Effect of biomechanical footwear on knee pain in people with knee osteoarthritis : the BIOTOK randomized clinical trial

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Title: Effect of biomechanical footwear on knee pain in people with knee osteoarthritis: the BIOTOK randomized clinical trial

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Key points

Question Is an individualized biomechanical footwear therapy effective for reducing knee pain in people with osteoarthritis?

Findings In this randomized trial that included 220 participants with knee pain due to osteoarthritis, treatment with an individualized biomechanical footwear therapy compared with control footwear resulted in a lower WOMAC pain subscore (range 0 to 10), 1.3 pts vs 2.6 pts after 24 weeks, a difference that was statistically significant.

Meaning Although use of biomechanical footwear compared with control footwear resulted in an improvement in knee pain at 24 weeks that was statistically significant, the difference was of uncertain clinical importance, and further research is needed to assess longer term efficacy and safety.

Abstract

Importance: Individually calibrated biomechanical footwear therapy may improve pain and function in people with symptomatic knee osteoarthritis, but benefits of this therapy are unclear.

Objective: To assess the effect of a biomechanical footwear therapy vs control footwear over 24 weeks.

Design, Setting and Participants: Randomized, controlled, single-center superiority trial in a Swiss University hospital. Participants (N= 220) with symptomatic, radiologically confirmed knee osteoarthritis were recruited between April 20, 2015 and January 10, 2017. The last participant visit occurred on August 15, 2017.

Interventions: Participants were randomized to biomechanical footwear involving shoes with individually adjustable external convex pods attached to the outsole (n=111) or to control footwear (n=109) that had visible outsole pods that were not adjustable and did not create a convex walking surface.

Main Outcomes and Measures: The primary outcome was knee pain at 24 weeks assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore standardized to range from 0 (best) to 10 (worst). Secondary outcomes included WOMAC function, stiffness and global scores, all ranging from 0 (best) to 10 (worst) at 24 weeks, and serious adverse events.

Results: Among 220 randomized participants (mean age 65.1 years; 104 (47.3%) women), 219 received the allocated treatment and 213 (96.8%) completed follow-up. At 24 weeks, mean standardized WOMAC pain subscores improved from 4.3 to 1.3 in the intervention group, and from 4.0 to 2.6 in the control group (difference in scores at 24

weeks, -1.3; 95%-CI -1.8 to -0.9, p<0.001). Results were consistent for WOMAC function (difference -1.1; 95%-CI -1.5 to -0.7), stiffness (difference -1.4; 95%-CI -1.9 to -0.9), and global scores (difference -1.2; 95%-CI -1.6 to -0.8) at 24 weeks. Three serious adverse events occurred in the experimental group compared with 9 in the control group (2.7% *vs* 8.3%); none were treatment related.

Conclusions and Relevance: Among participants with knee pain from osteoarthritis, use of biomechanical footwear compared with control footwear resulted in improvement in pain at 24 weeks that was statistically significant but of uncertain clinical importance. Further research would be needed to assess longer term efficacy and safety, as well as replication, before reaching conclusions about the clinical value of this device.

Trial Registration: ClinicalTrials.gov Identifier: NCT02363712

INTRODUCTION

Knee osteoarthritis (OA) affects approximately 265 million people worldwide, and was estimated to account for 8.3 million years lived with disability in 2017.[1] The prevalence of knee OA is rising due to population aging and the increasing prevalence of obesity. Acetaminophen, non-steroidal anti-inflammatory drugs, and opioids are most commonly used to treat pain associated with OA,[2] but have limited effectiveness[3,4] and are associated with adverse effects.[3,5,6] In the US, rates of knee replacement surgery, almost all related to OA, have been increasing, in part because of ineffective nonsurgical treatments.

Biomechanical treatments for knee OA have been developed to reduce pain, improve function and~~, perhaps~~ potentially to slow disease progression,[7] but evidence of effectiveness is inconclusive.[8,9] Two small prospective, non-randomized controlled studies suggested that an individualized biomechanical footwear system may improve pain and function in people with symptomatic knee OA.[10,11] In those studies, the footwear system consisted of shoes with 2 convex pods on the outsoles, individually calibrated based on findings from detailed~~, repeatedly performed~~ gait studies. Adjustment of the location of the pods may alter limb biomechanics and reduce stress on osteoarthritic knee compartments.[12–14] Walking on the convex pods results in gait alterations, which in turn is hypothesized to induce reconditioning of the neuromuscular system and ~~improvement of~~ improve pathological gait patterns.[15] The objective of this study, the Biomechanical Therapy for Osteoarthritis of the Knee (BIOTOK) randomized trial, was to determine whether ~~compare~~ biomechanical footwear were more effective

than~~with~~ control footwear for improving knee pain in participants with knee pain from osteoarthritis.

METHODS

Study design and participants

This was an investigator-initiated single-center randomized ~~single-center controlled superiority~~ clinical trial in participants with symptomatic knee OA that compared biomechanical footwear therapy using shoes with two individually calibrated convex pods on the outsoles (AposTherapy, Apos Medical Assets, New York, NY; eFigures 1 and 2) with a similarly appearing control footwear ~~therapy~~. The trial protocol and statistical analysis plan are in Supplement 1 and Supplement 2.

We enrolled men and non-pregnant women aged ≥40 years, with symptomatic, radiologically confirmed knee OA according to the criteria of the American College of Rheumatology.[16] Participants had knee pain lasting 6 months or longer, and a score ≥3 at the screening visit on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[17] standardized to range from 0 to 10. Exclusion criteria included history of inflammatory rheumatic disease, knee surgery in the previous 6 months or planned hip or knee surgery within 24 weeks of baseline assessment, glucocorticoid knee injections in the previous three months, or a high risk of falls (see Supplement 3 for full eligibility criteria and selection of index knee). The trial was approved by the independent Research Ethics Committee of Canton Bern (KEK-BE 041/215). All participants gave written informed consent.

Randomization and masking

Participants were randomized 1:1 to experimental footwear or control footwear using a concealed, secure web-based system. Randomization was computer-generated,

blocked with randomly varied block sizes of 2 and 4, and stratified by unilateral vs bilateral knee disease and predominantly affected compartment (medial vs. lateral) in the index knee.

The biomechanical footwear device consisted of 2 shoes with 2 convex adjustable rubber pods screwed to the outsole at the heel and forefoot (eFigures 1 and 2 in Supplement 3). The control footwear was specifically designed by the manufacturer for this trial to have a similar appearance to the biomechanical footwear, but with pods embedded in the transparent outsole so that they were visible yet did not create a convex walking surface (eFigure 3 in Supplement 3). To ~~avoid between-group differences in the magnitude of placebo effects~~ try to maintain blinding of participants, participants were kept unaware of the study design and use of control footwear. Participants were informed in a neutral manner that two different types of footwear were compared (Supplement 3). Experimental and control footwear were both presented on the manufacturer's website, and the control footwear was described as a device with a novel design of the sole (eFigure 3 in Supplement 3).

Technicians and study nurses who coordinated the clinical visits could not be blinded to treatment allocation but were asked not to disclose treatment allocation or the nature of the control footwear study component to participants. As technicians were from Israel and did not speak German, direct interaction between technicians and participants was limited, with verbal communication carried out through translating study nurses, who were independent of the manufacturer and encouraged to ~~ensure~~ facilitate unbiased participant interaction. The remaining study personnel performing data entry,

management and cleaning, and the statistician were blinded to the allocated intervention until all primary and secondary analyses were completed.

The consent form did not state that the control footwear was intended to be ineffective (i.e. a sham). Rather, the consent form implied that both types of shoes may have been effective. Furthermore, the manufacturer's website was altered to imply potentially therapeutic benefits of both the intervention and control shoe. Therefore, the trial could be considered potentially deceptive according to the International Ethical Guidelines for Health-related Research Involving Humans[18]—however, both experimental and control footwear included some therapeutic elements. Both were high-top shoes, which provided more stability and proprioceptive input than loose shoes or sandals. Furthermore, proposed mechanisms of the experimental footwear were hypothetical at the time of initiation of this trial, and the trial was considered to entail no more than minimal risks and burdens to participants according to Article 2 of the Swiss Clinical Trials Ordinance.[19] Therefore, the responsible Research Ethics Committee did not classify the trial as involving incomplete participant information (i.e., did not consider the study procedures to be 'deceptive') according to Article 18 of the Swiss Human Research Act.[20] Nonetheless, because the trial may have been considered deceptive by some individuals, participants were debriefed after the trial was completed. Participants were advised of the rationale of the sham-controlled design, informed of differences between experimental and control footwear, and about their group allocation, and were given the opportunity to withdraw consent to participate. Supplement 3 discusses the criteria specified in the International Ethical Guidelines for

Health-related Research Involving Humans for trials that withhold information or use deception[18] with respect to this trial.

Procedures

Participants in both groups underwent initial fitting of their assigned device by technicians at baseline and re-calibration at 4, 8, 12 and 16 weeks. The positioning of the external pods was individually adjusted on experimental devices, in accordance with gait patterns and reported pain intensity during walking, with the aim of decreasing clinically observed malalignment and reported pain intensity, and increasing gait symmetry[13,14,21,22] as determined by two-dimensional computerized spatiotemporal gait analysis (Zeno walkway and PKMAS software, ProtoKinetics, Havertown, PA; Supplement 3). Participants allocated to control footwear received a simulated calibration, which mimicked calibration of the experimental footwear. Technicians, provided by the manufacturer, performed all device-related procedures (gait analyses, fitting, calibrations of experimental and control footwear).

Participants were instructed to use the footwear during indoor activities for a half hour each day during the first week of the intervention, with subsequent increases of 10 minutes per week on average, but were not given explicit instructions to perform specific home-based exercises. After 6 weeks, the participants were advised to use the footwear to walk outdoors. Participants were asked to stop their regular pain medication and advised that other interventions such as physical therapy should be avoided during the trial. They were permitted daily therapy as needed with acetaminophen at a maximum dose of 2 g, with amounts recorded at each visit.

Outcomes

The prespecified primary outcome was knee pain at the end of treatment (24-week follow up) in the index knee, as assessed with the WOMAC pain subscore (visual analogue version) (standardized 0-10 scale, 0=best).[17] The secondary outcomes prespecified in the protocol were WOMAC global score (standardized 0-10 scale, 0=best), WOMAC physical function and stiffness subscores (standardized 0-10 scale, 0=best) at 12 and 24 weeks follow-up; WOMAC pain subscore at 4, 8, 12 and 16 weeks; the physical and mental component summary scores of the Medical Outcomes Study Short Form 36-item Health Survey (SF-36) (standardized to have a mean of 50 and a standard deviation of 10 for the general population, with theoretical range 0-100, 100=best)[23] at 12 and 24 weeks; gait velocity, step length, and single limb support, as measured by two-dimensional computerized gait analysis when walking barefoot at 4, 8, 12, 16 and 24 weeks; self-reported time spent wearing footwear per day; self-reported health care utilization; and analgesic use, as between-group differences in analgesic use could result in performance bias.[24] Minimal clinically important differences were not considered when planning the trial. Other prespecified outcomes were treatment response defined as a 30% decrease in WOMAC pain from baseline and ~~as~~ a 50% decrease in WOMAC pain from baseline.[25] Treatment response defined as a 50% decrease in WOMAC pain from baseline was not prespecified in the protocol, but was included in the statistical analysis plan. The adverse events prespecified in the protocol were falls, any adverse events, serious adverse events, dropouts, and dropouts due to adverse events (Supplement 3). WOMAC scores,[17] analgesic intake, and gait analysis

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parameters were recorded at baseline, 4, 8, 12, 16 and 24 weeks; SF-36 scores and healthcare utilization were recorded at baseline and 12 and 24 weeks. Adverse events and time spent wearing footwear were recorded at each follow-up visit. Two investigators blinded to the assigned treatment adjudicated all potential adverse events based on notes by participants and nurses, and, in case of potential serious adverse events, based on relevant medical records.

Statistical analysis

A sample size of 100 participants per group yielded 80% power to detect a difference of 1.05 on a standardized WOMAC pain scale ranging from 0 to 10 at a two-sided alpha of 0.05. The difference corresponds to a moderate effect size of 0.4 standard deviation units assuming a typical standard deviation of 2.65.[4] The protocol prespecified the use of analyses of covariance for all continuous outcomes, adjusted for the outcome's baseline values. For this approach, a sample size of 100 participants per group would yield approximately 90% power, assuming a correlation of 0.5 between baseline and 24-week follow-up. Anticipating an attrition rate of 10%, the target sample size was 220 participants.

Continuous outcomes were analyzed using analysis of covariance adjusted for the outcome's baseline values and variables used for stratified randomization, considering only the assessments of the index knee of each participant. Binary outcomes were analyzed using Cochran-Mantel-Haenszel tests stratified by stratification variables.[26] All randomized participants were included in analyses according to their randomized allocation,[27] using multiple imputation to impute missing

outcome data, using all baseline characteristics (age, sex, BMI, blood pressure, medical history, WOMAC scores, SF-36 scores, and parameters of gait analysis), outcomes at all time-points, the treatment indicator, and stratification variables to generate 20 imputed datasets (Supplement 3).

Pre-specified subgroup analyses of the primary outcome were performed according to the predominantly affected compartment and the presence or absence of symptomatic contralateral knee OA and accompanied by tests for interaction. A post-hoc subgroup analysis was done according to WOMAC pain intensity at baseline.[28] Pre-specified sensitivity analyses of the primary outcome included a per-protocol analysis, a complete case analysis, adjustments for potential procedural confounders, and a linear mixed effects model to analyze all knees (i.e., index or both index and contralateral knee) with a baseline WOMAC pain subscale score of ≥3. Post-hoc sensitivity analyses of WOMAC scores, SF-36 scores and parameters of gait analyses were performed using all time points in a linear mixed-effects regression model (Supplement 3). P-values and 95% confidence intervals (CIs) were two-sided, p-values ≤0.05 were considered statistically significant. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. Analyses were performed in R version 3.3.2,[29] by an independent statistician of an academic clinical trials unit (CTU Bern, Switzerland) who was unaware of group assignment. The statistical analysis plan was finalized after completion of follow-up, but before examination of the data. Data were interpreted and conclusions formulated prior to unblinding investigators.

RESULTS

Between April 20, 2015 and January 10, 2017, 220 participants were randomized: 111 to the experimental footwear and 109 to control footwear (Figure 1). One participant in the experimental group refused treatment and did not receive the intervention. Seven and 13 participants, respectively, discontinued treatment during follow-up. One hundred nine (98.2%) and 104 participants (95.4%) completed the primary outcome at 24 weeks follow-up, respectively. After trial completion, 217 of the 220 randomized participants were reached and advised of the potential for deception in the study design. Of three participants who were not reached, one participant in the experimental group had died, and two participants in the experimental group were lost to follow-up. None of the 217 participants withdrew consent after learning that the trial involved randomization to either experimental footwear or a control footwear that was expected to be ineffective.

Baseline characteristics were similar between the participants randomized to each group (Table 1 and eTable 1 in Supplement 3). The study population had a mean age of 65.2 years (SD 9.3), included 47.3% females and had a mean BMI of 28.0 kg/m^2 (SD 4.6). Medial knee osteoarthritis was present in 90.9% and unilateral disease in 67.7% of participants. The number of participants with missing data was between 0 and 3 (1.4%) for baseline characteristics (eTable 2 in Supplement 3) and between 2 (0.9%) and 29 (13.2%) for outcomes (eTable 3 in Supplement 3).

Primary outcome

The experimental group had a larger decrease in standardized WOMAC pain scores at 24 weeks than the control group (mean scores at 24 weeks, 1.3 vs 2.6, difference -1.3; CI -1.8 to -0.9; p<0.001) (Figure 2, Table 2).

Secondary outcomes

The experimental group had larger declines in the secondary outcomes of WOMAC function and stiffness subscores and global score at 24 weeks (Figure 2 and Table 2). Between-group differences in velocity, step length and single limb support emerged in favor of the experimental group between 12 and 24 weeks (Table 2). The mean self-reported time spent wearing the footwear at 24 weeks was 209 vs 174 minutes per day (difference 35 minutes; CI, 4 to 67 minutes). There was no statistically significant difference in the SF-36 physical component summary score between the intervention vs. the control groups (mean, 45.9 vs 44.5, difference 1.4, CI -0.5 to 3.2). There were no significant differences between change in the SF-36 mental component summary score, analgesic use, or health care between the two groups. eTable 4 in Supplement 3 presents the additional prespecified secondary outcomes, types of analgesics, health care providers, corticosteroid injections, and performed or planned knee replacement surgery. eTable 5 in Supplement 3 reports the other prespecified outcomes, treatment response achieving a 30% or 50% reduction in WOMAC pain from baseline to 24 weeks. Ninety-two vs 58% of participants achieved a 30% reduction (risk difference 34%; 95% CI 23% to 45%), and 83% vs 42% achieved a 50% reduction (risk difference 41%; 95% CI 28% to 52%) in the experimental and control groups, respectively, corresponding to numbers-needed-to-treat of 3 (95% CI 2 to 5) and 3 (95% CI 1 to 4).

Pre-specified subgroup analyses of the primary outcome according to predominantly affected compartment and symptomatic contralateral disease did not show significant treatment-by-subgroup interactions (eTable 6 in Supplement 3). Sensitivity analyses of the primary outcome, including a per-protocol analysis, a complete case analysis, adjustments for potential procedural confounders, and a linear mixed effects model to analyze all knees with a baseline WOMAC pain subscore of ≥3 were consistent with main analyses (eTables 7 to 11 in Supplement 3).

Adverse events

Twenty-six (23%) participants in the intervention group and 38 participants (35%) in the control group experienced an adverse event (Table 3). Three (2.7%) and 9 participants (8.3%), respectively, experienced serious adverse events. None were considered treatment related. None vs. 4 serious adverse events were musculoskeletal, 1 vs. 3 were circulatory, 2 vs. 2 were in other categories, respectively (eTable 12 in Supplement 3). One or more falls occurred in 2 (1.8%) and 4 participants (3.7%), respectively; 1 participant in the control group fell while wearing the control footwear.

Post-hoc analyses

A post hoc subgroup analysis of the primary outcome by WOMAC pain intensity at baseline did not show significant treatment-by-subgroup interactions (eTable 6 in Supplement 3). The post-hoc use of a mixed-effects model simultaneously including all timepoints showed results similar to those of main analyses. In the mixed-effects models, there were significant differences in WOMAC pain and physical function

subscores and WOMAC global scores at 12, 16 and 24 weeks, and WOMAC stiffness subscores at 16 and 24 weeks follow-up. Significant differences in parameters of gait analysis were observed for velocity and step length at weeks 12, 16 and 24, and for single limb support at week 24 (eTable 13 in Supplement 3). eFigure 4 in Supplement 3 contrasts WOMAC pain subscores with the time spent wearing the footwear over the duration of the trial. The maximal difference in time spent wearing the footwear occurred at 16 weeks, while the maximum difference in WOMAC pain scores was observed 8 weeks later, at 24 weeks.

DISCUSSION

In this randomized trial, a biomechanical footwear system with individually calibrated outsole convex pods was more effective than a control biomechanical footwear at reducing pain at 24 weeks in participants with knee pain from symptomatic knee OA. Results were consistent for secondary outcomes of WOMAC function and stiffness subscores and global score at 24 weeks. There were no significant differences between groups in physical and mental components of the SF-36.

There are two differences between the biomechanical footwear system tested in this trial, and other biomechanical devices such as shoes[9] or wedges.[8] First, in this trial, the individualized calibration of proximal and distal pods of the experimental device in coronal and sagittal planes shifts the trajectory of the foot's center of pressure, thereby specifically changing the direction of the ground reaction force vector as appropriate for each individual.[12,13,30] Second, the convexity of the pods in the experimental footwear results in repetitive gait perturbation, with mild destabilization of the knee during walking, which in turn may elicit neuromuscular responses.

To our knowledge, no other published randomized trials have investigated the effectiveness of this biomechanical footwear system in people with symptomatic knee OA. Of six published clinical studies,[10,11,15,31–33] four were uncontrolled studies conducted by the manufacturer,[15,31–33] the remaining two were prospective and controlled, but non-randomized.[10,11] The most rigorous investigation was a prospective non-randomized controlled study in 57 participants with symptomatic knee OA,[10] which found improved pain and function with the biomechanical footwear system as compared to a control shoe. However, the difference between groups in WOMAC pain subscores

at 8 weeks was not consistent with the negative 8-week resultestimate near null in the current study. The reason for this difference is unclear, but may be due to lack of randomization in the prior trial.

Limitations

This study has several limitations. First, the appearance of the experimental footwear and control footwear was different. To overcome this limitation and minimize the likelihood that participants would correctly guess that they were not receiving the active intervention, participants were kept unaware that the control shoe was not expected to have therapeutic benefits. Participants were informed in a neutral fashion that two different types of footwear were compared. The manufacturer's website described the control footwear as a device with a novel design of the sole, and participants allocated to the control group received a simulated calibration that mimicked the actual calibration. Second, the use of a blinding index[34] to determine success of blinding was not performed, because such an index assumes indistinguishable interventions. Third, the self-reported time per day wearing the footwear was longer in the experimental group than in the control group. It is possible that the greater benefit in the intervention group was due to longer wear time. Fourth, analgesic treatment for pain was allowed during the trial, but rates of analgesic use did not differ between groups. Fifth, it was not possible to explore changes in knee adduction moments using three-dimensional gait analyses. Sixth, the trial was conducted in a single center, potentially limiting generalizability. Seventh, between-group differences occurred only late during follow-up and were smaller than the observed within-group change from baseline in the control

group. Therefore, the clinical importance of these findings remains uncertain. Eighth, the findings from this trial are not generalizable to people at high risk of falls, as these individuals were ineligible. Ninth, the findings are not generalizable to people with severe knee pain, as these individuals were underrepresented in the trial.

Conclusions

Among participants with knee pain from osteoarthritis, use of biomechanical footwear compared with control footwear resulted in an improvement in pain at 24 weeks that was statistically significant but of uncertain clinical importance. Further research would be needed to assess longer term efficacy and safety, as well as replication, before reaching conclusions about the clinical value of this device.

Author Contributions:

Drs Reichenbach and Jüni had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Reichenbach, Felson, Jones, Jüni

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Reichenbach, Hincapié, Jüni.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Lenz, Bütikofer, da Costa, Jüni.

Obtained funding: Reichenbach, Jüni.

Administrative, technical, or material support: Jüni.

Supervision: Reichenbach, Jüni.

Conflict of Interest Disclosures:

Dr. Jüni serves as unpaid member of the steering group of cardiovascular trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company, has received research grants to the institution for cardiovascular studies from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company, and honoraria to the institution for participation in advisory boards from Amgen and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. No other disclosures were reported.

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Role of the Funder/Sponsor:

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: Supplement 4

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Figures

Figure 1. Participant recruitment, randomization, and follow-up

NOTE- THERE APPEARS TO BE A MATH ERROR IN FIGURE 1- "NOT ELIGIBLE" SHOULD BE 455 (NOT 457).

Definitions for WOMAC scores and Kellgren-Lawrence grades can be found in footnote to Table 1. STEADI, Stopping Elderly Accidents, Deaths, and Injuries score; STEADI score of 4 or greater at the screening visit was considered to indicate a high risk of falls.

**The 2 and 5 participants without primary outcome data all also discontinued treatment and were therefore counted as part of the 7 and 13 participants reported to have discontinued treatment.*

Figure 2. WOMAC scores during the 24-week follow up period

Box and whisker plots, with the box representing median and interquartile range, whiskers the most extreme values within 1.5 times of the interquartile range beyond the 25th and 75th percentile, and circles the more extreme values. Panel A shows the pain subscores (primary outcome) of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Panels B and C display the WOMAC physical function and stiffness subscores, respectively. Panel D shows the WOMAC global scores. Definitions for WOMAC scores can be found in footnote to Table 1.

570 **Tables**

Table 1. Participant Characteristics at Baseline

Characteristic	Biomechanical Footwear (N=111)	Control Footwear (N=109)
Sex — no. (%)		
Female	51 (45.9)	53 (48.6)
Male	60 (54.1)	56 (51.4)
Age yr — mean (SD)	65.3 (9.2)	65.0 (9.3)
Weight kg — mean (SD)	80.6 (15.7)	82.7 (14.2)
Height cm — mean (SD)	170.4 (8.6)	170.9 (8.2)
Body mass index[a] kg/m^2 — mean (SD)	27.7 (4.8)	28.3 (4.3)
History of meniscal resection — no. (%)	55 (49.5)	50 (45.9)
Knee joint effusion — no. (%)	18 (16.2)	17 (15.6)
Kellgren-Lawrence grade[b] — no. (%)		
2	33 (29.7)	36 (33.0)
3	50 (45.9)	46 (41.4)
4	28 (25.2)	27 (24.8)
Medial knee osteoarthritis — no. (%)	101 (91.0)	99 (90.8)
WOMAC scores[c] — mean (SD)		
Pain	4.3 (1.8)	4.0 (2.0)
Physical function	3.5 (1.8)	3.4 (1.8)
Stiffness	5.0 (2.4)	4.4 (2.4)
Global	3.8 (1.7)	3.6 (1.7)
SF-36 scores[d] — mean (SD)		
Physical component	40.4 (7.1)	40.3 (6.2)
Mental component	57.0 (7.4)	56.4 (8.8)
Used analgesics in the past week — no. (%)	44 (40)	35 (32)

Continuous variables are summarized as mean and standard deviation (SD). Knee-related characteristics are with regard to the index knee. Percentages may not total 100 because of rounding. For additional baseline characteristics, see eTable 1 in Supplement 3.

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[b] Kellgren-Lawrence grades range from 0 to 4; a grade ≥2 indicates definite osteoarthritis on anteroposterior weight-bearing radiograph; grade 2, definite osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity; grade 4, large osteophytes, marked JSN, severe sclerosis and definite bony deformity

[c] WOMAC, Western Ontario McMaster Universities Osteoarthritis Index, a self-administered questionnaire including 5 questions on pain, 17 questions on physical function and 2 questions on stiffness; all 4 composite scores were standardized to range from 0 to 10 (0, no symptoms; 10, extreme symptoms). For the WOMAC pain subscore, scores ≤4 indicate mild pain, scores >4 to ≤7 moderate pain, and scores >7 severe pain.[28]

[d] The 36-Item Short-Form Health Survey (SF-36) comprises physical and mental component summary scores. Each component score having a mean of 50 and standard deviation of 10 for the general population, with higher summary scores indicating better health.

Table 2. Primary and Secondary Outcomes				
Outcome	**Biomechanical Footwear (N=111)**	**Control Footwear (N=109)**	**Mean or risk difference (95% CI)**	***P* Value**
Primary outcome				
WOMAC Pain at 24 weeks	1.3 (1.3)	2.6 (2.0)	-1.3 (-1.8 to -0.9)	< 0.001
Secondary outcomes				
WOMAC Pain				
4 weeks	3.2 (1.9)	3.4 (2.0)	-0.4 (-0.9 to 0.0)	0.04
8 weeks	2.5 (1.6)	2.6 (1.8)	-0.3 (-0.7 to 0.1)	0.19
12 weeks	2.3 (1.7)	2.6 (2.1)	-0.5 (-0.9 to -0.1)	0.03
16 weeks	2.0 (1.7)	2.4 (1.9)	-0.5 (-1.0 to -0.1)	0.02
WOMAC Physical function				
12 weeks	2.1 (1.4)	2.5 (2.0)	-0.5 (-0.9 to -0.1)	0.01
24 weeks	1.4 (1.2)	2.4 (1.8)	-1.1 (-1.5 to -0.7)	< 0.001
WOMAC Stiffness				
12 weeks	2.9 (2.0)	2.8 (2.3)	-0.3 (-0.8 to 0.2)	0.25
24 weeks	1.6 (1.5)	2.8 (2.2)	-1.4 (-1.9 to -0.9)	< 0.001
WOMAC Global				
12 weeks	2.2 (1.4)	2.5 (2.0)	-0.5 (-0.9 to -0.1)	0.25
24 weeks	1.4 (1.2)	2.5 (1.8)	-1.2 (-1.6 to -0.8)	< 0.001
SF-36 Physical component				
12 weeks	43.1 (7.6)	43.8 (7.3)	-0.7 (-2.4 to 0.9)	0.39
24 weeks	45.9 (7.4)	44.5 (8.0)	1.4 (-0.5 to 3.2)	0.14
SF-36 Mental component				
12 weeks	57.1 (7.0)	56.2 (8.9)	0.6 (-1.2 to 2.4)	0.51
24 weeks	56.8 (6.7)	56.0 (9.0)	0.5 (-1.4 to 2.4)	0.59
Any health care use up to 24 weeks[a] — no. (%)	41 (37.3)	29 (27.0)	10.3% (-2.5 to 22.7%)	0.10
Any analgesic use at 24 weeks — no. (%)	45 (40.5)	49 (45.0)	-4.4% (-17.5 to 8.8%)	0.51
Analgesic dose in those with analgesic use at 24 weeks[b]	(N=45) 875 (250-2569)	(N=49) 875 (250, 2500)	0 (-1038 to 1038)	1.00
Gait analysis (barefoot)				
Velocity (cm/sec) — mean (SD)				
4 weeks	107.7 (16.1)	109.9 (17.7)	1.1 (-1.8 to 4.0)	0.44
Outcome	**Biomechanical Footwear**	**Control Footwear**	**Mean or risk difference**	***P* Value**

	(N=111)	(N=109)	(95% CI)	
8 weeks	111.9 (16.8)	112.2 (19.5)	2.9 (-0.7 to 6.4)	0.12
12 weeks	114.0 (17.3)	112.8 (19.3)	4.3 (0.7 to 7.9)	0.02
16 weeks	114.3 (18.0)	113.2 (19.1)	4.0 (-0.1 to 8.2)	0.06
24 weeks	115.7 (17.1)	114.8 (19.2)	3.6 (-0.4 to 7.6)	0.08
Step length, index knee (cm) — mean (SD)				
4 weeks	60.4 (6.5)	60.4 (7.6)	0.7 (-0.3 to 1.6)	0.16
8 weeks	61.3 (6.9)	61.1 (8.3)	0.9 (-0.3 to 2.1)	0.15
12 weeks	61.8 (7.0)	60.9 (8.3)	1.5 (0.3 to 2.8)	0.02
16 weeks	62.3 (7.1)	61.2 (8.0)	1.6 (0.2 to 3.1)	0.03
24 weeks	62.5 (6.9)	61.6 (8.2)	1.4 (-0.1 to 3.0)	0.07
Single limb support, index knee (% of gait cycle) — mean (SD)				
4 weeks	37.0 (1.7)	37.0 (1.9)	0.1 (-0.2 to 0.4)	0.39
8 weeks	37.3 (1.7)	37.3 (1.9)	0.1 (-0.2 to 0.4)	0.59
12 weeks	37.4 (1.7)	37.3 (1.9)	0.3 (0.0 to 0.6)	0.09
16 weeks	37.4 (1.6)	37.4 (1.8)	0.1 (-0.2 to 0.5)	0.43
24 weeks	37.5 (1.5)	37.3 (2.0)	0.3 (0.0 to 0.7)	0.07
Time spent wearing footwear (min/d during the past week) — mean (SD)				
4 weeks	70.3 (48.6)	58.1 (34.2)	12.6 (1.4 to 23.8)	0.03
8 weeks	129.3 (60.8)	98.9 (45.2)	30.4 (15.9 to 44.9)	< 0.001
12 weeks	176.7 (82.3)	133.3 (66.1)	43.4 (23.0 to 63.8)	< 0.001
16 weeks	207.8 (90.0)	146.7 (99.2)	61.2 (35.1 to 87.3)	< 0.001
24 weeks	209.2 (102.9)	173.5 (122.9)	35.4 (4.2 to 66.6)	0.03

Continuous outcomes are summarized within group as mean (SD) and were analyzed at each time point using a linear regression model adjusted for the outcome's baseline values and stratification variables, and considering only the assessments of the index knee of each participant. Refer to footnotes of Table 1 for definitions of WOMAC and SF-36 scales.

For additional secondary outcomes, see eTables 4 and 5 in Supplement 3. Mantel-Haenszel risk differences were adjusted for the two stratification factors (medial or lateral osteoarthritis status, and unilateral or bilateral knee disease at randomization).

[a] Includes any self-reported visits to a primary care physician, rheumatologist, orthopedic surgeon, physiotherapist, occupational therapist, complementary or alternative health care practitioner, and community nurse.

[b] Analgesic dose in participants in experimental and control groups who reported any analgesic use at 24 weeks, expressed as acetaminophen equivalence dose in mg per day and summarized within groups as median with interquartile range and difference in medians between groups with 95% CI.

Table 3. Adverse Events		
Event	**Biomechanical Footwear Group (N=111)**	**Control Footwear Group (N=109)**
Any adverse events	26 (23.4)	38 (34.9)
Minor adverse events	23 (20.7)	30 (27.5)
Musculoskeletal	15 (13.5)	21 (19.3)
Knee pain or swelling[a]	2 (1.8)	3 (2.8)
Low back pain	5 (4.5)	5 (4.5)
Hip pain	5 (4.5)	3 (2.8)
Foot pain	2 (1.8)	3 (2.8)
Other	3 (2.7)	8 (7.3)
Injury	6 (5.4)	9 (8.3)
Ankle sprain	2 (1.8)	1 (0.9)
Fall[b]	2 (1.8)	4 (3.7)
Other	2 (1.8)	4 (3.7)
Genitourinary	2 (1.8)	2 (1.8)
Circulatory	1 (0.9)	1 (0.9)
Nervous system	0	2 (1.8)
Eye	0	1 (0.9)
Respiratory system	1 (0.9)	0
Digestive system	1 (0.9)	0
Serious adverse events[c]	3 (2.7)	9 (8.3)
Musculoskeletal	0	4 (3.7)
Total hip or knee replacement surgery	0	3 (2.8)
Low back pain[d]	0	1 (0.9)
Circulatory	1 (0.9)	3 (2.8)
Coronary heart disease[e]	1 (0.9)	2 (1.8)
Other	0	1 (0.9)
Genitourinary	1 (0.9)	0
Eye	0	1 (0.9)
Digestive system	1 (0.9)	1 (0.9)

Presented are numbers of participants who experienced a specific type of event and percentages. Adverse event categories correspond to ICD 10 chapters and are summarized as clinical subcategories if at least 3 participants experienced a specific type of event.

[a] Corresponds to local adverse events as prespecified in the protocol.

[b] Corresponds to adverse events due to a fall, as prespecified in the statistical analysis plan. One participant in the control footwear group experienced a fall while wearing the study footwear.

[c] Serious adverse events were defined as events resulting in hospitalization, prolongation of

hospitalization, persistent or significant disability, congenital abnormality or birth defects of offspring, life-threatening events, or death.

[d] One participant in the control footwear group with lumbar disc herniation surgery.

[e] One participant in the biomechanical footwear group with acute myocardial infarction.

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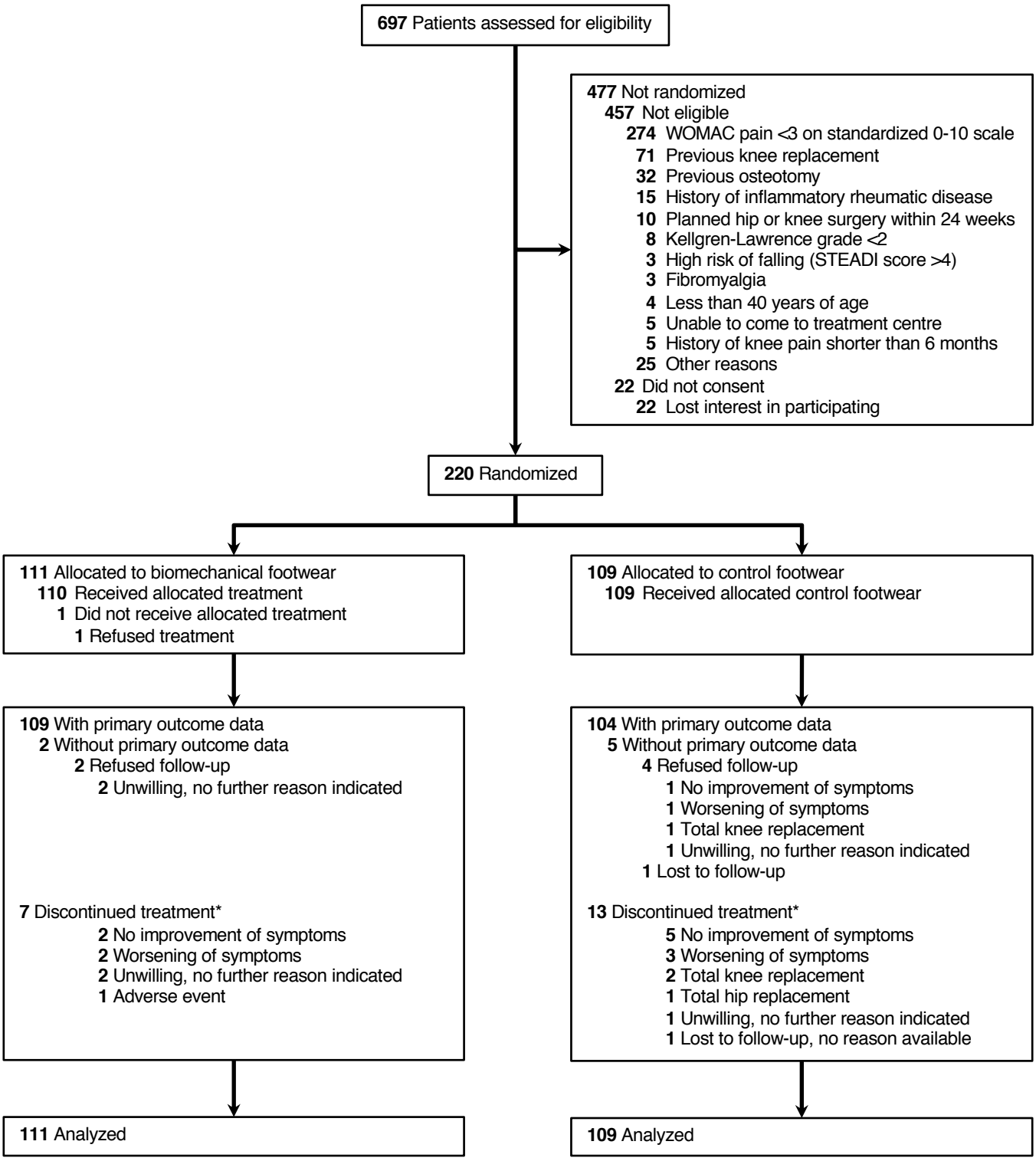
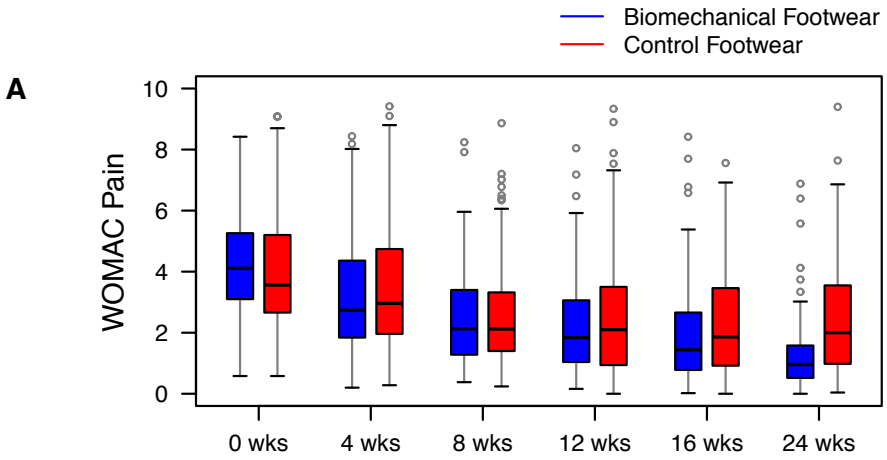
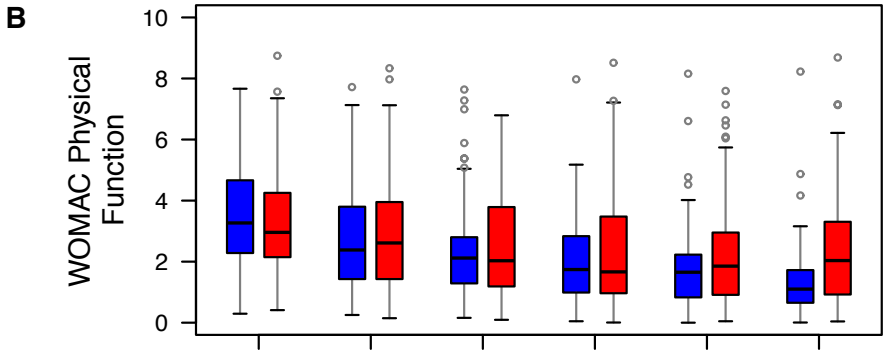
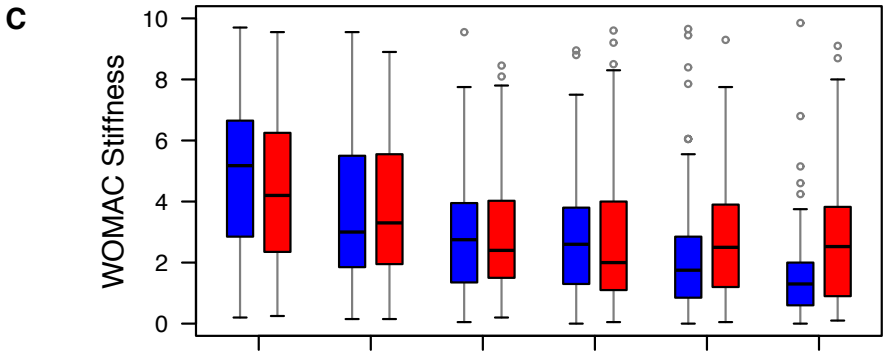

697 Patients assessed for eligibility
477 Not randomized
457 Not eligible
274 WOMAC pain <3 on standardized 0-10 scale
71 Previous knee replacement
32 Previous osteotomy
15 History of inflammatory rheumatic disease
10 Planned hip or knee surgery within 24 weeks
8 Kellgren-Lawrence grade <2
3 High risk of falling (STEADI score >4)
3 Fibromyalgia
4 Less than 40 years of age
5 Unable to come to treatment centre
5 History of knee pain shorter than 6 months
25 Other reasons
22 Did not consent
22 Lost interest in participating
220 Randomized
111 Allocated to biomechanical footwear
110 Received allocated treatment
1 Did not receive allocated treatment
1 Refused treatment
109 Allocated to control footwear
109 Received allocated control footwear
109 With primary outcome data
2 Without primary outcome data
2 Refused follow-up
2 Unwilling, no further reason indicated
7 Discontinued treatment*
2 No improvement of symptoms
2 Worsening of symptoms
2 Unwilling, no further reason indicated
1 Adverse event
104 With primary outcome data
5 Without primary outcome data
4 Refused follow-up
1 No improvement of symptoms
1 Worsening of symptoms
1 Total knee replacement
1 Unwilling, no further reason indicated
1 Lost to follow-up
13 Discontinued treatment*
5 No improvement of symptoms
3 Worsening of symptoms
2 Total knee replacement
1 Total hip replacement
1 Unwilling, no further reason indicated
1 Lost to follow-up, no reason available
111 Analyzed
109 Analyzed



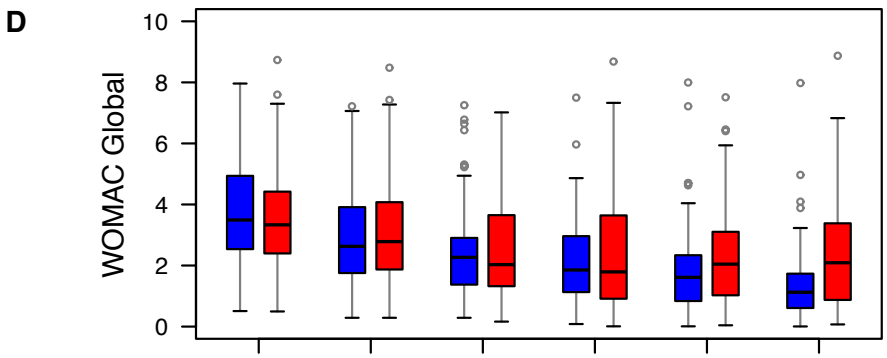
No. of participants						
Biomechanical Footwear	110	109	110	109	109	109
Control Footwear	109	109	107	105	105	104



No. of participants						
Biomechanical Footwear	110	109	110	109	109	109
Control Footwear	109	109	107	105	105	105



No. of participants						
Biomechanical Footwear	110	109	110	109	109	109
Control Footwear	109	109	107	105	105	104



No. of participants						
Biomechanical Footwear	110	109	110	109	109	109
Control Footwear	109	109	107	105	105	104