Personalised gait retraining for medial compartment knee osteoarthritis: a randomised controlled trial

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Research in context

Evidence before this study

Knee osteoarthritis is a painful condition that limits mobility, making it a leading cause of disability worldwide. No disease-modifying treatments are available; thus, pharmacological interventions and joint replacements are used to manage symptoms. Excessive mechanical loading in an osteoarthritic knee accelerates disease progression, suggesting that biomechanical interventions that reduce loads in the knee (e.g., gait retraining) might provide a promising treatment option. However, randomized trials have not conclusively shown these interventions to be effective. Systematic reviews and meta-analyses conducted by the American Academy of Orthopedic Surgeons (2013; reviewed studies from PubMed, EMBASE, CINAHL, and Cochrane databases prior to May 2012) and the Osteoarthritis Research Society International (2019; reviewed studies from Medline, PubMed, EMBASE, Google Scholar, and Cochrane databases prior to December 2017) could not recommend biomechanical interventions for clinical adoption due to a lack of evidence of efficacy. We searched PubMed without language restrictions for (gait retraining OR gait modification OR toe-in OR toe-out) AND (knee osteoarthritis) AND (trial) from inception to December 31, 2015 (prior to beginning the study, 32 results) and from inception to May 14, 2025 (while writing the manuscript, 86 results). We screened results for randomized controlled trials of gait retraining interventions for knee osteoarthritis that used a sham control group and evaluated clinical outcomes over time. To our knowledge, no sham-controlled trials of gait retraining interventions for knee osteoarthritis have been conducted. In our first search, we found two short-term, uncontrolled studies that demonstrated that a gait retraining intervention—modifying the foot angle—reduced joint loading and pain on average, but not all individuals benefited. In healthy individuals, we previously demonstrated that prescribing a personalized foot angle modification, rather than the same angle to everyone, greatly enhanced the joint-offloading effect. Thus, we hypothesized that retraining individuals with medial compartment knee osteoarthritis to adopt a personalized foot angle modification during walking would improve pain and reduce loading over one year more than sham gait retraining. In our second search, after the study was completed, we found

three randomized controlled trials of gait retraining interventions that used walking exercise, but not sham gait retraining, as a control. Two short-term trials that displayed joint loading on a screen and instructed individuals to reduce it found pain improvements, while one trial that delivered the same foot angle modification to all individuals did not find a between-group improvement in pain. Thus, there remains a paucity of high-quality evidence to conclusively support gait retraining interventions, in part because no prior trials have used a sham intervention in the control group, used personalized intervention selection, or evaluated the effect of gait retraining on the structural progression of knee osteoarthritis.

Added value of this study

This study addresses a key limitation of previous trials that prescribed the same intervention to all individuals, resulting in some individuals not reducing or even increasing their joint loading. In contrast, we only included biomechanical responders (i.e., those who could reduce loading at baseline with a modified foot angle; 75% of our cohort), and we personalized the intervention selection (i.e., selected the modification that maximally reduced the knee load). This individualized approach is a key distinction and may have contributed to the statistically significant and clinically meaningful pain improvements that we observed, which were not observed in previous trials of uniformly prescribed interventions. Another key addition of this study is the use of a sham intervention as a control, which is rare in biomechanical intervention trials. Our sham intervention had a moderate effect on pain, similar to the previously reported placebo effect in osteoarthritis trials. The personalized gait retraining intervention reduced pain more than this sham intervention by an amount comparable to over-the-counter pain medications, and a greater proportion of the intervention group experienced a clinically meaningful pain improvement. Our use of a sham intervention, as opposed to a commonly used exercise control group, provides stronger evidence that the pain improvement was due to the intervention itself, rather than the placebo effect of gait retraining. Notably, the intervention also slowed MRI-based measures of cartilage degeneration (secondary outcome), a finding that has not been shown in trials of biomechanical interventions. Taken together, the improvements in pain, joint loading, and cartilage microstructure observed in our study provide evidence

for the efficacy of biomechanical interventions for knee osteoarthritis, which prior meta-analyses were unable to conclusively recommend. Our biomechanical patient selection strategy and personalized approach likely played a key role in the intervention's effectiveness and should be considered in future biomechanical intervention studies and clinical practice.

Implications of all the available evidence

Our study provides evidence that personalized retraining of the foot angle during walking is an effective treatment for some individuals with mild or moderate medial compartment knee osteoarthritis. Our MRI findings suggest that this intervention may not only decrease pain but also slow cartilage degeneration, a longstanding goal in the field. Notably, our findings highlight the importance of personalizing osteoarthritis treatments. Recently developed mobile sensing technologies can retrain walking patterns and estimate joint loading outside of a gait laboratory, making personalized gait retraining feasible in a clinical setting. A future trial leveraging these technologies, in conjunction with the evidence from our study, could provide clinicians with an effective treatment for a condition with limited therapeutic options.

Summary

Background: Retraining individuals with medial compartment knee osteoarthritis to walk with a patient-specific change in their foot angle (i.e., toe-in or toe-out angle) can reduce deleterious joint loading. This study investigated the clinical, biomechanical, and structural efficacy of personalized foot progression angle modifications compared to sham treatment in patients with mild-to-moderate medial compartment knee osteoarthritis.

Methods: In this parallel, single-center, participant-blinded randomized controlled trial, we recruited individuals with symptomatic medial compartment knee osteoarthritis in California, USA using online and print media. Eligible participants were randomly assigned 1:1 by a computer to an intervention or sham group. During six walking retraining visits to a university gait laboratory, all participants received real-time biofeedback instructing them to walk consistently with a personalized target foot progression angle. The intervention group's target was the 5° or 10° change in foot progression angle that maximally reduced their knee loading, and the sham group's target was their natural foot progression angle. Participants and staff involved in data analysis were blinded to group allocation; staff performing the gait analysis visits were not. Primary outcomes were one-year changes in medial knee pain (numeric rating scale) and medial knee loading (knee adduction moment peak). Secondary outcomes were one-year changes in cartilage microstructure estimated from magnetic resonance imaging ($T_{1\rho}$ and T_2 relaxation times). We also evaluated safety by monitoring the number and type of adverse events. Intent-to-treat linear regression analyses, comprising all randomized participants, were conducted. People with relevant lived experience were involved in the design and conduct of this study. This study is registered with clinicaltrials.gov (NCT02767570, closed to enrollment).

Findings: Sixty-eight patients (recruited between August 1, 2016 and June 25, 2019) were randomly assigned to the intervention (n=34, 21 [62%] female, 64·3 [SD 7·7] years at enrollment, 28 [82%] White)

or sham group (n=34, 20 [59%] female, 64·5 [SD 7·6] years at enrollment, 26 [76%] White). After one year, the intervention group had greater reductions in medial knee pain (between-group difference=-1·2; 95% confidence interval: -1·9, -0·5; *P*=·0013) and peak knee adduction moment (between-group difference=-0·26%bodyweight*height; 95% confidence interval: -0·39, -0·13%bodyweight*height; *P*=·0001) than the sham group. Compared to the sham group, 26% more individuals in the intervention group experienced a clinically meaningful improvement in medial knee pain (relative likelihood=1.26; 95% confidence interval: 1.04, 1.56). The magnetic resonance imaging–estimated change in cartilage microstructure ($T_{1\rho}$) in the intervention group was less than the sham group (between-group difference=-3·74ms; 95% confidence interval: -6·42, -1·05ms), suggesting that the intervention slowed cartilage degeneration. There were no significant between-group differences in T_2. There were no severe adverse events; however, two participants (6%) of 34 in the intervention group and one (3%) of 34 in the sham group dropped out of the study due to increased knee pain.

Interpretation: Personalized foot angle modifications improve pain, reduce knee loading, and may slow osteoarthritis progression, making them a promising non-surgical treatment option for some individuals with medial compartment knee osteoarthritis.

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Introduction

Osteoarthritis is a leading cause of disability among adults, affecting 22% of individuals over the age of 40.[1] The knee is the most common site of symptomatic osteoarthritis,[1] and excessive compressive loading during walking accelerates osteoarthritis progression.[2] Isolated medial compartment osteoarthritis is three times more prevalent than isolated lateral compartment osteoarthritis,[3] likely because roughly 70% of compressive force is transmitted through the medial compartment during walking.[4] The knee adduction moment is a surrogate measure for the medio-lateral distribution of compressive loading,[5] and the knee adduction moment peak during walking relates to the progression of medial knee osteoarthritis.[2] Loading can be shifted from the medial to the lateral compartment by reducing the knee adduction moment; thus, reducing the knee adduction moment peak is a target for conservative interventions, like gait modifications.

Altering the foot progression angle (i.e., toeing-in or toeing-out) is a subtle way to reduce the knee adduction moment that is preferred by patients over more conspicuous gait modifications[6] and can be delivered inexpensively in a clinic[7] or with a wearable device.[8] Previous studies showed that assigning the same toe-in or toe-out gait modification to individuals with medial knee osteoarthritis reduced pain on average; however, these studies did not have control groups, and not all participants reduced their knee adduction moment peak or pain.[6,9] A trial that retrained all individuals to toe-out did not find a pain improvement that was significantly greater than the control group.[7] Compared to assigning the same foot progression angle to all individuals, assigning a personalized foot progression angle modification produces greater reductions in the knee adduction moment peak, while avoiding a potentially harmful increase in loading.[10,11] The importance of personalizing gait modifications is reinforced by the short-term pain reductions elicited by instructing patients to change their gait in any way possible to reduce the visually displayed knee adduction moment curve.[12] Recent gait retraining randomized trials have provided control participants with supervised walking[7,12] but not sham biofeedback on their gait mechanics, which may have a large placebo effect.[13]

Personalized foot progression angle modifications appear to be an effective and scalable way to reduce the knee adduction moment, but their clinical efficacy compared to sham gait retraining remains unknown.

The treatment of early-stage osteoarthritis primarily focuses on symptom management. Treatments that reverse, halt, or slow disease progression are needed. Previous studies of interventions that reduce the knee adduction moment have not demonstrated an effect on disease progression, likely because conventional imaging methods, like radiographs, are unable to detect early compositional and structural changes in cartilage. $T_{1\rho}$ and T_2 relaxation times are quantitative Magnetic Resonance Imaging (MRI) parameters that are often used to monitor cartilage degeneration, due to their association with proteoglycan content and collagen matrix integrity, respectively.[14] Quantitative MRI is sensitive to subtle cartilage changes due to disease progression over one year,[15] with increasing $T_{1\rho}$ and T_2 values associated with increasing cartilage degeneration.[14] Furthermore, $T_{1\rho}$ and T_2 predict the progression of cartilage lesions and the reduction in function at 2 years, while cartilage morphology (i.e., cartilage thickness) does not.[16] Quantitative MRI is also sensitive to cartilage changes induced by joint offloading.[17] The high sensitivity of quantitative MRI to microstructural and compositional changes in cartilage and its ability to predict disease progression makes it an ideal candidate to monitor the effect of load-reducing interventions like gait retraining.

The purpose of this randomized controlled trial was to evaluate the efficacy of personalized foot progression angle modifications compared to sham gait retraining. Both groups were given biofeedback training them to walk consistently at a target foot progression angle. The biofeedback instructed the intervention group to walk consistently with the 5° or 10° change in foot progression angle (i.e., toe-in or toe-out foot progression angle modification) that maximally reduced their knee adduction moment peak. The biofeedback instructed the sham group to walk more consistently with their natural foot progression angle. Our primary hypotheses were that the intervention group would have a greater reduction in medial knee pain and retain a greater reduction in their knee adduction moment peak compared to the sham group after one year. Our secondary hypotheses were that the intervention group would experience smaller increases

in $T_{1\rho}$ and T_2 (i.e., slowed cartilage degeneration) in the medial weightbearing femoral cartilage compared to the sham group.

Methods

Study design and participants

This parallel, participant-blinded randomized controlled trial (clinicaltrials.gov NCT02767570; https://clinicaltrials.gov/ct2/show/NCT02767570) took place at the Human Performance Laboratory and Lucas Center for Imaging at Stanford University, CA, USA. The trial protocol was approved by the Institutional Review Board of Stanford University and the US Department of Veterans Affairs Office of Research & Development. The authors assume responsibility for overseeing the trial, assuring its fidelity to the protocol, and the accuracy and completeness of data collection and analysis.

Individuals with medial compartment knee osteoarthritis were recruited for this study. Participants were recruited via approved searches of medical record databases and advertisements in print media and online. Eligible individuals were adults (18+) who met the following criteria: 1) medial compartment knee osteoarthritis grade between one and three on the Kellgren-Lawrence scale as determined by a radiologist (GEG) from radiographs, 2) medial knee pain of three or greater on an 11-point numeric rating scale (NRS), 3) able to walk safely on a treadmill without an ambulatory aid for 25 minutes, and 4) body mass index less than 35 kg/m^2. Prior to randomization, the gait of all participants who met the radiographic inclusion criteria was assessed in a gait laboratory (Supplementary Appendix, p5–10). Those who reduced their knee adduction moment peak by at least 5% with a foot progression angle modification were included. A complete list of the exclusion criteria is provided in Figure 1. All participants provided written informed consent. Participants self-reported their sex through a free-form survey question, and gender information was not collected.

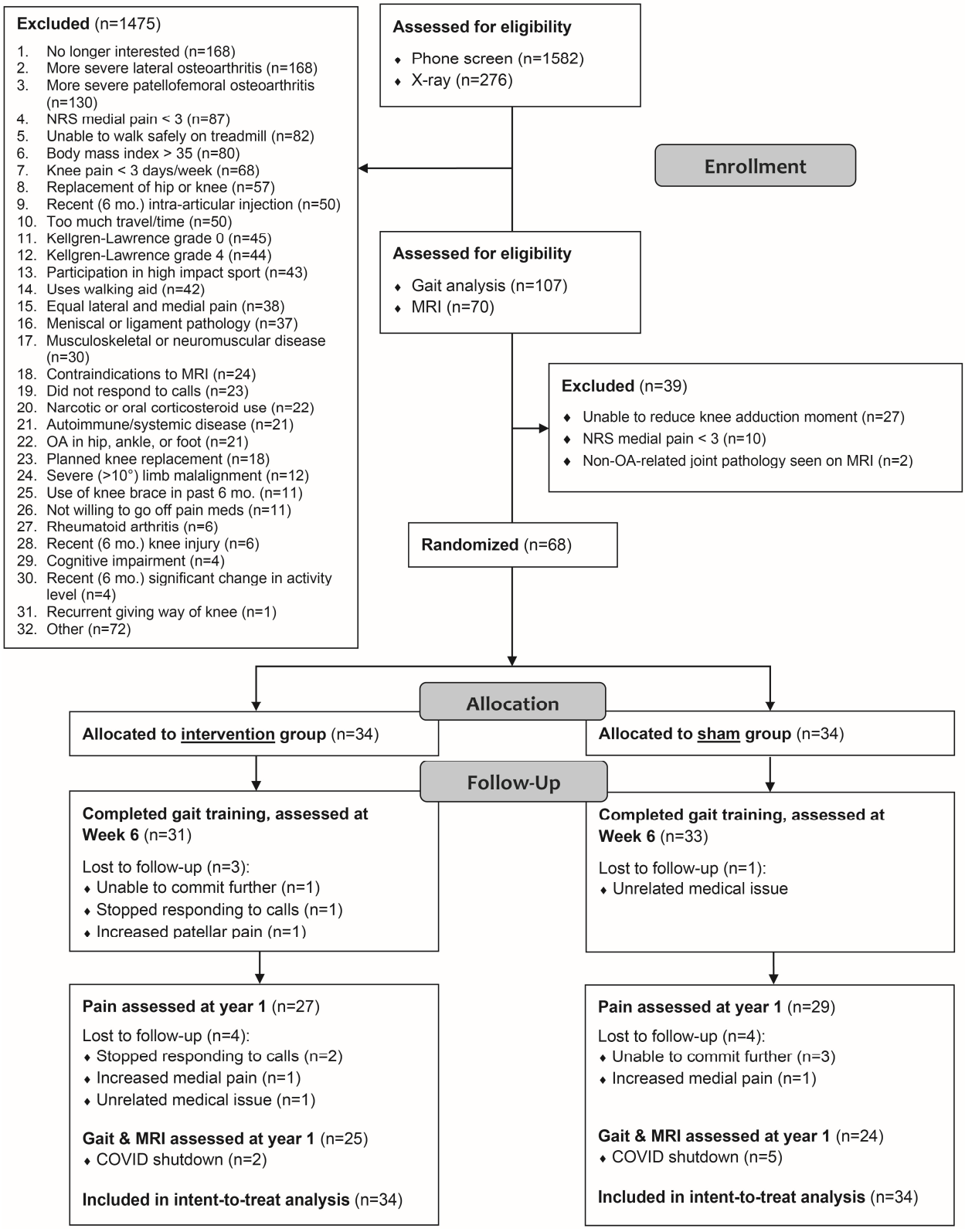


Figure 1: Participant flow diagram.

Involvement of people with lived experience

Several individuals on the study team have lived experience with knee osteoarthritis. This influenced the design of gait retraining sessions, selection of outcome measures, and contextualization of results against existing treatment options.

Randomization and masking

Prior to randomization, participants visited the gait laboratory two times to evaluate whether a foot progression angle modification could reduce their knee adduction moment peak. During the initial visit, participants practiced walking naturally on a force-instrumented treadmill and with vibrotactile feedback teaching them toe-in and toe-out.[11] One week later, participants completed the foot progression angle personalization visit (i.e., week 0). Participants performed a natural walking trial, followed by four foot progression angle–evaluation trials, where they were given feedback to walk with 5° and 10° of toe-in and toe-out. Participants' larger knee adduction moment peak (i.e., the peak during either the first or the second half of the stance phase) during natural walking was identified along with the foot progression angle modification that maximally reduced this peak (Supplementary Appendix, p10).

Prior to study initiation, the study coordinator generated a randomization spreadsheet (all rows were initially hidden) using a computerized random allocation generator (block size=8, 1:1) and stored it on a computer in the gait laboratory. Included participants were randomized to either the intervention or sham group (group descriptions in *Methods: Procedures*) one hour prior to the first gait retraining session (week 1, after meeting all inclusion criteria). The staff member who was conducting the gait retraining revealed the participant's group allocation by unhiding a row in the spreadsheet. Staff were not blinded to group allocation during gait retraining sessions or NRS pain assessments. All other primary and secondary outcome assessments (gait and MRI) were blinded as they were collected digitally and staff were blinded during data processing (patient data were saved independent of group allocation). Statistical analysts were

blinded and were not involved in group allocation or data collection. Participants were blinded to their allocation to an intervention or a sham group. They were told that it was a two-group study investigating which type of personalized foot progression angle walking training was most effective (scripts in Supplementary Appendix, p7). The success of participant blinding was not assessed at the end of the study.

Procedures

Included participants received biofeedback at a gait laboratory during six once-per-week gait retraining visits (weeks 1–6). Participants were told that they would receive biofeedback teaching them to walk consistently with a personalized foot progression angle selected from their week 0 visit and that the training could improve the loading environment in their knee in some way. The only difference between study groups was the target foot progression angle. The target angle for the intervention group was the 5° or 10° change in foot progression angle (toe-in or toe-out) that maximally reduced their larger knee adduction moment peak, and the target for the sham group was their natural foot progression angle from week 0. Notably, we described the study as a two-arm study investigating different types of walking training, not a comparison of an intervention and a sham treatment (scripts used to describe interventions in Supplementary Appendix, p7). We used the term 'personalized foot progression angle' to describe the target for biofeedback to study participants; in this article, we refer to this target angle as the 'target foot progression angle,' and we refer to a 'personalized foot progression angle modification' as the toe-in or toe-out change in foot progression angle assigned to the intervention group. During gait retraining visits, participants performed a two-minute pre-training evaluation trial without biofeedback followed by four trials with biofeedback instructing them to walk with their target foot progression angle (12–24 minutes total per visit using a faded feedback scheme, Figure S1 in Supplementary Appendix, p9). To deliver the biofeedback, the foot progression angle was computed in real time using an optical motion capture system (Motion Analysis Corp., Santa Rosa, CA, USA) and custom software (Matlab 2015b, MathWorks Inc., Natick, MA, USA). Vibrotactile feedback was delivered using two tactors (Engineering Acoustics, Casselberry, FL, USA) affixed to the proximal tibia if a participant's foot progression angle deviated by

more than 2° from the target angle. Participants were instructed to practice walking outside the laboratory consistently with their target angle for at least 20 minutes daily and, once comfortable, to walk with this angle at all times. Participants who walked at least 20 minutes per day at week 0 were not instructed to increase daily walking time; those who walked less than 20 minutes per day at week 0 were encouraged to meet the 20-minute daily walking goal. Participants kept daily walking logs throughout the duration of the study; during visits to the gait laboratory, study staff reviewed the logs and encouraged participants to meet the study's walking goals. Further details about the interventions, gait analysis methods, and trial procedures are reported in Supplementary Appendix: Protocol Summary (p5–10).

Participants visited the laboratory at ten weeks, six months, nine months, and 12 months (i.e., year 1 visit) following the week 0 visit for follow-up visits. During these visits, they first performed a two-minute pre-training evaluation trial where they were instructed to walk how they walk outside of the laboratory. During all follow-up visits except the year 1 visit, participants subsequently received 18 minutes of biofeedback. Knee adduction moment peak results presented here represent an average of the final 20 steps of the week 0 natural walking trial, the week 6 pre-training evaluation trial, or the year 1 evaluation trial.

At the beginning of the week 0, week 6, and follow-up visits, study staff assessed self-reported outcomes. We evaluated NRS pain as the typical pain in the medial compartment of the knee over the preceding week, and participants completed the Western Ontario and McMaster Universities Osteoarthritis Index survey on a computer without assistance from the investigators. Participants also delivered their pedometer and walking logs, in which they reported the daily walking time and the perceived percentage of time that they walked consistently with their target foot progression angle. At the year 1 visit, participants reported their compliance to the intervention during the past week as the percentage of their walking time during the past week that they walked consistently with their target foot progression angle. Exploratory outcomes are described further in the Supplementary Appendix (p15).

We used quantitative MRI ($T_{1\rho}$ and T_2) to assess femoral cartilage microstructure at week 0 and at year 1. All scans were performed at 3T using custom sequences. One-year changes in $T_{1\rho}$ and T_2 were extracted in the medial and lateral weight-bearing compartments of the femoral cartilage. Details on image acquisition and processing are reported in the Supplementary Appendix (p11).

Outcomes

The primary outcomes were changes in NRS medial pain and knee adduction moment peak from week 0 to year 1. We also evaluated safety by recording the number and type of adverse events per group. Secondary outcomes were changes in $T_{1\rho}$ and T_2 over one year. Exploratory outcomes included the proportion of participants who experienced the minimal clinically meaningful reduction in pain (≥1 point)[18], the proportion of individuals who experienced a 5% reduction in the knee adduction moment peak[19] (results from a pain-reducing intervention were used in lieu of an established clinically meaningful improvement threshold), Western Ontario and McMaster Universities Osteoarthritis Index pain and functional subscores, daily steps, foot progression angle error, and self-reported compliance to the intervention (Supplementary Appendix, p15). We conducted a sensitivity analysis of the statistical analysis approach (Supplementary Appendix, p12–14), comparing intent-to-treat analysis of all randomized participants, intent-to-treat analysis of all randomized participants unaffected by the COVID-19 institutional shutdown, and per-protocol analysis of participants with complete data for each primary outcome.

Statistical analysis

An *a priori* power analysis was conducted for the primary medial pain hypothesis, and an effect size of 0·57 was assumed.[6,20] To achieve 80% power with a two-sided alpha of 0·05, 39 participants per group were needed, so our recruitment goal was 40 participants per group. Expected attrition of 24% was accounted for with planned intent-to-treat analyses and missing data methods.[19] Every effort was made to collect missing data from participants.

All primary and secondary outcomes were examined using intent-to-treat analyses; all randomized participants (n=68) were analyzed in their assigned group. Data were normally distributed and assumed to be missing at random. Missing data were imputed using the Markov chain Monte Carlo method[21] for Continuous Variables because the pattern of missing data was arbitrary, and all outcome variables were continuous. All statistical analyses were conducted in SAS (version 9·04·01); multiple imputation was conducted using SAS PROC MI. The imputed datasets were analyzed in SAS and combined to yield the final parameter estimates and inferences.

Linear regression models, adjusting for the baseline (week 0) value of the analyzed outcome measure, were used to test group differences in the primary outcomes. A multiplicity correction was not applied to the primary outcomes because the hypotheses were separate. Linear regression models were also used to test for group differences in the secondary outcomes. A multiplicity correction for the secondary and exploratory outcomes was not prespecified, so *P*-values are not reported, and confidence intervals are not corrected for multiplicity. Logistic regression was used for the exploratory analysis of the proportion of individuals who reduced pain and the knee adduction moment peak. Due to the aggregation of imputed datasets used to compute these proportions, they do not correspond with a whole number of individuals; the reported number of individuals represented by a proportion is rounded to the nearest whole number. An unplanned interim analysis was performed to ensure the quality of MRI data after we identified an issue with an MRI sequence (unrelated to the sequences used for the secondary MRI outcomes). It was not intended to and did not influence the conduct of the study and did not affect the planned final analyses, so we did not adjust *P*-values for this analysis. The statistical analysis plan, written prior to breaking the randomization code, is included in the Supplementary Appendix (p134–137).

Role of the funding source

The funder of the study (the US Department of Veterans Affairs) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between August 1, 2016 and June 25, 2019, 1582 individuals were screened for eligibility (Figure 1). 107 participants completed an initial gait analysis and 27 (25%) were excluded for the inability to reduce their knee adduction moment peak. We enrolled and randomized 68 of the desired 80 participants (85%) due to the conclusion of funding. All 68 (100%) randomized individuals were included in the intent-to-treat analysis of primary outcomes. In the intervention group (n=34), 21 (62%) participants were female, age at enrollment was 64·3 (standard deviation: 7·7) years, and 28 (82%) identified as White. In the sham group (n=34), 20 (59%) were female, age at enrollment was 64·5 (standard deviation: 7·6) years, and 26 (76%) identified as White. Baseline characteristics were similar between groups (Table 1).

The trial was concluded four months early, prior to the final seven (10%) of 68 participants completing the study, due to an institutional shutdown caused by the COVID-19 pandemic. Prior to the shutdown, all seven (100%) of these participants had completed the six-month visit, and five (71%) of the seven participants had completed the nine-month visit. For the visits affected by the shutdown, we collected survey data (including the NRS pain primary outcome) over the phone but were unable to collect gait (knee adduction moment primary outcome) or MRI (secondary outcomes) data. We treated the data that was unable to be collected due to the shutdown as missing-at-random and conducted the intent-to-treat analysis as originally planned. We do not believe the random event of the COVID-19 pandemic biased the study results (see sensitivity analyses below). Of the 68 individuals randomized, 56 participants (82%; 70% of pre-specified sample size) had complete NRS pain data, and 49 (72%; 61% of pre-specified sample size) had complete knee adduction moment and MRI data.

Table 1: Participant demographics and baseline characteristics.

	Intervention group (n=34, 100%)	**Sham group** (n=34, 100%)
Age (years)	64·3 (7·7)	64·5 (7·6)
Sex		
Female	21 (62%)	20 (59%)
Male	13 (38%)	14 (41%)
Race		
Asian	4 (12%)	6 (18%)
Black	0 (0%)	1 (3%)
Native Hawaiin or other Pacific Islander	1 (3%)	1 (3%)
White	28 (82%)	26 (76%)
Unknown	1 (3%)	0 (0%)
Ethnicity		
Hispanic	0 (0%)	0 (0%)
Non-Hispanic	34 (100%)	34 (100%)
Body Mass Index (kg/m^2)	25·5 (3·3)	27·4 (3·9)
Kellgren-Lawrence grade*		
I	7 (21%)	7 (21%)
II	14 (41%)	17 (50%)
III	13 (38%)	10 (29%)
NRS medial pain†	4·3 (1·3)	4·0 (1·2)
Natural foot progression angle (°)	6·8 (3·6)	6·7 (3·8)
Knee adduction moment peak, natural foot angle (%bodyweight*height)	3·25 (1·05)	3·30 (1·05)
Knee adduction moment peak, target foot angle (%bodyweight*height)	2·87 (1·05)	3·30 (1·05)
$T_{1\rho}$ medial (ms)‡	60·45 (7·92)	58·79 (6·16)
T_2 medial (ms)‡	37·06 (3·00)	38·19 (3·83)
$T_{1\rho}$ lateral (ms)‡	56·34 (7·26)	55·32 (6·61)
T_2 lateral (ms)‡	36·57 (2·84)	37·55 (4·21)

Values reported as mean (standard deviation).

*The Kellgren and Lawrence system for classifying radiographic osteoarthritis severity ranges from 0 to 4, with 0 indicating no radiographic features of osteoarthritis.

†The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment of the knee over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain. A one-point change is considered clinically meaningful.[18]

‡Quantitative MRI values. Larger relaxation times indicate worse cartilage quality.

In the intervention group, 22 (65%) of 34 individuals were trained to toe-in by 10°, six (18%) to toe-in by 5°, one (3%) to toe-out by 5°, and five (15%) to toe-out by 10°. During the week 0 visit, individuals in the intervention group reduced their knee adduction moment peak by an average of 0·38 %bodyweight*height (-13·5%).

Primary outcomes are shown in Figure 2 and Table 2. The change in NRS medial pain from week 0 to year 1, was -2·5 (95% confidence interval [CI]: -3·3, -1·7) for the intervention group and -1·3 (95% CI: -2·1, -0·6) for the sham group. The intervention group experienced a greater reduction in NRS medial pain compared to the sham group at year 1 (difference=-1·2; 95% CI: -1·9, -0·5; *P*=·0013). The change in the knee adduction moment peak from week 0 to year 1 was -0·17 %bodyweight*height (95% CI: -0·33, -0·02 %bodyweight*height) for the intervention group and 0·08 %bodyweight*height (95% CI: -0·03, 0·19 %bodyweight*height) for the sham group, with a between-group difference of -0·26 %bodyweight*height (95% CI: -0·39, -0·13 %bodyweight*height; *P*=·0001). This indicates that the intervention group experienced a reduction in their knee adduction moment peak that was 7.5% greater than the change observed in the sham group at year 1. Mean values of primary outcomes at week 0 and year 1 are reported in Table S6 (Supplementary Appendix, p18–19).

Adverse events were reported for 3 participants (Supplementary Appendix, p33–34). Two (6%) of 34 intervention-group participants dropped out due to increased pain: one (3%) in the medial compartment and one (3%) in the patellofemoral compartment. One (3%) of 34 sham-group participants dropped out due to increased medial knee pain (chose to receive intra-articular injection). For these participants, all data from the visit during which they reported their increased pain and chose to withdraw was included in the intent-to-treat analysis.

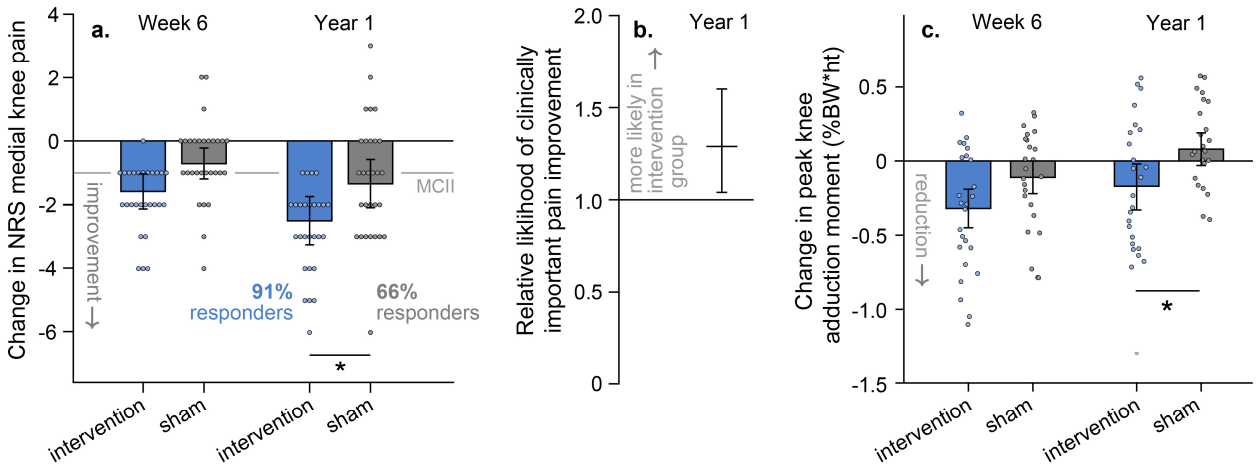


Figure 2: Changes in primary outcomes. The mean and 95% confidence interval (*p<0.05) of the change in numeric rating scale (NRS, 0–10 range) medial knee pain (**a**., n=68 [100%], intent-to-treat). Negative values indicate an improvement in pain. A one-point improvement in NRS pain is considered a minimal clinically important improvement (MCII).[18] Individual changes (dots) are shown for the 56 individuals who completed the year 1 pain assessment, and the proportion of responders (pain improvement ≥ 1) is shown for all 68 individuals (100%, intent-to-treat). The relative likelihood (95% confidence interval) of the intervention group experiencing a clinically meaningful improvement in pain, compared to the sham group (**b**). Values greater than 1 indicate higher likelihood of clinically meaningful pain improvement in the intervention group. The mean and 95% confidence interval of changes in the peak knee adduction moment from week 0 (**c**., n=68, 100%); negative values indicate reduced loading in the medial compartment of the knee. Individual changes (dots) are shown for the 49 (72%) of 68 individuals who underwent gait analysis at year 1.

Table 2: Between-group comparisons of one-year changes in primary and secondary outcomes.

	Intervention group	Sham group	Mean difference	*P*-value
Primary outcomes				
Δ NRS medial pain*	-2·5 (2·23)	-1·3 (2·3)	-1·2 (-1·9, -0·5)	**·0013**
Δ knee adduction moment peak (%bodyweight*height) [%]†	-0·17 (0·47) [-4·0%]	0·08 (0·33) [3·5%]	-0·26 (-0·39, -0·13) [-7·5%]	**·0001**
Secondary outcomes				
Δ $T_{1\rho}$ medial (ms)‡	-1·72 (5·68)	2·02 (5·53)	**-3·74 (-6·42, -1·05)**	
Δ T_2 medial (ms)‡	-0·58 (2·65)	-0·52 (3·11)	-0·06 (-1·42, 1·30)	
Δ $T_{1\rho}$ lateral (ms)‡	-1·11 (6·07)	-0·83 (6·80)	-0·29 (-3·38, 2·80)	
Δ T_2 lateral (ms)‡	-0·02 (2·14)	-0·02 (1·88)	0·00 (-0·89, 0·90)	

The mean and standard deviation of changes (Δ) from week 0 to year 1 in addition to the mean between-group difference and 95% confidence interval (CI) estimates from linear regression models. An intent-to-treat analysis of all randomized individuals (n=68) was used. (bold: $P<\cdot 05$ or 95% CI excludes 0)

*The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment of the knee over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain. A one-point change is considered clinically meaningful.[18]

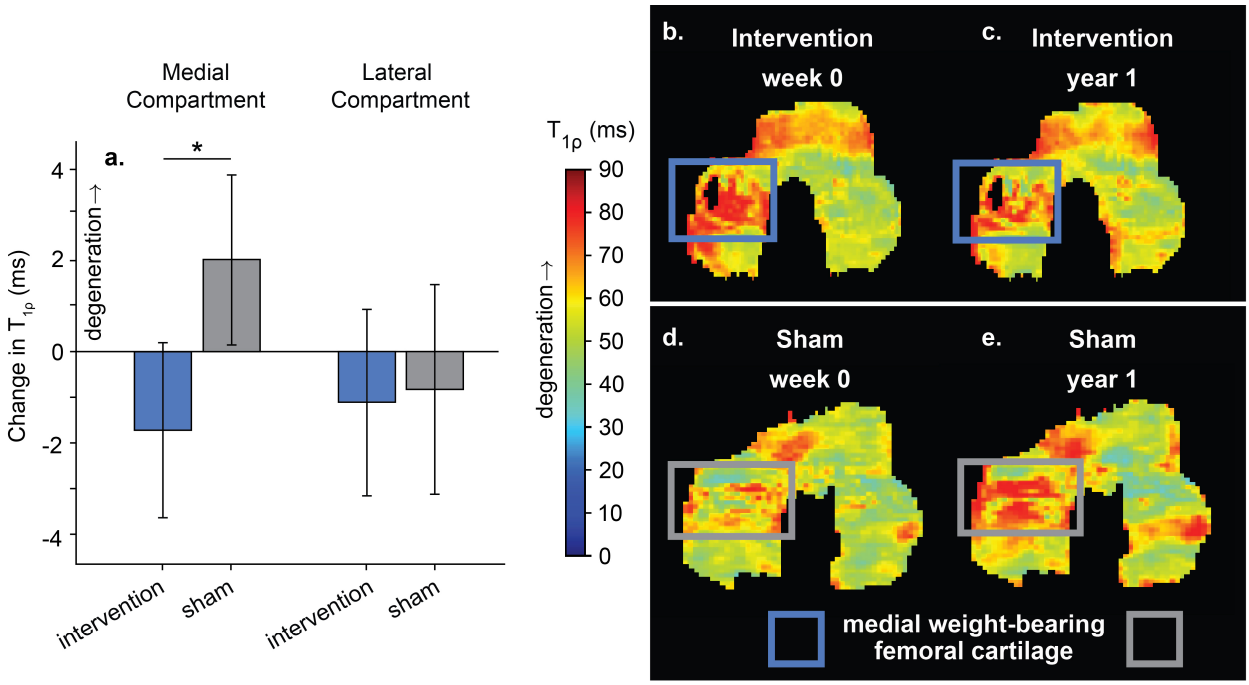
†The knee adduction moment normalized by bodyweight and height. Lower values indicate less joint loading. No clinically meaningful change threshold has been established.

‡Larger relaxation times indicate worse cartilage quality. No clinically meaningful thresholds have been established for changes in quantitative-MRI measures of cartilage quality.

Secondary outcomes are shown in Figure 3 and Table 2. At year 1, $T_{1\rho}$ in the medial weight-bearing femoral cartilage increased less in the intervention group compared to the sham group (between-group difference=-3·74 ms; 95% CI: -6·42, -1·05 ms), indicating slowed cartilage degeneration in the intervention compared to the sham group. Changes in T_2 in the medial compartment, as well as changes in $T_{1\rho}$ and T_2 in the lateral compartment were not statistically different between groups.

In the exploratory responder analysis, 91% (31/34) of the intervention group experienced a clinically meaningful one-point improvement in NRS medial pain, compared to 66% (22/34) of the sham group (26% between-group difference, relative risk=1·29, 95% CI=1·04, 1·60). 50% (17/34) of the intervention group retained at least a 5% reduction in the knee adduction moment peak at year 1 compared to 22% (7/34) of the sham group (29% between-group difference, relative risk=2·36; 95% CI: 1·00, 5·55). All other exploratory outcomes are described in the Supplementary Appendix (p15–17). The only other significant between-group difference in exploratory outcomes was the intervention group's 29% (95% CI: 12, 46%) greater self-reported compliance to walking with the target foot angle outside of the laboratory, compared to the sham group.

The results of the sensitivity analysis of primary outcomes were consistent with the originally planned statistical analysis method (Supplementary Appendix, p12–14). When comparing the intent-to-treat analysis of all 68 randomized participants to the intent-to-treat analysis of the 61 (90%) of 68 participants who completed the trial prior to the COVID-19 institutional shutdown, the between-group differences in primary outcomes remained statistically significant. Per-protocol results, obtained by analyzing the participants with complete data for each primary outcome (n=56 [82% of 68] for NRS pain, n=49 [72% of 68] for knee adduction moment), were consistent with the intent-to-treat analysis. Per-protocol results, disaggregated by sex, are shown in the Supplementary Appendix (p31–32).



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423 **Figure 3: Changes in femoral cartilage quality from MRI.** The mean and 95% confidence interval for changes in

424 $T_{1\rho}$ from week 0 to year 1 (**a.**, n=68 [100%], intent-to-treat). Increases in $T_{1\rho}$ indicate cartilage degeneration. Projected

425 $T_{1\rho}$ maps of femoral cartilage are shown for representative participants at week 0 and year 1 (**b–e**). Regions of red

426 correspond to long $T_{1\rho}$ relaxation times and lower cartilage quality (i.e., more degenerated cartilage).

Discussion

The purpose of this study was to evaluate the efficacy of personalized gait retraining compared to sham gait retraining for individuals with mild-to-moderate medial knee osteoarthritis. Our primary hypotheses were confirmed: after one year, individuals who adopted a personalized foot progression angle modification reduced their medial knee pain and knee adduction moment peak more than the sham group. The intervention group also showed slowed microstructural cartilage degeneration in the medial weight-bearing femoral cartilage, compared to the sham group.

These positive results highlight the potential of personalized gait retraining to become an effective conservative intervention for medial knee osteoarthritis. The between-group difference in pain improvement is both statistically significant and clinically meaningful, as demonstrated by a responder analysis (recommended approach for determining clinical importance by IMMPACT).[22] There is variance in the definition of a clinically important pain improvement (0·8–2·0 points),[18,23] but our analysis is robust to different thresholds; the difference in the proportion of responders is maintained whether using the 1-point threshold that we selected (26% more responders in intervention) or a 2-point threshold (29% more responders). Additionally, the between-group difference in pain improvement (standardized mean difference [SMD]=0·53) was similar to the estimated effects of other common knee osteoarthritis treatments (Supplementary Appendix, p30), including non-steroidal anti-inflammatory drugs (SMD=0·31) and opioids (SMD=0·27),[24] but gait retraining avoids pharmacological side effects. Unlike pain medications, gait retraining addresses a contributor to knee osteoarthritis progression—joint loading[2]—and it slowed cartilage degeneration in our study. Personalized gait retraining appears to be safe. The 6% (2 of 34) drop-out rate in the intervention group is similar to the 0–12% rate reported in other exercise interventions.[25]

Recently developed mobile sensing technologies can estimate knee loading and retrain walking in a clinical setting; along with the evidence from our study, these technologies could provide clinicians with an

effective treatment for medial knee osteoarthritis. When we began this study, a gait laboratory was required to accurately measure the knee adduction moment and retrain the foot angle. We have since shown that smartphone videos can detect how gait modifications change the knee adduction moment,[26,27] enabling knee load–based screening and personalization to be conducted in a clinic. Sensor-embedded shoes can deliver the foot angle biofeedback in free-living conditions.[8] Together, these technologies can allow for personalized gait retraining to be delivered at scale, but further optimization and clinical evaluation in real-world conditions is necessary prior to it becoming a readily accessible treatment.

Notably, the sham intervention had a similar pain-relieving effect (Cohen's d=0·60) as physical activity (d=0·49)[28] and other placebo interventions (d=0·51)[13] for osteoarthritis. The benefit of a structured walking program, the placebo effect of receiving biofeedback, and regression to the mean[29] could have contributed to the sham group's pain improvement. Neither group increased their daily steps over one year (Supplementary Appendix, p17), so the placebo effect and regression to the mean likely played the dominant roles. The pain effect in our sham group was larger than a recent gait retraining trial that used treadmill walking, but not sham gait retraining, as a control,[12] which highlights the importance of delivering sham treatment in trials of conservative interventions for osteoarthritis.

The intervention group's initial 13·5% reduction in knee adduction moment peak is similar to other biomechanical interventions (unloader brace, 13% reduction),[30] but less than surgical re-alignment of the tibia (high tibial osteotomy, 46% reduction).[31] An intervention that reduces knee loading and pain through a subtle change in walking pattern, compared to surgery or wearing a brace, may be preferable to many patients. The intervention group's initial reduction in knee loading was partially, but not entirely, retained after one year. Despite the maintained between-group difference, both groups' knee adduction moment peak appeared to increase over one year (3·5% in control group, not tested statistically). This aligns with the 5% annual increase that occurs as a part of the natural disease progression.[32] This suggests that reductions in the knee adduction moment peak from gait retraining can be maintained over time relative to

natural progression (i.e., sham), but gait retraining may not interrupt the progressive increase in the knee adduction moment peak that occurs over time.

Our biomechanical screening process and personalized intervention selection may have enhanced the intervention's efficacy. Our findings add support to the exclusion of biomechanical non-responders to reduce the number of pain non-responders.[33] While our personalized intervention significantly improved pain, a trial of a uniformly assigned toe-out intervention reported a between-group difference in pain change with a confidence interval that narrowly included zero.[7] This study used a clinically viable gait retraining method, but it did not include biomechanical screening or load-based intervention personalization. Since up to 46% of individuals increase their larger knee adduction moment peak when toeing-out;[10] excluding these biomechanical non-responders or prescribing them a more effective intervention may have improved the pain-relieving effect of our intervention compared to a uniform toe-out intervention.

The MRI results suggest that gait retraining affects osteoarthritis-related changes in cartilage microstructure. While $T_{1\rho}$ and T_2 are both sensitive to cartilage extracellular matrix changes, $T_{1\rho}$ is also sensitive to proteoglycan content.[14] In this study, $T_{1\rho}$ detected cartilage changes induced by gait retraining, while T_2 did not. This may indicate slowed proteoglycan depletion and possible regeneration following joint offloading.[34] However, while quantitative MRI can predict OA progression,[16] further research is required to understand the exact biochemical origin of these changes. The lack of observed between-group MRI differences in the lateral compartment suggests that shifting load from the medial to lateral compartment does not harm lateral cartilage.

There are several limitations to this study. First, investigators were unblinded during retraining visits due to the hands-on nature of the intervention. Unblinded investigators also collected NRS pain scores, which may have introduced bias into this outcome. However, several other blinded outcome measures—changes

in the knee adduction moment, $T_{1\rho}$, and Western Ontario and McMaster University Osteoarthritis Index pain—also favored the intervention, aligning with the NRS pain results. The consistency of blinded and unblinded outcomes strongly suggests that the improvements we observed are primarily a result of the intervention, though we cannot entirely rule out a contribution from assessor bias on the NRS pain outcome. Additionally, although we described the study to participants as a two-arm trial without referring to intervention or sham groups, we cannot assess the strength of the participant blind because we did not test it at year 1. Next, the 13 required laboratory visits made it difficult to meet our pre-specified sample size and contributed to participant dropout, which may have introduced bias. However, our sensitivity analyses comparing the pre-specified intent-to-treat analysis, intent-to-treat excluding COVID-19-related dropouts, and a per-protocol analysis yielded consistent results, suggesting that our pre-specified intent-to-treat results are robust. Additionally, we excluded individuals with BMI>35 due to the potential inability to enter a standard MRI scanner and individuals with severe radiographic knee osteoarthritis due to a lower likelihood of benefitting from an unloading intervention.[35] Thus, our results may not generalize to patients with severe obesity or advanced osteoarthritis.

In conclusion, we found that personalized foot progression angle modifications improved pain, reduced joint loading, and slowed cartilage degeneration in the medial compartment of the knee more than sham gait retraining over one year. These results suggest that personalized gait modifications are a promising treatment for some individuals with medial knee osteoarthritis.

Contributors

SDU, AS, GEG, SLD, GSB, and JAK conceptualized the study. SDU, AS, FK, VM, and JAK collected the data. SDU, VM, AKF, and JAK analyzed the data; all authors interpreted the data. SDU, VM, AF, and JAK directly accessed and verified the underlying data reported in the manuscript; all authors had full access to the data. SLD, GSB, and GEG acquired funding for the study. SDU, VM, AKF, and JAK wrote the manuscript. All authors revised and approved of the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Upon publication, the de-identified data set with and without imputed values will be publicly available at https://simtk.org/projects/gait_retraining. All primary, secondary, and exploratory outcomes for all 68 participants are included. The study protocol and statistical analysis plan are included in the Supplementary Appendix (p5–9, p37–137).

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