Running Title: neuromuscular exercise and knee adduction moment

Neuromuscular versus quadriceps strengthening exercise in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial

Kim L Bennell[1§], Mary Kyriakides[1], Ben Metcalf[1], Thorlene Egerton[1], Tim V Wrigley[1], Paul W Hodges[2], Michael A. Hunt[3], Ewa M Roos[4], Andrew Forbes[5], Eva Ageberg[6,], Rana S Hinman[1]

[1] The University of Melbourne, Centre for Health, Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, Melbourne, Vic, Australia
[2] The University of Queensland, School of Health and Rehabilitation Sciences, St Lucia, Brisbane, QLD, Australia
[3] University of British Columbia, Department of Physical Therapy, Vancouver, BC, Canada
[4] University of Southern Denmark, Department of Sports Science and Clinical Biomechanics, Odense, Denmark
[5] Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Vic, Australia
[6] Lund University, Department of Health Sciences, Lund, Sweden

This study was funded by a National Health and Medical Research Council grant (#628644). Kim Bennell is supported in part by an Australian Research Council Future Fellowship (#FT0991413) and Paul Hodges is supported by a National Health and Medical Research Council Fellowship (#1002190).

Corresponding author
Professor Kim Bennell
Centre for Health, Exercise and Sports Medicine
Department of Physiotherapy
University of Melbourne
Parkville, Victoria, Australia 3010

Ph: + 61 3 83444135 Fax: +61 3 83444188
k.bennell@unimelb.edu.au

Email addresses:
KLB: k.bennell@unimelb.edu.au
MK: mky@unimelb.edu.au
BM: b.metcalf@unimelb.edu.au
TE: thor@sutmap.com
TVW: timw@unimelb.edu.au
PH: p.hodges@uq.edu.au
MH: michael.hunt@ubc.ca
ER: eroos@health.sdu.dk
AF: andrew.forbes@monash.edu
EA: Eva.Ageberg@med.lu.se
RSH: ranash@unimelb.edu.au

Abstract

Objective: To compare the effects of neuromuscular exercise (NEXA) and quadriceps strengthening (QS) on the knee adduction moment (an indicator of medio-lateral distribution of knee load), pain and physical function in people with medial knee joint osteoarthritis (OA) and varus malalignment.

Methods: 100 people with medial knee pain, mostly moderate to severe radiographic medial knee OA, and varus malalignment were randomly allocated to one of two 12-week exercise programs. Each program involved 14 individually supervised exercise sessions with a physiotherapist plus a home exercise component. Primary outcomes were peak external knee adduction moment (3D gait analysis), pain (visual analogue scale), and self-reported physical function (Western Ontario and McMaster Universities Osteoarthritis Index).

Results: 82 participants (38 (76%) NEXA, 44 (88%) QS) completed the trial. There was no significant between-group difference in the change in the peak knee adduction moment (mean difference (95% CI) 0.134 (-0.069 to 0.337) Nm/(BW.HT)%), pain (2.4 (-6.0 to 10.8) mm) or physical function (-0.8 (-4.0 to 2.4) units). Neither group showed a change in knee moments following exercise, whereas both groups showed similar significant reductions in pain and physical dysfunction.

Conclusions: Although comparable improvements in clinical outcomes were found for both neuromuscular and quadriceps strengthening exercise in people with moderate varus malalignment and mostly moderate to severe medial knee OA, these forms of exercise did not affect the knee adduction moment, a key predictor of structural disease progression.

Australia and New Zealand Clinical Trials Registry (#ACTRN12610000660088)

Key words: neuromuscular exercise, strengthening, knee adduction moment, osteoarthritis

Background

Knee osteoarthritis (OA), predominantly affecting the medial tibiofemoral compartment, is a common chronic condition leading to pain, loss of function and reduced quality-of-life. People with medial knee OA and varus malalignment have greater functional (1) and structural (2) decline than those with more neutrally aligned knees. Interventions that not only reduce symptoms but also slow disease progression are particularly needed for this subgroup of people with knee OA.

The poorer prognosis for such patients is likely facilitated by greater compressive load on the diseased compartment (3). Three dimensional gait analysis is typically used to infer compressive joint loads. The most widely studied parameter in knee OA is the external knee adduction moment (KAM) which reflects medio-lateral joint load distribution. The KAM is higher in people with varus malalignment than in those without (4-6) and higher KAM indices are associated with increased risk of OA structural progression (7, 8). The KAM is therefore a relevant target for treatments to slow disease progression.

Quadriceps strengthening is effective at improving pain and physical function in people with knee OA (9, 10). However, quadriceps strengthening may be ineffective at reducing pain in those with varus malalignment (11) and it does not seem to reduce the KAM (11, 12). This may be because quadriceps strengthening aims to increase muscle force production, rather than more directly targeting biomechanical contributors to medial compartment load (such as knee adduction moment lever arm length) which may require more specific focus on using muscles to control limb and overall body position.

Neuromuscular exercise is typically performed in functional weight-bearing positions and emphasises quality of movement and alignment of the trunk and lower limb (13). Studies show that neuromuscular exercise can improve pain and function in people with knee OA (13-15) but that its addition to a strengthening program does not confer additional benefits (16, 17). As some features of neuromuscular exercise could affect knee joint load (via limb and trunk alignment) this intervention may be beneficial for people with varus malalignment. There are no direct comparisons of neuromuscular and strengthening exercise, only preliminary findings from two uncontrolled studies supporting the potential efficacy of neuromuscular exercise for reducing the KAM (14,18), and no studies of neuromuscular training for this specific knee OA subgroup.

This randomised controlled trial aimed to compare the effects of a 12-week neuromuscular exercise program with those of quadriceps strengthening in people with medial knee OA and varus malalignment. The primary hypotheses were that: (H1) peak KAM during walking would be reduced by neuromuscular exercise but not by quadriceps strengthening, leading to a significant difference between groups; and (H2) neuromuscular exercise would improve self-reported physical function and pain to a greater extent than quadriceps strengthening.

Methods

Participants

100 community volunteers aged ≥ 50 years with medial knee OA were recruited from July 2010 to June 2012 via advertisements. The Institutional ethics committee approved the study and all participants provided written informed consent.

People were eligible if they reported average knee pain over the past week ≥ 25 on a 100 mm visual analogue scale, had pain/tenderness predominantly over the medial knee region, and had radiographic medial tibiofemoral joint OA. Specific inclusion criteria from a weight-bearing, postero-anterior radiograph were (i) Kellgren-Lawrence grade ≥ 2 (19); (ii) anatomical axis angle of < 181° for females or < 183° for males, indicating varus alignment based on mechanical axis values using gender-specific regression equations from Krauss et al (20) (21); (iii) medial tibiofemoral joint narrowing grade > lateral tibiofemoral joint narrowing grade (22); and (iv) medial compartment osteophyte grade ≥ lateral compartment osteophyte grade (22). Major exclusion criteria included: (i) knee surgery or intra-articular corticosteroid injection within six months; (ii) current or past (within four weeks) oral corticosteroid use; (iii) systemic arthritic conditions; (iv) prior hip or knee joint replacement or tibial osteotomy surgery; (v) other non-pharmacological treatment within past six months; (vii) body mass index above 36 kg/m^2.

Procedures

This was a randomised, assessor-blinded, controlled trial. A detailed protocol has been published (23). Potential participants underwent telephone screening, then radiographic examination. Following baseline assessment, participants were randomised in permuted blocks of 6 or 8, stratified by physiotherapist, to one of two 12-week exercise groups; neuromuscular exercise (NEXA) or quadriceps strengthening (QS). The randomisation schedule was prepared by the study biostatistician using a computer generated random numbers table. Allocations were sealed in opaque consecutively numbered envelopes by a person not involved with the trial and these were kept in a central locked location. The

envelopes were opened in sequence by an independent administrator who then revealed the group allocation to the relevant physiotherapist by email before the participant presented for their first appointment.

Interventions

Nine physiotherapists in private practices delivered both interventions. They had an average of 12 (range 2-30) years of clinical musculoskeletal experience. Three (30%) had postgraduate masters level qualifications. They attended a three-hour training session and were provided with a treatment manual.

The exercise programs have been described in detail elsewhere (23). For both programs, only the study leg was specifically exercised. Participants visited their physiotherapist 14 times during the 12-weeks: twice in the first and second weeks, and weekly thereafter. Each visit lasted 30-40 minutes. Participants were asked to perform home exercises four times per week in addition to the supervised physiotherapy sessions.

Neuromuscular exercises

Participants in the NEXA group performed six exercises aiming to improve position of the trunk and lower limb joints relative to one another while dynamically and functionally strengthening the lower limb (Table 1, Figure 1, Appendix). During all exercises, the level of effort was to be self-rated as at least 5 out of 10 on a modified Borg Rating of Perceived Exertion (RPE) CR-10 scale (24). Progression, determined by the physiotherapist, was provided by varying the repetitions, direction, and velocity of the movements by increasing the load and/or changing the support surface.

Quadriceps strengthening

Participants in the QS group completed five non-weight-bearing exercises based on those used in our previous clinical trial (11) (Table 1). The dosage was 2-3 sets of 10 repetitions with the starting weight matched to the participant's 10-repetition maximum weight if possible or a weight needed to achieve a self rating of 5-8 out of 10 on the modified Borg RPE CR-10 scale (24). Progression was achieved by increasing the number of sets, the duration of the hold phase of the exercise, and the ankle weight or elastic band resistance as guided by the physiotherapist.

Outcome measures

Measurements were performed at baseline and follow-up by the same blinded assessor.

Gait analysis

Participants underwent 3-dimensional gait analysis during walking at their self-selected usual/comfortable speed. Movement was recorded using a 12-camera motion analysis system (Vicon MX, Oxford, UK) and force plates (AMTI, MA, USA) as participants walked barefoot along a 10m walkway. Speed was determined using two photoelectric beams. Five successful trials (complete foot strike from one foot on one force plate) were obtained. The motion of 37 reflective markers (sample rate 120Hz) and the ground reaction force (sample rate 1200Hz) were used to calculate the external KAM via inverse dynamics using the University of Western Australia model, programmed in Vicon Body Builder (25). Test–retest reliability (coefficient of multiple determination, r^2) of knee adduction/abduction moment curves has been reported as at least 0.75 (25). The primary variable was the overall

peak KAM, normalised by dividing by body weight (N) times height (m) and expressed as a percentage (Nm/(BWxHT)%), averaged over five trials. The normalised positive KAM angular impulse (positive area under KAM-time curve) (Nm.s/(BWxHt)%) was calculated as a secondary frontal plane knee moment variable. We also calculated the normalised peak knee flexion moment during stance (KFM: Nm/(BWxHt)%) to ensure that this sagittal plane moment did not concurrently increase, and thus potentially counteract any beneficial effects of intervention on knee load (26).

Self-reported pain and physical function

The primary pain outcome was average overall knee pain during the past week. This, together with pain on walking during the past week, was assessed using a 100 mm visual analogue scale with terminal descriptors of "no pain" and "worst pain possible" (27). Such measurement has demonstrated reliability in OA (27). Pain was also assessed, along with stiffness and physical function, using the disease-specific valid and reliable Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index (28). The physical function subscale, which comprises 17 questions, was used as a primary outcome measure.

At the follow-up assessment, participants were asked to rate their a) overall change, b) change in pain and c) change in physical function (compared to baseline) on a seven-point ordinal scale (1 = much worse to 7 = much better). All three ratings were dichotomised so that *improvement* was defined as a rating of 'moderately better' or 'much better'.

Muscle strength

Maximum, normalised, isometric strength (Nm/kg) was recorded for key muscle groups. Quadriceps and hamstring strength was measured in sitting at 60° knee flexion using an isokinetic dynamometer (KinCom 125-AP, Chattanooga Corp, TN, USA) with the best of 3 maximal contractions used. Isometric hip abductor and hip internal and external rotation muscle strength were measured using a hand held dynamometer (Lafayette Manual Muscle Test System 01163, Lafayette, IN) (29). For the hip strength measurements, the mean of two maximal trials was used (29).

Physical performance measures

These included: timed stair climb assessing the time to walk up and down six 17.5 cm high steps as quickly as possible, using a hand rail if preferred (30); thirty second sit-to-stand test assessing the number of sit-stand-sits performed in 30 seconds (31); and balance tests including: timed single leg stance assessing the length of time single limb standing can be maintained up to 30 seconds with the best attempt from two trials recorded (32), step test whereby the participant stands on the study leg and the number of steps by the non-study leg onto a 15 cm high step and back to the floor in 15 seconds performed as quickly as possible is recorded (33), and four-square step test which assesses the person's ability to change directions while stepping (34).

Health-related quality of life

The Assessment of Quality of Life Instrument Version Two (AQoL II) was used to measure health-related quality of life. This questionnaire has strong psychometric properties and is more responsive than other widely-used scales (35).

Other measures

Radiographic disease severity was rated using the Kellgren-Lawrence system (36). Baseline demographic information was collected. Co-interventions and adverse effects were determined from participant log books and physiotherapist treatment notes. Adherence was assessed by the number of physiotherapy sessions attended and by the number of home exercise sessions completed as recorded by participants in a log book. The percentage home exercise adherence was calculated by dividing the number completed by the maximum required number of 48.

Physical activity was self-reported using the Physical Activity Scale for the Elderly (PASE) (37). This records both the level and type of recreational and occupational physical activity undertaken by participants during the previous week.

Sample size

Our primary endpoints were peak KAM during stance phase of walking, VAS overall knee pain, and WOMAC physical function score. The minimum clinically important difference (MCID) to be detected for a change in KAM is unknown. We powered the study to detect a between-group difference in change in KAM of 7.5% (an approximate decrease of 0.30 Nm/(BW.HT)% in the NEXA group with no change in the QS group) as this may be associated with a significant decrease in risk of disease progression (7). The MCID for OA trials is a change in pain of 18 mm on VAS (38) and a change of six physical function WOMAC units (out of 68) (39). Based on our previous data, we assumed a between-participant standard deviation of change in KAM of 0.40 Nm/(BW*HT)%, 30 mm for pain, and 12 units for WOMAC physical function, and a baseline to 13 week correlation in each

outcome measure of 0.60. Thus, the required sample for a two-tailed comparison of two groups using analysis of covariance with baseline values as covariates and assuming a baseline-to 13 week correlation of 0.60, when the standardised effect size is 0.5 (WOMAC physical function), power is 0.8 and type I error is .05 was 41 participants per group (40). This was increased to 50 per group to allow for a 15% dropout rate. Due to their larger standardised effect sizes, power for VAS and peak KAM endpoints was greater (92% and 99%, respectively).

Statistical analysis

Main comparative analyses between groups were performed blinded to exercise type using an intention-to-treat approach with p-values of less than 0.05 considered statistically significant. To account for missing data, multiple imputation of missing follow-up measures were performed as a sensitivity analysis. Missing data were imputed for 12 participants in the NEXA group and 6 participants in the QS group using multiple imputation assuming data was missing at random (41). For continuous outcome measures, differences in mean change (follow-up minus baseline) was compared between groups using analysis of covariance adjusted for baseline values of the outcome. Walking speed was also included as a covariate for the KAM and peak KFM parameters in a subsequent analysis. Model diagnostic checks utilised residual plots. Results are presented as estimated differences with 95% confidence intervals. Likelihood of improvements overall, and in pain and function, were compared between groups using log binomial regression. Results are presented as relative risks with 95% confidence intervals.

Results

Of the 999 volunteers, 899 (90%) were ineligible or chose not to participate. In total, 100 participants (50 NEXA, 50 QS) were randomised and 82 (38 (76%) NEXA, 44 (88%) QS) completed follow-up assessment (Figure 2). Baseline participant characteristics were similar between groups (Table 2). The cohort had mainly moderate to severe radiographic OA, was overweight and had moderate varus malalignment, on average 6^{o} varus in males and 5^{o} in females. More participants in the NEXA group withdrew due to increased pain or unanticipated decision to undergo total joint replacement (n=7) than in the QS group (n=1). Baseline characteristics of the 18 participants lost to follow-up were similar to those completing the study (data not shown).

Outcome measures

Table 3 demonstrates no differences between the NEXA and QS groups for changes in the peak KAM (0.148 (95% CI -0.039 to 0.335) Nm/BW.HT %, p=0.23), overall VAS pain (2.4 (-6.0 to 10.8) mm, p=0.57) or WOMAC physical function (-0.8 (-4.0 to 2.4) units p=0.63). Observed between-group differences were smaller than the MCID and the 95% confidence intervals indicated that the ranges of plausible between-group differences were unlikely to have included differences of any practical importance. Results were unchanged when the sensitivity analysis was performed. Neither group showed a significant change in peak KAM from baseline whereas significant improvements in pain and physical function were achieved for both groups (Table 3).

There were no between-group differences for changes in any of the secondary outcomes except for the timed single leg stance test, where the NEXA group improved and the QS group showed a decrement ($p<0.001$) (Table 3). Results were unchanged when a sensitivity

analysis was performed. In the NEXA group, significant improvements were achieved in all secondary outcomes except for the KAM impulse, peak KFM and the PASE. In the QS group, significant improvements achieved in all outcomes except for KAM impulse, peak KFM, PASE, strength of the hip abductors, extensors and internal rotators, and timed single leg stance test.

Likelihood of participant-perceived improvement overall, or for pain and physical function was not different between groups. Improvement overall and improvement in pain was reported by 27/46 (59%) participants in the NEXA group and 27/45 (60%) in the QS group (Relative risk (95% CI) 0.94 (0.67-1.33) p=0.74). Improvement in physical function was reported by 28/46 (61%) participants in the NEXA group and 29/45 (64%) in the QS group (0.91 (0.66-1.26) p=0.57).

Adherence, adverse events, medication use and co-interventions

The number of physiotherapy sessions attended ranged from 0-14 with a median (IQR) of 12 (3.8) for the NEXA group, and a range of 1-14 with a median (IQR) of 12 (4.5) for the QS group (p=0.98). The median (IQR) of the percentage of home exercise sessions completed was 82 (31)% by the NEXA group and 91 (26)% by the QS group (p=0.048). For those who completed the trial, adverse events were reported by 14/46 (28%) of the NEXA group and 10/44 (23%) of the QS group (p=0.483) and mostly related to increased knee pain (Table 5). Medication use and co-interventions during the trial were similar across groups (Table 4).

Discussion

This study showed that neither 12 weeks of neuromuscular exercise nor quadriceps strengthening significantly influenced the external KAM during walking in individuals with mostly moderate to severe medial tibiofemoral OA and varus malalignment. However, both exercise programs provided similar improvements in clinical outcomes including pain, function and quality of life.

The finding of no difference in change in KAM between exercise groups does not support our hypothesis. There are three main considerations in relation to this finding. The first is that neuromuscular exercise was unable to influence the biomechanical contributors to the KAM as intended, most likely the length of the ground reaction force lever arm at the knee. Shortening the lever arm to reduce the KAM can be achieved through biomechanical alterations proximal or distal to the knee to bring the ground reaction force vector closer to the knee, and/or the knee closer to this vector (42). While neuromuscular exercises were performed in weight bearing and focused on lower limb and knee position control, they did not specifically target changes in KAM during walking. Instead, it may be that gait retraining interventions are needed. For example, there is evidence that teaching people to lean the trunk towards the affected limb, alter the foot progression angle or adopt a medial thrust type gait can reduce the KAM during walking (42, 43). It is also possible that training both limbs in a neuromuscular exercise program is necessary to facilitate stabilisation at the pelvis and hip, utilize the cross-over effect of motor learning, and maintain ideal lower limb alignment. We chose to exercise only the affected limb to reduce participant-burden. However, this may have attenuated any potential KAM-reducing benefits.

The second issue relates to our choice of task to measure KAM. We selected walking because of the established link between KAM during walking and OA structural disease progression (7, 8). It is possible that reductions in KAM following exercise training might have been observed if a more demanding task was used. An uncontrolled pilot study (14) involving 13 middle-aged people with early knee OA evaluated a comparable neuromuscular exercise and found a 14% reduction in peak KAM during a difficult one-legged rise task but not during walking. However, the clinical implications of a reduction in KAM during a one-legged rise task in terms of disease progression are not clear.

The third issue relates to the impact of the attributes of our medial knee OA sample. Our participants had a mean static varus of approximately 5 degrees representing moderate malalignment with 10% having severe malalignment (>10 degrees). It could be suggested that reducing the KAM with exercise (or other interventions) in the face of a seemingly fixed varus deformity and more severe disease may not be possible. However, while static varus malalignment is an important driver of the KAM (44), alignment is also a dynamic characteristic that can change during gait (45) and independently influence the KAM (46). Thus, there is at least potential for neuromuscular changes from exercise to influence this dynamic alignment and therefore the KAM, particularly where that exercise targets a more neutral dynamic alignment and muscular control of proximal and distal segments. In light of this, the subgroup of people with medial knee OA and varus malalignment are relevant to investigate the effects of neuromuscular exercise given their generally higher KAM (44). However, as we found no effect, it is possible that any benefits of neuromuscular exercise may be more evident in those at risk of knee OA (such as following joint injury) or with early OA as has been found in uncontrolled pilot studies (14, 18).

We also showed no significant effect of quadriceps strengthening exercise on the KAM despite significant strength gains of 10%. This is not necessarily surprising as single plane, non-weight bearing exercises are not specifically targeted at altering the magnitude or orientation of the ground reaction force or position of the knee – the primary determinants of the KAM during walking. This concurs with our prior RCT in people with medial knee OA with or without varus malalignment using the same exercise program (11). Other clinical trials have found no change in the KAM following a hip strengthening program in people with medial knee OA (48, 49) or following a high intensity lower limb strengthening exercise in people with knee OA involving any compartment (12, 50). Taken together, there is currently little evidence to support a KAM-modifying effect of exercise in people with medial or generalised moderate to severe knee OA.

Although there was no influence of exercise on the KAM, an indicator of medio-lateral knee load *distribution*, we cannot exclude an effect of exercise on the *magnitude* of compressive knee load. While good correlations have been found between the KAM and compressive joint load as calculated by complex musculoskeletal modeling (51), single patient studies using instrumented knee replacements have shown that under some circumstances the two may not always correspond. This lack of concordance may be due to concomitant alterations in other knee joint moments, particularly the KFM (26), and to alterations in muscle activation patterns (52); (53) that are not accounted for in estimation of KAM using inverse dynamics. While the KFM was not different between groups and did not change, it is possible that muscle activation may have been affected by exercise and hence altered knee load.

While the KAM itself is a predictor of disease progression (7, 8), we cannot determine the direct effects of neuromuscular exercise on structural outcomes. A more intensive 16-week supervised neuromuscular exercise program performed for one hour thrice weekly demonstrated improved cartilage quality assessed using delayed gadolinium-enhanced magnetic resonance imaging in middle-aged people (54). However, the only RCT to assess the effects of exercise on structural disease progression as the primary outcome in patients with established knee OA found a non-significant tendency toward less frequent progression of joint space narrowing over 30 months (55). Further longer-term studies are needed before definitive conclusions can be made as to whether exercise can modify structural disease progression in subgroups at risk of, or with established OA.

Contrary to our hypothesis, both exercise groups showed similar improvements in pain (NEXA 37%, Effect Size 1.04; QS 41%, ES 1.20) and physical function (NEXA 29%, ES 0.80; QS 26%, ES 0.74) with large effect sizes. The between group differences were small with confidence intervals that fell well short of the minimal clinically important differences (38, 39). The benefits of exercise for clinical outcomes in knee OA are supported by meta-analyses (9) and although there are few direct comparisons of different types of exercise, the results of pooled analyses suggest similar improvements for all types (9). Our findings concur with this conclusion. Overall, our data indicate that practitioners should prescribe the type of exercise that most suits the patient's needs and/or preferences based on individual assessment.

Our findings of improvements in pain and function with quadriceps strengthening in people with medial knee OA and varus malalignment do not completely agree with those of our

previous clinical trial using the same strength exercise program (11). A potential explanation may be the greater number of therapist sessions in the current study (14 versus 7). This is supported by a Cochrane review showing significantly greater benefits for pain and function with exercise programs involving more than 12 contacts with a health professional compared with those involving 12 or less contacts (9).

The strengths of our study include the RCT design with attention to key methodological features. Limitations include an inability to blind participants to treatment allocation, although the research hypotheses were not disclosed. We did not include a control group not receiving treatment, and as such, the symptomatic benefits may be related to the therapeutic environment and/or expectation of benefit rather than exercise *per se* (56). Another limitation is the greater number of drop-outs in the NEXA group due to pain and joint replacement surgery. However the results were unaltered when sensitivity analyses were performed. Nevertheless, the weight bearing nature of neuromuscular exercises may be more symptom-provocative compared to non-weight bearing quadriceps strengthening. This might also partly explain the lower home exercise adherence rates in the NEXA group. Finally, as our sample comprised patients with mostly moderate to severe knee OA with moderate varus malalignment, our results cannot necessarily be generalised to those with milder disease or differing amounts of malalignment. While different effects may be seen in early stage disease, we restricted our sample to those with definitive OA to achieve a more homogenous sample.

In conclusion, our results showed similar improvements in pain and function following neuromuscular or quadriceps strengthening exercise in a cohort with moderate varus

malalignment and mostly moderate to severe medial knee OA. They do not support the premise that such forms of exercise can influence the KAM, a key predictor of structural disease progression.

Authors' contributions

KLB, MH and RH conceived the project and KLB lead the co-ordination of the trial. KLB, RH, TW, PH, MH, ER, AF and EA assisted with protocol design and procured the project funding. TW and BM designed the biomechanical and physical impairment measures. KLB, RH, PH, MH, EA and ER designed the neuromuscular exercise program and KLB and RH trained the therapists. AF performed the sample size calculations and designed the statistical analyses. TE wrote the protocol manual. KLB wrote the first draft of the manuscript. BM was the blinded assessor on the project while MK recruited and screened the participants and managed the project. All authors provided feedback on drafts of this paper and read and approved the final manuscript.

Acknowledgements

This trial was funded by the National Health and Medical Research Council (Project #628644). None of the funders had any role in the study other than to provide funding. KLB is funded in part by an Australian Research Council Future Fellowship and PH is funded by a National Health and Medical Research Council Fellowship.

The Study Physiotherapists providing the physiotherapy treatments were Katherine Edmonds, Frances Gray, Jonathan Harris, Susan Hong Labberton, Arthur Lee, Tim McCoy, Jack Mest, Gabrielle Molan, Michael Ranger, and Tim Simpson.

References

1. Sharma, L., J. Song, D.T. Felson, S. Cahue, E. Shamiyeh, and D.D. Dunlop, The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA, 2001;286:188-95.
2. Sharma, L., J. Song, D. Dunlop, D. Felson, C.E. Lewis, N. Segal, et al., Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis, 2010.
3. Andriacchi, T.P., Dynamics of knee malalignment. Orthop Clin North Am, 1994;25:395-403.
4. Kumar, D., K.T. Manal, and K.S. Rudolph, Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. Osteoarthritis Cartilage, 2013;21:298-305.
5. Baliunas, A.J., D.E. Hurwitz, A.B. Ryals, A. Karrar, J.P. Case, J.A. Block, et al., Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage, 2002;10:573-9.
6. Mundermann, A., C.O. Dyrby, and T.P. Andriacchi, Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum, 2005;52:2835-44.
7. Miyazaki, T., M. Wada, H. Kawahara, M. Sato, H. Baba, and S. Shimada, Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis, 2002;61:617-22.
8. Bennell, K.L., K.A. Bowles, Y. Wang, F. Cicuttini, M. Davies-Tuck, and R.S. Hinman, Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis, 2011;70:1770-4.

9. Fransen, M. and S. McConnell, Exercise for osteoarthritis of the knee. Cochrane Database of Systematic Reviews, 2008;4:CD004376.
10. Lange, A.K., B. Vanwanseele, and M.A.F. Singh, Strength training for treatment of osteoarthritis of the knee: A systematic review. Arthritis Rheum, 2008;59:1488-1494.
11. Lim, B.W., R.S. Hinman, T.V. Wrigley, L. Sharma, and K.L. Bennell, Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. Arthritis Rheum, 2008;59:943-51.
12. Foroughi, N., R.M. Smith, A.K. Lange, M.K. Baker, M.A. Fiatarone Singh, and B. Vanwanseele, Lower limb muscle strengthening does not change frontal plane moments in women with knee osteoarthritis: A randomized controlled trial. Clin Biomech, 2011;26:167-174.
13. Ageberg, E., A. Link, and E.M. Roos, Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord, 2010;11:126.
14. Thorstensson, C.A., M. Henriksson, A. von Porat, C. Sjodahl, and E.M. Roos, The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis--a pilot study. Osteoarthritis Cartilage, 2007;15:1163-70.
15. Skou, S.T., A. Odgaard, J.O. Rasmussen, and E.M. Roos, Group education and exercise is feasible in knee and hip osteoarthritis. Danish Med J, 2012;59:A4554.
16. Knoop, J., J. Dekker, M. Vd Leeden, M. van der Esch, C.A. Thorstensson, M. Gerritsen, et al., Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. Osteoarthritis Cartilage 2013.

17. Fitzgerald, G.K., S.R. Piva, A.B. Gil, S.R. Wisniewski, C.V. Oddis, and J.J. Irrgang, Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Phys Ther, 2011;91:452-69.

18. Thorp, L.E., M.A. Wimmer, K.C. Foucher, D.R. Sumner, N. Shakoor, and J.A. Block, The biomechanical effects of focused muscle training on medial knee loads in OA of the knee: a pilot, proof of concept study. J Musculoskelet Neuronal Interact, 2010;10:166-73.

19. Kellgren, J.H. and J.S. Lawrence, Radiological assessment of osteo-arthrosis. Ann Rheum Dis, 1957;16:494-502.

20. Kraus, V.B., T.P. Vail, T. Worrell, and G. McDaniel, A comparative assessment of alignment angle of the knee by radiographic and physical examination methods. Arthritis Rheum, 2005;52:1730-5.

21. Hinman, R.S., R.L. May, and K.M. Crossley, Is there an alternative to the full-leg radiograph for determining knee joint alignment in osteoarthritis? Arthritis Rheum, 2006;55:306-13.

22. Altman, R.D. and G.E. Gold, Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis & Cartilage, 2007;15 (Supplement A):A1-A56.

23. Bennell, K.L., T. Egerton, T.V. Wrigley, P.W. Hodges, M. Hunt, E.M. Roos, et al., Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomised controlled trial protocol. BMC Musculoskelet Disord, 2011;12:276.

24. Day, M.L., M.R. McGuigan, G. Brice, and C. Foster, Monitoring exercise intensity during resistance training using the session RPE scale. J Strength Cond Res, 2004;18:353-8.

25. Besier, T.F., D.L. Sturnieks, J.A. Alderson, and D.G. Lloyd, Repeatability of gait data using a functional hip joint centre and a mean helical knee axis. J Biomech, 2003;36:1159-68.

26. Walter, J.P., D.D. D'Lima, C.W.J. Colwell, and B.J. Fregly, Decreased knee adduction moment does not guarantee decreased medial contact force during gait. J Orthopaed Res 2010;28:1348-1354.

27. Bellamy, N., Osteoarthritis clinical trials: candidate variables and clinimetric properties. J Rheumatol, 1997;24:768-78.

28. Bellamy, N., W.W. Buchanan, C.H. Goldsmith, J. Campbell, and L.W. Stitt, Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol, 1988;15:1833-40.

29. Pua, Y.-H., T.W. Wrigley, S.M. Cowan, and K.L. Bennell, Intrarater test-retest reliability of hip range of motion and hip muscle strength measurements in persons with hip osteoarthritis. Arch Phys Med Rehabil, 2008;89:1146.

30. Rejeski, W.J., W.H. Ettinger, Jr., S. Schumaker, P. James, R. Burns, and J.T. Elam, Assessing performance-related disability in patients with knee osteoarthritis. Osteoarthritis Cartilage, 1995;3:157-67.

31. Csuka, M. and D.J. McCarty, Simple method for measurement of lower extremity muscle strength. Am J Med, 1985;78:77-81.

32. Franchignoni, F., F. Horak, M. Godi, A. Nardone, and A. Giordano, Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. J Rehabil Med, 2010;42:323-31.

33. Hinman, R.S., K.L. Bennell, B.R. Metcalf, and K.M. Crossley, Balance impairments in individuals with symptomatic knee osteoarthritis: a comparison with matched controls using clinical tests. Rheumatology, 2002;41:1388-94.

34. Dite, W. and V.A. Temple, A clinical test of stepping and change of direction to identify multiple falling older adults. Arch Phys Med Rehabil, 2002;83:1566-71.

35. Osborne, R.H., G. Hawthorne, E.A. Lew, and L.C. Gray, Quality of life assessment in the community-dwelling elderly: validation of the Assessment of Quality of Life (AQoL) Instrument and comparison with the SF-36. J Clin Epidemiol, 2003;56:138-47.

36. Kellgren, J.H. and E.P. Samuel, The sensitivity and innervation of the articular capsule. Journal of Bone and Joint Surgery (Br), 1950;32B:84-92.

37. Martin, K.A., W.J. Rejeski, M.E. Miller, M.K. James, W.H. Ettinger, Jr., and S.P. Messier, Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sports Exerc, 1999;31:627-33.

38. Bellamy, N., W.F. Kean, W.W. Buchanan, E. Gerecz-Simon, and J. Campbell, Double blind randomized controlled trial of sodium meclofenamate (Meclomen) and diclofenac sodium (Voltaren): post validation reapplication of the WOMAC Osteoarthritis Index. J Rheumatol, 1992;19:153-9.

39. Tubach, F., P. Ravaud, G. Baron, B. Falissard, I. Logeart, N. Bellamy, 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.

40. Borm, G.F., J. Fransen, and W.A. Lemmens, A simple sample size formula for analysis of covariance in randomized clinical trials. J Clin Epidemiol, 2007;60:1234-8.

41. Little, R.J.A. and D.B. Rubin, Statistical analysis with missing data. Second Edition. 2002, New York: John Wiley.

42. Simic, M., R.S. Hinman, T.V. Wrigley, K.L. Bennell, and M.A. Hunt, Gait modification strategies for altering medial knee joint load: a systematic review. Arthritis Care Res, 2011;63:405-26.

43. Shull, P.B., A. Silder, R. Shultz, J.L. Dragoo, T.F. Besier, S.L. Delp, et al., Six-week gait retraining program reduces knee adduction moment, reduces pain, and improves function for individuals with medial compartment knee osteoarthritis. J Orthopaed Res, 2013;31:1020-5.

44. Foroughi, N., R. Smith, and B. Vanwanseele, The association of external knee adduction moment with biomechanical variables in osteoarthritis: A systematic review. Knee, 2009;16:303-9.

45. Chang, A.H., J.S. Chmiel, K.C. Moisio, O. Almagor, Y. Zhang, S. Cahue, et al., Varus thrust and knee frontal plane dynamic motion in persons with knee osteoarthrits. Osteoarthritis Cartilage, 2013;epub.

46. Chang, A., K. Hayes, D. Dunlop, D. Hurwitz, J. Song, S. Cahue, et al., Thrust during ambulation and the progression of knee osteoarthritis. Arthritis Rheum, 2004;50:3897-903.

47. Barrios, J.A., T.D. Royer, and I.S. Davis, Dynamic versus radiographic alignment in relation to medial knee loading in symptomatic osteoarthritis. J Appl Biomech, 2012;28:551-9.

48. Bennell, K.L., M.A. Hunt, T.V. Wrigley, D.J. Hunter, F.J. McManus, P.W. Hodges, et al., Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. Osteoarthritis Cartilage, 2010;18:621-8.

49. Sled, E.A., L. Khoja, K.J. Deluzio, S.J. Olney, and E.G. Culham, Effect of a home program of hip abductor exercises on knee joint loading, strength, function, and pain in people with knee osteoarthritis: A clinical trial. Phys Ther., 2010;90:895-904.

50. King, L.K., T.B. Birmingham, C.O. Kean, I.C. Jones, D.M. Bryant, and J.R. Giffin, Resistance training for medial compartment knee osteoarthritis and malalignment. Med Sci Sports Exerc, 2008;40:1376-84.

51. Zhao, D., S.A. Banks, K.H. Mitchell, D.D. D'Lima, C.W. Colwell, Jr., and B.J. Fregly, Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. J Orthopaed Res, 2007;25:789-97.

52. Lloyd, D.G. and T.S. Buchanan, A model of load sharing between muscles and soft tissues at the human knee during static tasks. J Biomech Eng, 1996;118:367-76.

53. Meyer, A.J., D.D. D'Lima, T.F. Besier, D.G. Lloyd, C.W. Colwell, Jr., and B.J. Fregly, Are external knee load and EMG measures accurate indicators of internal knee contact forces during gait? J Orthopaed Res, 2013;31:921-9.

54. Roos, E.M. and L. Dahlberg, Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum, 2005;52:3507-14.

55. Mikesky, A.E., S.A. Mazzuca, K.D. Brandt, S.M. Perkins, T. Damush, and K.A. Lane, Effects of strength training on the incidence and progression of knee osteoarthritis. Arthritis Rheum, 2006;55:690-9.

56. Crow, R., H. Gage, S. Hampson, J. Hart, A. Kimber, and H. Thomas, The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. Health Technol Assess, 1999;3:1-96.

57. Zhang, W., J. Robertson, A.C. Jones, P.A. Dieppe, and M. Doherty, The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheumat Dis, 2008;67:1716-23.

Figure 1: Diagram showing two examples of exercises from the neuromuscular program. In these exercises, note that the participant is required to maintain their knee in an aligned neutral position as they slide the leg forwards/backwards or sideways. An elastic resistance band applies a varus directed force that requires the participant to counteract this by pulling in a valgus direction in order to maintain the knee position.

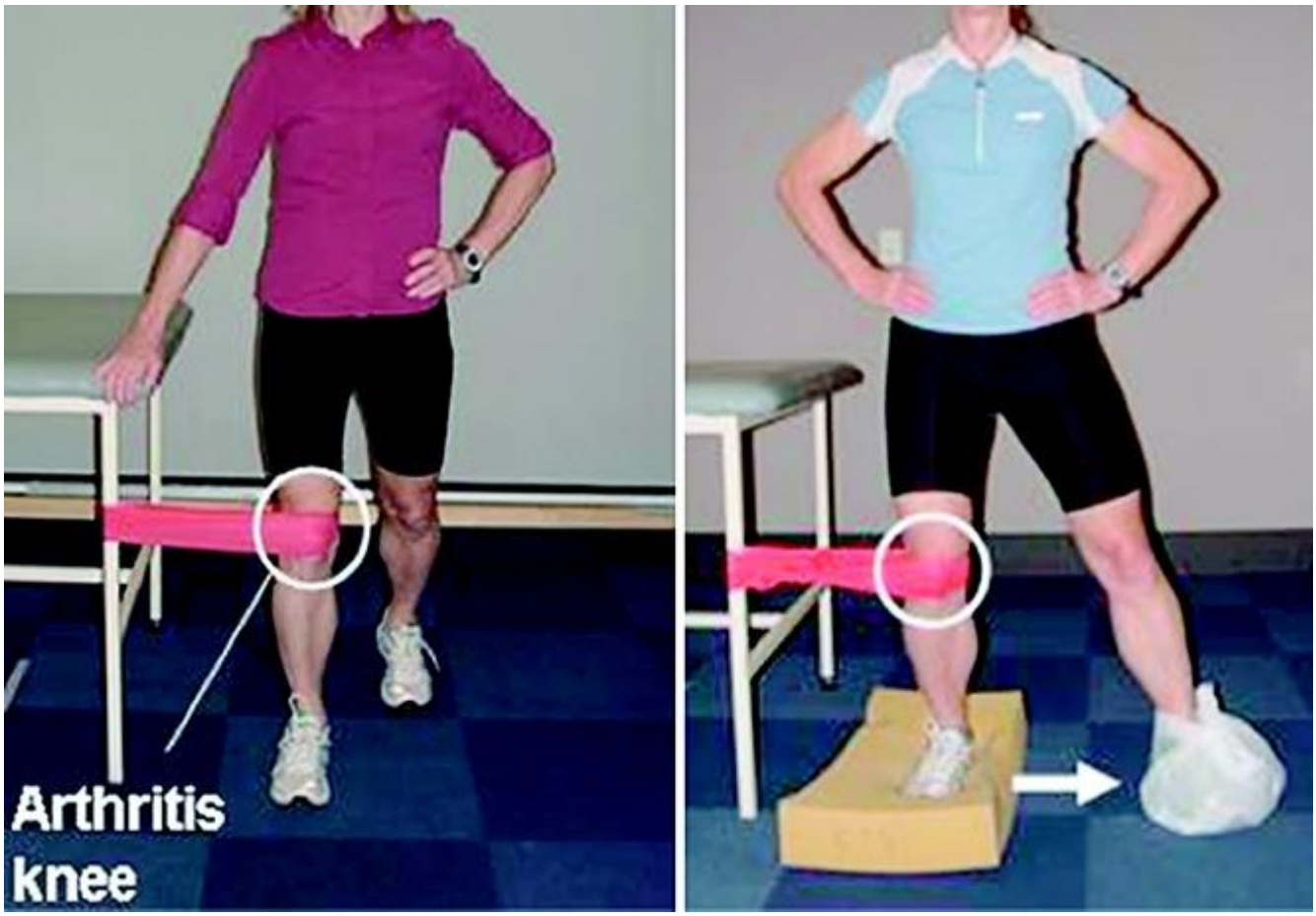

Figure 2. Flow diagram of study protocol

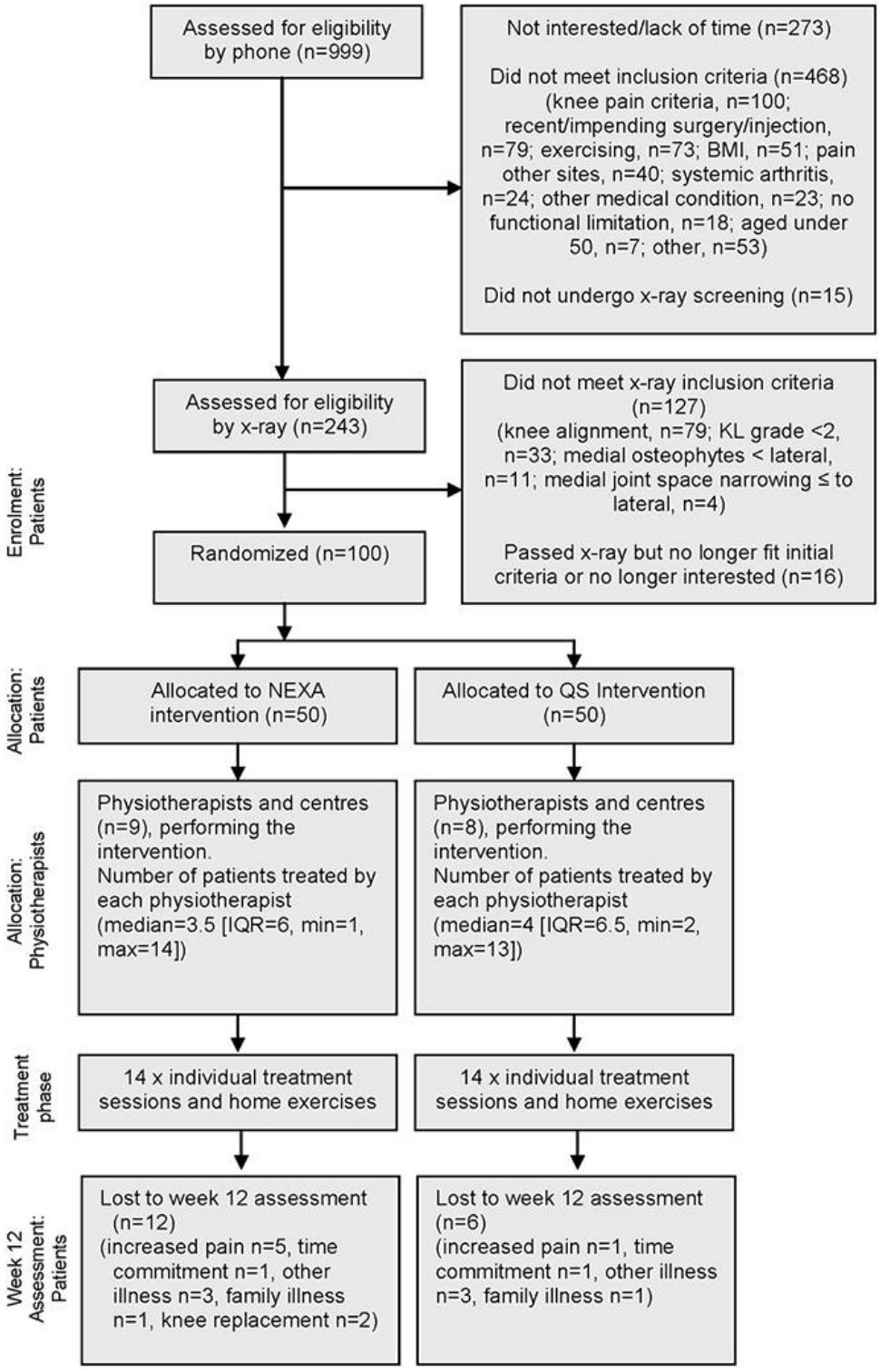

Table 1. Summary of exercise programs (see Appendix for further details)

Neuromuscular exercise	Quality of movement emphasised with aim to position knee over foot, and to avoid a medial or lateral position of the knee in relation to the foot. Effort rating of 5-8 out of 10†
1. Forwards and backwards sliding or stepping	Standing on affected leg and sliding or stepping opposite leg forward and backwards. This was progressed by adding elastic resistance band around the affected leg to apply a varus directed force during the movement which the patient had to counteract in order to maintain the knee in the neutral aligned position. 3 sets of 10 repetitions
2. Sideways exercises	Standing on affected leg and sliding or stepping opposite leg sideways progressing to adding elastic resistance band around the study leg to apply a varus directed force throughout movement (which the patient had to counteract in order to maintain the knee in the neutral aligned position), standing on foam and closing eyes during the movement. 3 sets of 10 repetitions
3. Functional hip muscle strengthening	Standing isometric abduction (2 sets of 5 repetitions) with progression through to elastic band resisted abduction during side stepping (2 x 30 steps)
4. Functional knee muscle strengthening	Squatting against a wall progressing through to rising from sitting with increased weight taken through the study leg 3 sets of 10 repetitions
5. Step-ups and down	Stepping on to a step with progression to add 2kg hand weights and then step down with forward touch down of opposite leg. 3 sets of 10 repetitions
6. Balance	Standing on affected leg. Progressions include adding arm movements and then stepping forward on to foam. 2 minutes practice
Quadriceps strengthening exercise	Each exercise 2-3 sets of 10 repetitions with 5-10 second hold

	Resistance equivalent to 10-repetition maximum and rating of 5-8 out of 10†
1. Quads over a roll (inner range knee extension)	Using resistance of ankle weights
2. Knee extension in sitting	Sitting with knee at 90° flexion, fully extend knee using resistance of ankle weights
3. Knee extension with hold at 30° knee flexion	Sitting with knee at 90° flexion, extend to 30° using resistance of ankle weights
4. Straight leg raise	Supine, raise leg to 30° hip flexion using resistance of ankle weights
5. Outer range knee extension	Sitting with knee at 90° flexion, extend to 60° against resistance of elastic band

† using modified Borg rating of perceived exertion scale (24)

Table 2: Demographic and clinical characteristics of the NEXA and QS groups given as the mean (standard deviation) or number (%) unless otherwise stated

Characteristic	NEXA n=50	QS n=50
Age (years)	62.7 (7.3)	62.2 (7.4)
Symptom duration (months - median and interquartile range)	60.0 (96.0)	84.0 (93.6)
Height (cm)	168.1 (9.2)	165.6 (10.1)
Body mass (kg)	83.8 (13.5)	81.6 (15.1)
Body mass index (kg/m^2)	29.6 (3.9)	29.7 (4.3)
Male (n-%)	24 (48%)	24 (48%)
Affected Knee (Right:Left)	30:20	23:27
Unilateral symptoms (n-%)	20 (40%)	19 (38%)
Dominant side affected (n-%)	28 (56%)	25 (50%)
Knee alignment (°) ¥	177.3 (3.0)	176.4 (3.9)
Males	178.1 (2.7)	175.2 (4.5)
Females	176.5 (3.1)	177.1 (3.3)
Radiographic disease severity (n-%)†		
Grade 2	9 (18%)	13 (26%)
Grade 3	21 (42%)	22 (44%)
Grade 4	20 (40%)	15 (30%)
Current drug use (n-%)††		
Analgesia (paracetamol combinations)	17 (34%)	20 (40%)
Non-steroidal anti-inflammatories	10 (20%)	10 (20%)
COX-2 inhibitors	3 (6%)	4 (8%)
Opioids	1 (2%)	1 (2%)
Topical anti-inflammatories	3 (6%)	5 (10%)
Glucosamine/chondroitin products	24 (48%)	23 (46%)
Topical liniment rubs	9 (18%)	10 (20%)
Fish oil	3 (6%)	8 (16%)

† using the Kellgren and Lawrence grading system
†† defined as at least once per week
¥ anatomical alignment where neutral alignment is 181° for females and 183° for males and varus is <181° for females and < 183° for males.

Table 3. Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups adjusted for baseline scores

Outcome	Groups				Difference within groups		Difference between groups *	
	Week 0		Week 13		Week 13 minus Week 0		NEXA minus QS	
	NEXA (n=50)	QS (n=50)	NEXA (n=38)	QS (n=44)	NEXA (n=38)	QS (n=44)	Mean [CI]	P
Peak KAM (Nm/(BW.BH)%)	3.05 (0.90)	3.21 (0.88)	3.26 (0.95)	3.30 (0.79)	0.12 [-0.04, 0.29]	-0.04 [-0.18, 0.10]	0.13 [-0.08, 0.33]	0.23
Overall VAS pain (mm)	54.0 (13.3)	54.2 (16.8)	34.1 (23.6)	31.4 (19.3)	-19.9 [-26.9, -12.9]	-22.0 [-27.9, -16.1]	2.4 [-6.0, 10.8]	0.57
WOMAC Physical Function (0-68)	26.0 (9.1)	28.2 (9.9)	18.3 (9.6)	20.1 (9.8)	-7.5 [-10.1, -4.9]	-7.3 [-9.7, -4.9]	-0.8 [-4.0, 2.4]	0.63
KAM Impulse (Nm.sec/(BW.BH)%)	1.15 (0.37)	1.21 (0.36)	1.20 (0.36)	1.23 (0.37)	0.02 [-0.05, 0.09]	-0.02 [-0.08, 0.03]	0.03 [-0.05, 0.12]	0.47
Peak KFM (Nm/(BW.BH)%)	4.02 (1.38)	3.96 (1.59)	3.89 (1.64)	4.05 (1.79)	-0.03 [-0.39, 0.32]	0.07 [-0.18, 0.32]	-0.11 [-0.54, 0.31]	0.60
Walking velocity (m/sec)	1.21 (0.18)	1.19 (0.22)	1.25 (0.20)	1.24 (0.21)	0.04 [0.00, 0.09]	0.03 [0.00, 0.07]	0.01 [-0.04, 0.07]	0.67
Walking VAS pain (mm)	59.5 (15.0)	55.3 (22.4)	39.6 (25.9)	40.0 (22.9)	-19.6 [-27.5, -11.8]	-15.8 [-22.7, -8.9]	-2.0 [-11.3, 7.4]	0.67
WOMAC Pain (0-20)	8.1 (2.2)	8.8 (3.3)	6.4 (3.1)	6.4 (2.9)	-1.7 [-2.6, -0.9]	-2.4 [-3.1, -1.7]	0.4 [-0.6, 1.4]	0.43
WOMAC Stiffness (0-8)	4.3 (1.6)	4.4 (1.6)	3.6 (1.4)	3.9 (1.8)	-0.7 [-1.1, -0.2]	-0.5 [-1.0, 0.0]	-0.2 [-0.8, 0.3]	0.41
AQoL2 (-0.04 -1.00)	0.73 (0.14)	0.73 (0.18)	0.78 (0.14)	0.78 (0.16)	0.04 [0.00, 0.09]	0.03 [0.00, 0.06]	0.01 [-0.03, 0.05]	0.67
PASE (0->400)	159.9 (82.7)	171.7 (89.8)	175.8 (112.0)	196.2 (88.4)	15.0 [-13.4, 43.5]	19.2 [-2.8, 41.2]	-9.1 [-42.9, 24.6]	0.59
Quadriceps Strength (Nm/kg)	1.44 (0.42)	1.47 (0.47)	1.59 (0.47)	1.62 (0.51)	0.15 [0.08, 0.21]	0.09 [0.02, 0.16]	0.06 [-0.04, 0.16]	0.22
Hamstring Strength (Nm/kg)	0.66 (0.20)	0.71 (0.23)	0.71 (0.23)	0.79 (0.26)	0.04 [0.00, 0.08]	0.05 [0.01, 0.09]	-0.02 [-0.07, 0.04]	0.57
Hip Abduction Strength (Nm/kg)	1.09 (0.38)	1.19 (0.44)	1.20 (0.45)	1.23 (0.41)	0.11 [0.02, 0.20]	-0.01 [-0.08, 0.06]	0.09 [-0.02, 0.21]	0.11
Hip Extension Strength (Nm/kg)	1.63 (0.56)	1.78 (0.75)	1.75 (0.54)	1.86 (0.70)	0.14 [0.02, 0.26]	-0.03 [-0.14, 0.08]	0.11 [-0.04, 0.26]	0.15
Hip Int Rotation Strength (Nm/kg)	0.47 (0.17)	0.52 (0.18)	0.50 (0.17)	0.56 (0.17)	0.05 [0.03, 0.08]	0.03 [-0.01, 0.06]	0.01 [-0.03, 0.05]	0.60

Hip Ext Rotation Strength (Nm/kg)	0.38 (0.14)	0.39 (0.14)	0.41 (0.12)	0.45 (0.14)	0.03 [0.01, 0.06]	0.04 [0.01, 0.07]	-0.02 [-0.05, 0.02]	0.42
Timed Stair Climb (s)	7.89 (2.45)	8.08 (3.89)	7.11 (2.23)	6.84 (1.88)	-0.67 [-1.17, -0.18]	-0.69 [-1.21, -0.16]	0.11 [-0.46, 0.68]	0.69
30 Second Sit to Stand (reps)	10.7 (2.3)	10.6 (2.9)	11.7 (2.1)	12.0 (2.5)	1.0 [0.4, 1.6]	0.9 [0.4, 1.4]	-0.03 [-0.72, 0.66]	0.93
Four Square Step Test (s)	9.1 (2.1)	8.6 (2.3)	8.1 (1.8)	7.9 (1.7)	-0.8 [-1.2, -0.5]	-0.3 [-0.6, 0.0]	-0.38 [-0.79, 0.03]	0.07
Step Test (reps)	12.5 (3.1)	13.1 (3.6)	14.1 (3.2)	14.4 (4.3)	1.5 [0.8, 2.1]	0.9 [0.2, 1.6]	0.46 [-0.45, 1.37]	0.32
One Leg Balance Test (s) ¥	15.2 (11.9)	20.1 (11.5)	20.7 (9.9)	18.9 (11.2)	5.0 [2.7, 7.3]	-1.8 [-3.7, 0.1]	5.58 [3.04, 8.11]	<0.001

¥ Number completed 30 secs: NEXA 0 weeks n=15 (30%) and 13 weeks n=16 (42%); QS 0 weeks n=23 (46%) and 13 weeks n=17 (39%)
* controlling for baseline values of the variable

Table 4: Adverse events, medication use and co-interventions according to group

Measures	NEXA	QS
Adverse events †	13/46 (28%)	10/44 (23%)
Increased knee pain	10 (22%)	8 (18%)
Back pain	1 (2%)	1 (2%)
Pain in other area	2 (4%)	1 (2%)
Hip pain	2 (4%)	1 (2%)
Swelling/inflammation	3 (7%)	1 (2%)
Stiffness	1 (2%)	0 (0%)
Medication use ¥		
Analgesia (paracetamol combinations)	15 (32%)	10 (23%)
Non-steroidal anti-inflammatories	10 (21%)	6 (14%)
COX-2 inhibitors	1 (2%)	3 (7%)
Opioids	2 (4%)	0 (0%)
Topical anti-inflammatories	5 (11%)	1 (2%)
Glucosamine/chondroitin products	26 (55%)	23 (52%)
Topical liniment rubs	5 (11%)	5 (11%)
Fish oil	1 (2%)	4 (9%)
Co-interventions	4/47 (9%)	2/44 (5%)
Other physiotherapy	2 (4%)	1 (2%)
Exercise	3 (6%)	0 (0%)
Osteopathy	0 (0%)	1 (2%)
Hydrotherapy	1 (2%)	0 (0%)
Elastic bandage	1 (2%)	0 (0%)

† defined as any problem from the treatment that lasted for more than two days and/or caused participant to seek other treatment
¥ n=47 in NEXA group and n=44 in QS group completed this information