Prompts for instruction: timing, cane placement at angle to facilitate off-loading. Feedback: verbal, tactile, or visual (mirror). • Additional feedback on upper body motion/positioning. Criteria for progression: see component 4.
6. Optimal body weight support	Teach participants the optimal amount of body weight support using vibration feedback. A biofeedback cane system that implements vibration feedback for the participants and visual feedback on-screen for the trainer will be used. On-screen, the lower limit of body weight support will be set as a target line, and a moving trace will monitor real-time cane loading.	Duration: 5 min Allow participants to experience the pressure needed on the cane: by putting pressure on cane, moving target should be kept above the target line on the computer screen. Implementation of vibration feedback into walking: once the cane hits the floor, body weight should be put on the cane until vibration is felt. Instruction on the duration of body weight support: vibration should be felt during the entire stance phase. Feedback: add vibration feedback. • Threshold settings of vibration feedback: lower limit 7.5% body weight and aim to achieve $\geq$10% body weight and that is comfortable. • Use visual feedback from the screen for additional (delayed) feedback. Criteria for progression: see component 4.
7. Stairs, outdoor walking	Improve learning effects by transfer to daily life conditions.	Duration: 5–10 min (as permitted) Increase confidence and facilitate walking with a cane as often as possible. Walking up/down stairs. • Prompts for instruction: trunk position, usual upper limb girdle motion, and knee/hip flexion and extension. • Progression from “step-to” to “step-through” gait. • No focus on body weight support, predominantly ensuring safe cane use. Criteria for progression: correct performance during at least half a flight of stairs. Walking outdoors. • Include footpath, grass, stepping off curb.

(b) Checklist for technique mastery and optimal motion patterns during the two point-cane gait pattern

Required Skills/Movement Patterns	Instructions
Usual knee flexion/extension	Participants will be prompted to avoid keeping their knee in a sustained position throughout the stance phase.
Maintain hip extension terminal stance	Care will be taken to avoid shortened stride lengths with cane use to maintain hip extension at terminal stance.
Natural trunk lean	An increase in trunk lateral flexion toward either the ipsilateral or the contralateral side relative to the study knee will be discouraged.
Usual step width	Participants will be observed to ensure that step width does not vary significantly, with any obvious wide step gait or tandem gait being discouraged.
Appropriate timing of cane placement	Placement of the cane on the ground simultaneously with or just prior to contact with the study limb is desired.
Appropriate width of cane placement	Placement of the cane on the ground should be at least 1 shoulder width apart and in line with the affected foot.
Appropriate stance phase of study limb	Participants will be encouraged to not prolong the stance phase of the study limb while simultaneously using the cane.
Unaltered upper limb girdle motion	Motion of the upper limb girdle, including excessively increased scapular elevation or protraction, will be discouraged.
Neutral wrist position	A neutral wrist position, i.e., midway between flexion and extension, will be achieved

Appendix 2. The effect of hypothetical levels of adherence to cane use on outcomes.

Analysis description

The effect of daily hours of cane use on outcomes was estimated using a two-stage least squares instrumental variables approach to

estimate a dose–response relationship.[1] This involved fitting two models jointly: a linear regression model for difference in change (baseline minus follow-up) for each outcome adjusted for the baseline score, stratifying variables and number of hours of daily cane use (averaged over the 3 months), and a linear regression model for daily hours of cane use adjusted for randomised group, baseline score and stratifying variables. Participants assigned to the control group were assumed to have 0 h of daily cane use (the monotonicity assumption).

Adjusted mean (95% CI) difference in change between groups for continuous outcome measures for a 1 h increase in the average hours of cane use (averaged across all 3 months), adjusting for baseline value of outcome and for the stratifying variables of site, KL grade and BMI strata.

Outcome	Difference in change between groups	
	Mean Difference (95% CI)	*P*-value
Primary		
Medial tibiofemoral bone marrow lesion volume per unit bone volume (mm^3/mm^3)	0.0004 (−0.0001, 0.0009)	0.11
Secondary		
Medial femoral bone marrow lesion volume per unit bone volume per unit bone volume (mm^3/mm^3)	0.0001 (−0.0003, 0.0004)	0.61
Medial tibial bone marrow lesion volume per unit bone volume (mm^3/mm^3)	0.0011 (−0.0004, 0.0026)	0.14
Knee pain (WOMAC)*	−0.3 (−0.8, 0.3)	0.36
Physical function (WOMAC)†	0.3 (−1.2, 1.7)	0.69
Average overall knee pain (NRS)‡	−0.2 (−0.6, 0.2)	0.39
Average knee pain with walking (NRS)‡	0.0 (−0.4, 0.4)	0.93
Average knee pain with walking in non-study knee (NRS)‡	0.2 (−0.1, 0.6)	0.15
Quality of life (AQoL-6D)§	−0.0 (−0.0, 0.0)	0.37
Additional		
Physical activity (PASE)‖	−3.9 (−15.7, 9.1)	0.60
Average daily step count¶	−242.2 (−572.0, 87.6)	0.15

KL grade: Kellgren–Lawrence grade; BMI: body mass index; WOMAC: Western Ontarior Mc Masters Universities Osteoarthritis Index physical function subscale; NRS: numeric rating scale; AQoL-6D: Assessment of Quality of Life 6D scale; PASE: Physical Activity Scale for the Elderly; CCMS: Cane Use Cognitive Mediators Scale.
*One participant in the control group dropped out and had all outcomes missing at 3 months.
* scores range 0–20; with higher scores indicating worse knee pain.
† score range 0–68; with higher scores indicating worse physical function.
‡ score range 0–10; with higher scores indicating worse knee pain.
§ scores range −0.04 to 1.00; with higher scores indicating better health-related quality of life.
‖ scores range 0–400; with higher scores indicating better physical activity levels.
¶ daily step count averaged over 7 subsequent days, measured at week 1 and week 12.

Appendix 3. Previous treatments and comorbidity history for all participants, and by treatment groups. Data are presented as *n*(%).

	All participants, $n = 79$	Cane Group, $n = 40$	Control Group, $n = 39$
Previous non-drug conservative treatments*			
Information/education	20 (25)	11 (28)	9 (23)
Getting counselling over the phone	0 (0)	0 (0)	0 (0)
Losing weight	56 (71)	31 (78)	25 (64)
Aerobic exercise class	34 (43)	22 (55)	12 (31)
Range of motion exercises	57 (72)	29 (73)	28 (72)
Muscle strengthening	55 (70)	28 (70)	27 (69)
Walking aids	10 (13)	3 (8)	7 (18)
Taping	21 (27)	11 (28)	10 (26)
Customized shoes with shock absorbing properties	22 (41)	18 (45)	14 (36)
Orthotics	33 (42)	18 (45)	15 (39)
Occupational therapy	2 (3)	1 (3)	1 (3)
Activity of daily living assistive device	7 (9)	3 (8)	4 (10)
Low level laser therapy	2 (3)	1 (3)	1 (3)
Any herbal therapies	18 (23)	8 (20)	10 (26)
Megavitamin therapy	7 (9)	3 (8)	4 (10)
Transcutaneous electrical nerve stimulation	8 (10)	3 (8)	5 (13)
Viscosupplementation	5 (6)	1 (3)	4 (10)
Hydrotherapy	20 (23)	13 (33)	7 (18)
Heat or cold	25 (32)	13 (33)	12 (31)
Massage therapy	21 (27)	8 (20)	13 (23)
Acupuncture	15 (19)	4 (10)	11 (28)
Magnet therapy	5 (6)	4 (10)	1 (3)

(*continued*)

	All participants, $n = 79$	Cane Group, $n = 40$	Control Group, $n = 39$
History of comorbidities†			
Stroke	0 (0)	0 (0)	0 (0)
Lung disease	4 (5)	0 (0)	4 (10)
Stomach disease	11 (14)	4 (10)	7 (18)
Kidney disease	4 (5)	3 (8)	1 (3)
Liver disease	5 (6)	3 (8)	2 (5)
Anaemia or other blood disorder	12 (15)	9 (13)	3 (8)
Osteoporosis or osteopenia	7 (9)	5 (13)	2 (5)
Cancer	9 (11)	7 (18)	2 (5)
Depression	11 (14)	7 (18)	4 (10)
Epilepsy	1 (1)	0 (0)	1 (3)
Memory problems	3 (4)	2 (5)	1 (3)
Hypertension	34 (43)	14 (35)	20 (51)
Heart disease	3 (4)	2 (5)	1 (3)
Diabetes	13 (17)	4 (10)	9 (23)

* Ever tried this treatment for knee osteoarthritis, currently using or stopped using.
† Currently or previously had this comorbidity.

Appendix 4. Use of adjuvant medication or other treatments during the trial measured at the 3 month follow-up, for all participants and by treatment group. Data are presented as n (%).

	All Participants, $n = 79$	Cane Group, $n = 40$	Control Group, $n = 38$*
Drugs or supplements	50 (63)	26 (65)	24 (63)
Anti-inflammatory tablets or capsules	34 (43)	19 (48)	15 (40)
Cox-2 inhibitors	50 (63)	26 (65)	25 (66)
Paracetamol	34 (43)	19 (48)	15 (40)
Paracetamol and codeine combinations	6 (8)	3 (8)	3 (8)
Tramadol	0 (0)	0 (0)	0 (0)
Topical anti-inflammatory gels or creams	17 (22)	9 (23)	8 (21)
Glucosamine or chondroitin	11 (14)	3 (8)	8 (21)
Oral corticosteroids	1 (1)	0 (0)	1 (3)
Topical liniment rubs	10 (13)	5 (13)	5 (13)
Opioid oral medication	0 (0)	0 (0)	0 (0)
Fish oil/krill oil	11 (14)	5 (13)	6 (16)
Other treatments	8 (10)	4 (10)	4 (11)
Physiotherapy	3 (4)	1 (3)	2 (5)
Exercises	7 (9)	3 (8)	4 (11)
Injections	0 (0)	0 (0)	0 (0)
Surgery	0 (0)	0 (0)	0 (0)
Hydrotherapy	3 (4)	1 (3)	2 (5)
Acupuncture	1 (1)	1 (3)	0 (0)
Walking Stick	0 (0)	na	0 (0)

na: not applicable.
* 1 participant dropped out and did not provide data at 3 months.

Appendix 5. Cane process measures following the initial cane training session, measured at week 0, and at 3 months. Data are presented as mean (SD)

Process measures	$n = 40$
After initial training	
Level of difficulty associated with using the biofeedback cane (NRS, 0–10)*	4.1 (2.3)
Level of effort required to adjust walking to feedback from the biofeedback cane (NRS, 0–10)†	4.1 (2.3)
Level of unnaturalness using the biofeedback cane (NRS, 0–10)‡	5.4 (2.2)
Level of usefulness of vibration feedback in learning about the level of pressure (NRS, 0–10)§	8.4 (1.6)
At 3 months	
Level of difficulty associated with cane use (NRS, 0–10)*	3.7 (3.0)
Level of effort associated with cane use (NRS, 0–10)†	3.4 (2.3)
Level of unnaturalness associated with cane use (NRS, 0–10)‡	4.8 (2.9)
Level of confidence in walking correctly unsupervised with the cane (NRS, 0–10)‖	8.6 (1.7)
Level of confidence in using the cane in daily life (NRS, 0–10)‖	8.2 (2.0)
Likelihood to continue cane use in daily life (NRS, 0–10)¶	6.0 (3.1)
Likelihood to recommend a cane to a friend with a similar condition (NRS, 0–10)¶	7.0 (2.8)

* with anchors "0 = not at all difficult" and "10 = extremely difficult".
† with anchors "0 = no effort" and "10 = maximum effort".
‡ with anchors "0 = completely natural" and "10 = completely unnatural".
§ with anchors "0 = not at all useful" and "10 = extremely useful".
‖ with anchors "0 = not at all confident" and "10 = extremely confident".
¶ with anchors "0 = not at all likely" and "10 = extremely likely".

Appendix 6. Adherence to the cane use instructions for participants in the cane group, by month. Data are presented as mean (SD).

Adherence measures	$n = 40$
Average amount of cane use whenever walking (NRS, 0–10)*	
Month 1	6.7 (1.8)
Month 2	6.8 (1.9)
Month 3	6.8 (2.0)
Average amount of cane use whenever walking over the 3-month trial (NRS, 0–10)†	6.7 (2.0)
Duration of daily cane use (hours)‡	
Month 1	2.6 (2.4)
Month 2	2.2 (1.7)
Month 3	2.0 (1.4)

* Level of compliance in using the cane whenever walking in the past week, with anchors "0 = not at all" and "10 = always when walking". Measured weekly, averaged for each month; the higher the score the greater the adherence.
† Level of compliance in using the cane whenever walking over the past 3 months, with anchors "0 = not at all" and "10 = always when walking". Measured at the 3-month follow-up; the higher the score the greater the adherence.
‡ Measured daily via a log book (in hours and minutes), averaged as hours for each month.

Appendix 7. Within and between-group differences in absolute BML volumes.

Table I
Mean values (SD) of absolute bone marrow lesion volumes at baseline and week 13, by treatment group.

	Baseline		Week 13	
	Cane Group($n = 40$)	Control Group ($n = 39$)	Cane Group ($n = 40$)	Control Group ($n = 38$)*
Medial tibiofemoral bone marrow lesion volume (mm^3)	440.3 (564.8)	582.7 (1021.8)	357.8 (379.9)	564.1 (767.5)
Medial femoral bone marrow lesion volume (mm^3)	105.0 (161.2)	179.6 (279.7)	98.6 (142.1)	157.3 (265.7)
Medial tibial bone marrow lesion volume (mm^3)	335.3 (504.0)	403.0 (868.7)	259.1 (340.8)	406.8 (645.9)

* One participant in the control group dropped out and had all outcomes missing at 13 weeks.

Table II
Mean change (SD) within groups and adjusted mean difference (95% CI) in change between groups, for absolute BML measures, adjusted for the stratifying variables of site, KL grade and BMI strata.

	Change within groups*		Difference in change between groups	*P*-value
	Cane Group	Control		
Medial tibiofemoral bone marrow lesion volume (mm^3)	82.5 (345.3)	33.6 (467.2)	−114.6 (−233.2, 4.0)	0.058
Medial femoral bone marrow lesion volume (mm^3)	6.4 (164.5)	27.1 (178.7)	−8.4 (−78.2, 61.5)	0.81
Medial tibial bone marrow lesion volume (mm^3)	76.2 (330.6)	6.6 (438.6)	−110.8 (−224.3, 2.6)	0.056

* positive change indicates an improvement compared to baseline.

Appendix 8. Posthoc moderator analyses of laterality of symptoms for treatment effects of cane use on total medial tibiofemoral BML volumes.

Table I
Mean change (SD) within groups and adjusted mean difference (95% CI) in change between groups by laterality of symptoms for the primary outcome, adjusted for the stratifying variables of site, KL grade and BMI strata.

Outcome	Symptom Laterality	Change within cane group	Change within control group	Mean Difference (95% CI)	*P*-value	Interaction *P*-value
Medial tibiofemoral bone marrow lesion volume per unit bone volume (mm^3/mm^3)	Unilateral	0.0003 (0.0026)	0.0018 (0.0060)	0.0010 (−0.0015, 0.0035)	0.45	0.98
	Bilateral	0.0011 (0.0039)	0.0003 (0.0050)	0.0010 (−0.0006, 0.0025)	0.21	

References

1. Callaghan MJ, Parkes MJ, Hutchinson CE, Gait AD, Forsythe LM, Marjanovic EJ, *et al.* A randomised trial of a brace for patello-femoral osteoarthritis targeting knee pain and bone marrow lesions. Ann Rheum Dis 2015;74:1164–70.
2. Dieppe P. Subchondral bone should be the main target for the treatment of pain and disease progression in osteoarthritis. Osteoarthritis Cartilage 1999;7:325–6.
3. Dore D, Quinn S, Ding C, Winzenberg T, Zhai G, Cicuttini F, *et al.* Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. Arthritis Res Ther 2010;12:R223.
4. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, *et al.* Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007;56:2986–92.
5. Tanamas SK, Wluka AE, Pelletier JP, Pelletier JM, Abram F, Berry PA, *et al.* Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology (Oxford) 2010;49:2413–9.
6. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, *et al.* Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage 2002;10:573–9.
7. Bennell KL, Creaby MW, Wrigley TV, Bowles KA, Hinman RS, Cicuttini F, *et al.* Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. Ann Rheum Dis 2010;69:1151–4.
8. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70:1770–4.
9. Felson DT, Parkes MJ, Marjanovic EJ, Callaghan M, Gait A, Cootes T, *et al.* Bone marrow lesions in knee osteoarthritis change in 6-12 weeks. Osteoarthritis Cartilage 2012;20:1514–8.
10. Simic M, Bennell KL, Hunt MA, Wrigley TV, Hinman RS. Contralateral cane use and knee joint load in people with medial knee osteoarthritis: the effect of varying body weight support. Osteoarthritis Cartilage 2011;19:1330–7.
11. Van Ginckel A, Hinman RS, Wrigley TV, Hunter DJ, Marshall CJ, Melo L, *et al.* Impact of cane use on bone marrow lesion volume in people with medial knee osteoarthritis (Cuba trial). Phys Ther 2017;97:537–49.
12. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
13. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
14. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15(Suppl A):A1–A56.
15. Simic M, Hunt MA, Bennell KL, Hinman RS, Wrigley TV. Trunk lean gait modification and knee joint load in people with medial knee osteoarthritis: the effect of varying trunk lean angles. Arthritis Care Res (Hoboken) 2012;64:1545–53.
16. Simic M, Wrigley TV, Hinman RS, Hunt MA, Bennell KL. Altering foot progression angle in people with medial knee osteoarthritis: the effects of varying toe-in and toe-out angles are mediated by pain and malalignment. Osteoarthritis Cartilage 2013;21:1272–80.
17. Simic M, Bennell KL, Hunt MA, Wrigley TV, Hinman RS. Characteristics of contralateral cane use in people with medial knee osteoarthritis. Ann Rheum Dis 2010;69:316.
18. Kumar R, Roe MC, Scremin OU. Methods for estimating the proper length of a cane. Arch Phys Med Rehabil 1995;76:1173–5.

19. Nielsen FK, Egund N, Peters D, Jurik AG. Measurement of bone marrow lesions by MR imaging in knee osteoarthritis using quantitative segmentation methods - a reliability and sensitivity to change analysis. BMC Muscoskelet Disord 2014;15.
20. Ratzlaff C, Guermazi A, Collins J, Katz JN, Losina E, Vanwyngaarden C, *et al*. A rapid, novel method of volumetric assessment of MRI-detected subchondral bone marrow lesions in knee osteoarthritis. Osteoarthritis Cartilage 2013;21:806–14.
21. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, *et al*. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19:990–1002.
22. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. J Rheumatol 2002;29:131–8.
23. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29–33.
24. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-mpq), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S240–52.
25. ten Klooster PM, Drossaers-Bakker KW, Taal E, van de Laar MA. Patient-perceived satisfactory improvement (PPSI): interpreting meaningful change in pain from the patient's perspective. Pain 2006;121:151–7.
26. Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. Aust N Z J Public Health 2005;29:136–42.
27. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WH, Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sport Exerc 1999;31:627–33.
28. Laslett LL, Dore DA, Quinn SJ, Boon P, Ryan E, Winzenberg TM, *et al*. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Ann Rheum Dis 2012;71:1322–8.
29. Van der Esch M, Heijmans M, Dekker J. Factors contributing to possession and use of walking aids among persons with rheumatoid arthritis and osteoarthritis. Arthritis Care Res 2003;49:838–42.
30. Shrier I, Feldman DE, Gaudet MC, Rossignol M, Zukor D, Tanzer M, *et al*. Conservative non-pharmacological treatment options are not frequently used in the management of hip osteoarthritis. J Sci Med Sport 2006;9:81–6.
31. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Routledge; 1988.
32. Driban JB, Lo GH, Lee JY, Ward RJ, Miller E, Pang J, *et al*. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. BMC Muscoskelet Disord 2011;12:217.
33. Maracy M, Dunn G. Estimating dose-response effects in psychological treatment trials: the role of instrumental variables. Stat Methods Med Res 2011;20:191–215.
34. Routson RL, Bailey M, Pumford I, Czerniecki JM, Aubin PM. A smart cane with vibrotactile biofeedback improves cane loading for people with knee osteoarthritis. IEEE Eng Med Biol Soc 2016:3370–3.
35. Hart J, Hall M, Wrigley TV, Marshall CJ, Bennell K. Body weight support through a walking cane in inexperienced users with knee osteoarthritis. Gait Posture 2019;67:50–6.
36. Henriksen M, Creaby MW, Lund H, Juhl C, Christensen R. Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials. BMJ open 2014;4,e005368.
37. Bennell KL, Bowles KA, Payne C, Cicuttini F, Williamson E, Forbes A, *et al*. Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. BMJ 2011;342:d2912.
38. Jones A, Silva PG, Silva AC, Colucci M, Tuffanin A, Jardim JR, *et al*. Impact of cane use on pain, function, general health and energy expenditure during gait in patients with knee osteoarthritis: a randomised controlled trial. Ann Rheum Dis 2012;71:172–9.
39. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70:60–7.
40. Barr AJ, Campbell TM, Hopkinson D, Kingsbury SR, Bowes MA, Conaghan PG. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. Arthritis Res Ther 2015;17:228.
41. Hall M, Bennell KL, Wrigley TV, Metcalf BR, Campbell PK, Kasza J, *et al*. The knee adduction moment and knee osteoarthritis symptoms: relationships according to radiographic disease severity. Osteoarthritis Cartilage 2017;25:34–41.
42. Doherty M, Dieppe P. The "placebo" response in osteoarthritis and its implications for clinical practice. Osteoarthritis Cartilage 2009;17:1255–62.
43. Gooberman-Hill R, Ebrahim S. Making decisions about simple interventions: older peoples use of walking aids. Age Ageing 2007;36:569–73.
44. Hart J, Hinman RS, Van Ginckel A, Hall M, Nelligan R, Bennell KL. Factors influencing cane use for the management of knee osteoarthritis: a cross sectional survey. Arthritis Care Res 2018;70(10):1455–60.
45. 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.
46. Bennell KL, Nelligan R, Dobson F, Rini C, Keefe F, Kasza J, *et al*. Effectiveness of an internet-delivered exercise and pain-coping skills training intervention for persons with chronic knee pain: a randomized trial. Ann Intern Med 2017;166:453–62.
47. Sharma L, Eckstein F, Song J, Guermazi A, Prasad P, Kapoor D, *et al*. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008;58:1716–26.
48. Khalaj N, Abu Osman NA, Mokhtar AH, Mehdikhani M, Wan Abas WA. Balance and risk of fall in individuals with bilateral mild and moderate knee osteoarthritis. PLoS One 2014;9,e92270.