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Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial

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SUMMARY

Objective: To investigate whether an exercise program, initially focusing on knee stabilization and subsequently on muscle strength and performance of daily activities is more effective than an exercise program focusing on muscle strength and performance of daily activities only, in reducing activity limitations in patients with knee osteoarthritis (OA) and instability of the knee joint.
Design: A single-blind, randomized, controlled trial involving 159 knee OA patients with self-reported and/or biomechanically assessed knee instability, randomly assigned to two treatment groups. Both groups received a supervised exercise program for 12 weeks, consisting of muscle strengthening exercises and training of daily activities, but only in the experimental group specific knee joint stabilization training was provided. Outcome measures included activity limitations (Western Ontario and McMaster Universities Osteoarthritis Index – WOMAC physical function, primary outcome), pain, global perceived effect and knee stability.
Results: Both treatment groups demonstrated large (~20–40%) and clinically relevant reductions in activity limitations, pain and knee instability, which were sustained 6 months post-treatment. No differences in effectiveness between experimental and control treatment were found on WOMAC physical function (B (95% confidence interval – CI) = −0.01 (−2.58 to 2.57)) or secondary outcome measures, except for a higher global perceived effect in the experimental group ($P = 0.04$).
Conclusions: Both exercise programs were highly effective in reducing activity limitations and pain and restoring knee stability in knee OA patients with instability of the knee. In knee OA patients suffering from knee instability, specific knee joint stabilization training, in addition to muscle strengthening and functional exercises, does not seem to have any additional value.
Dutch Trial Register (NTR) registration number: NTR1475.

Osteoarthritis (OA) of the knee leads to more chronic activity limitations among the elderly than any other disease[1]. However, no curative treatment is currently available[2]. Exercise therapy, which mainly concerns strength training, is considered an essential treatment in knee OA and is recommended in international guidelines[2–4]. Systematic reviews[5–7] clearly report the beneficial effects of exercise therapy in knee OA. However, these effects are moderate at best, with mean effect sizes of 0.40 and 0.37 reported for pain and activity limitations, respectively, compared to no exercise[5]. By improving the content of exercise programs, as well as

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the selection of patients, effects of exercise therapy might be improved.

Knee instability, which can be defined as the inability to maintain a position or control movements of the knee joint under differing external loads[8], has recently become a focus of research in knee OA. Patient-reported knee instability, described as 'a feeling of giving way, shifting or buckling of the knee during daily activities', was found to be prevalent in a majority (>60%) of knee OA patients[9–11] and independently associated with activity limitations (even after adjusting for pain, muscle weakness and radiographic severity)[9,10,12]. Dynamic neuromuscular control, which is provided by the interaction of proprioceptive stimuli (i.e., perception of position and movement of an extremity or a joint in space[13]) and muscle actions, and the passive restraint system (i.e., ligaments and capsule) are thought to be responsible for knee stabilization[8].

Muscle weakness in the upper leg is an established risk factor for activity limitations in knee OA, based on longitudinal data[14]. Recent cross-sectional studies from our group[15–18] suggested that the relationship between muscle weakness and activity limitations is affected by biomechanical factors involved in the knee joint stabilization process, namely proprioceptive accuracy of the knee, varus–valgus laxity of the knee (i.e., passive restraint system), and varus–valgus knee motion during walking. In these studies, muscle weakness was found to be more strongly related to activity limitations in those patients with impaired proprioceptive accuracy[15,16], high laxity[17], or high knee motion during walking[18] than in patients with adequate proprioceptive accuracy, low laxity, or low knee motion during walking. These findings may suggest that when upper leg muscles are weak and other biomechanical factors involved in the knee joint stabilization process are impaired as well, the knee joint becomes unstable, and more severe activity limitations may ensue (according to Neuromuscular model, see Fig. 1).

More importantly, these findings could imply that knee OA patients with knee instability may not benefit optimally from standard exercises targeting muscle strength. An exercise program that additionally targets other biomechanical factors involved in the knee joint stabilization process could be more beneficial for this subgroup. Moreover, knee joint stabilization training may need to be specifically provided in the first, low-intense phase of the intervention, prior to higher-intensity strength training, as patients suffering from knee instability may not be able to perform strengthening exercises safely (i.e., without risking joint-specific adverse events)[19], Currently, such an intervention has not been evaluated.

This study aims to investigate whether an exercise program, initially focusing on knee stabilization and subsequently on muscle strength and performance of daily activities is more effective than an exercise program focusing on muscle strength and performance of daily activities only, in reducing activity limitations in patients with knee OA and instability of the knee joint.

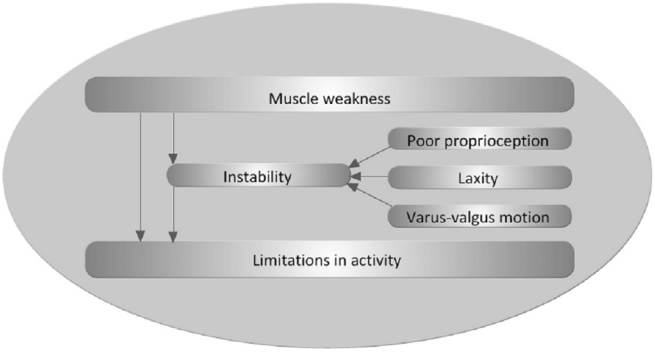

Fig. 1. Neuromuscular model.

Methods

Trial design

This study is a single-blind, randomized, controlled trial, conducted in an outpatient rehabilitation center (Reade, centre for rehabilitation and rheumatology, Amsterdam, the Netherlands), approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital) and in compliance with the Helsinki declaration. The assessor (SR) who performed measurements was blinded for group allocation.

Participants

Participants were recruited from February 2009 to March 2011 through advertisements in local and regional newspapers and from regular referral from rheumatologists or rehabilitation physicians from our rehabilitation center. Participants' eligibility was first assessed by screening questionnaire and telephone screening by the researcher, and subsequently by physical examination by a rheumatologist, rehabilitation physician and assessor. All participants provided written informed consent.

Inclusion criteria were (1) diagnosis of knee OA according to clinical American College of Rheumatology (ACR) criteria[20], (2) age between 40 and 75 years, and (3) presence of self-reported and/or biomechanically assessed knee instability. Self-reported knee instability was defined as at least one episode of buckling, shifting or giving way of the knee in the past 3 months, reported by the patient[21]. Biomechanically assessed knee instability was defined as the presence of muscle weakness (i.e., bodyweight-adjusted isokinetic hamstrings strength $\leq$0.80 Nm/kg for men or $\leq$0.55 Nm/kg for women) in combination with presence of (1) impaired proprioceptive accuracy (i.e., score $\geq$4.3°) and/or (2) high passive varus–valgus laxity (i.e., score $\geq$4.6° for men or $\geq$7.7° for women). Mean scores from both legs were used; cut-off points were based on previous data[15,17].

Exclusion criteria were (1) other forms of arthritis than OA (e.g., crystal arthropathy, septic arthritis, spondyloarthropathy) identified by radiography and/or blood- and urine samples, (2) presence of comorbidity resulting in severe activity limitations, (3) total knee arthroplasty (TKA) or TKA in near future, (4) severe knee pain (i.e., numeric rating scale (NRS) >8), (5) insufficient comprehension of Dutch language, (6) inability to be scheduled for therapy, and (7) unwillingness to give informed consent.

Randomization

A computer generated random sequence for group allocation was made prior to the study, using a permutated block randomization procedure comprising four participants per block. This randomization technique was chosen to ensure equal sample sizes between the two treatment groups. Group allocation was concealed by opaque, sealed, consecutively numbered envelopes. Every 12 weeks, around 16 eligible patients were randomly allocated (allocation ratio 1:1) over two parallel treatment groups (experimental and control group). In total, the study consisted of 11 consecutive pairs of parallel treatment groups.

Interventions

Experimental intervention

The experimental intervention comprised an exercise program of twelve weeks, with two sessions of 60 min weekly, and a home exercise program for 5 days weekly (non-treatment days only),

with gradual increase in training intensity, knee load and exercise difficulty during the program. The exercise program consisted of three phases: first phase (week 1–4) targeting knee joint stabilization, second phase (week 5–8) targeting muscle strength (i.e., muscle endurance) in addition to knee joint stabilization, and third phase (week 9–12) targeting performance of daily activities in addition to knee joint stabilization and muscle strength (i.e., maximal muscle power). In the first week only, sessions were located in a swimming pool to minimize knee loading, while from the second week, land-based therapy was provided.

In the first phase (week 1–4), specific knee joint stabilization training was provided. This training specifically focused on perception of knee position and motion to improve proprioceptive accuracy, and on maintenance of static or dynamic control of the knee (i.e., neuromuscular control[22]) to limit consequences of high laxity and to minimize high knee motion. Exercises in this phase were of relatively low intensity, to enable the patients to optimally focus on knee stabilization, and were performed with minimal knee load, to avoid joint-specific adverse events (e.g., pain flares, giving way of the knee). Exercises consisted of three sets of 15 repetitions. In addition, three educational sessions (i.e., information concerning OA disease, risk factors for functional decline and advice on self-management) were provided.

In the second phase (week 5–8), muscle strengthening exercises were added to the program, targeting muscle endurance. Training intensity and knee load gradually increased each week, but remained sub-maximal. Moreover, knee stabilization training increased in difficulty. Exercises consisted of three sets of 15 repetitions (in week 5 and 6) or 20 repetitions (in week 7 and 8).

In the third phase (week 9–12), functional, patient-tailored exercises, targeting specific daily activities which were indicated to be relevant and problematic by the patients themselves, and aerobic training (e.g., cross-trainer, treadmill) were added to the program. Training intensity and knee load further gradually increased each week to maximum level as possible, targeting maximal muscle power. In addition, knee stabilization training further increased in difficulty. Exercises consisted of three sets of 10 repetitions. Finally, participants were encouraged to remain physically active after completion of the exercise program. See supplementary file for more detailed information.

Control intervention

Patients in the control group received exercise therapy sessions of 60 min twice weekly for 12 weeks (hydrotherapy in first week, land-based therapy from week 2), including home exercises for 5 days a week, similar to the experimental group. The control intervention consisted of only two phases: first phase (week 1–8) targeting muscle strength (i.e., muscle endurance), and second phase (week 9–12) targeting performance of daily activities in addition to muscle strength (i.e., maximal muscle power).

In the first 4 weeks, exercises of low intensity and minimal knee load were provided, in addition to education on knee OA. From week 5, training intensity and knee load gradually increased, with muscle strengthening exercises targeting muscle endurance in week 5–8 and maximal muscle power in week 9–12, and with addition of functional and aerobic exercises from week 9, similar to the experimental intervention.

Contrast between interventions

The experimental intervention differed from the control intervention in the presence of specific knee joint stabilization training, consisting of (1) instructions and feedback on knee position and motion; and (2) specific exercises.

During the entire program, but explicitly in the first 4 weeks, patients in the experimental group were extensively instructed to focus on their knee position and to control this position (e.g., maintaining neutral knee alignment, avoiding sudden movements of the knee (e.g., giving way)). For this purpose, while exercising, patients received verbal and tactile feedback from physical therapists and visual feedback from mirrors on knee position. Although training intensity, knee load and difficulty of exercises increased during the program, patients were instructed to keep performing exercises in a controlled manner. Physical therapists from the control group were not allowed to provide instructions and feedback on knee position, meaning that patients from this group could perform exercises in any way they saw fit.

Additionally, only the experimental group received specific exercises, in which patients were challenged to maintain adequate knee position (see Fig. 2 for an example). Patients from the control group did not receive these specific exercises.

Training intensity and amount of attention from the physical therapists were intended to be similar in both groups.

Physical therapists

Each group, consisting of approximately eight patients, was supervised by two physical therapists, specifically trained to provide the particular treatment. Every 12 weeks, booster training sessions for participating physical therapists were provided, for experimental and control treatment separately. Physical therapists ($n = 17$) were assigned to only one treatment arm.

Outcomes

Primary outcome measure

Self-reported activity limitations was assessed by the Dutch translation of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), subscale physical function[23,24].

Secondary outcome measures

Knee pain severity during the last week was scored on an NRS ranging from 0 to 10 (0 = no pain; 10 = worst pain imaginable)[25]. Global perceived effect (GPE) was assessed on a 7-point scale (ranging from 1 = symptoms have never been worse, to 7 = symptoms are completely gone) and dichotomized as 'improved' (score 5–7) or 'not improved'[1–4]. Self-reported knee joint instability (i.e., ≥episode of buckling, shifting or giving way of the knee in the past 6 weeks[21]) and whether this knee instability resulted in activity limitations[9] were assessed by questionnaire. Isokinetic muscle strength of the upper leg (quadriceps and hamstrings strength) and proprioceptive accuracy of the knee (threshold detection of motion) were assessed as described in previous studies[15]. The Get Up and Go (GUG) test[26] was used to assess observed activity limitations. Self-reported performance of three daily activities most relevant to the patient was determined by the Patient Specific Functioning List (PSFL)[27]. Walking Questionnaire (WQ35)[28], Climbing Stairs Questionnaire (CStQ15)[29] and Questionnaire Rising and Sitting down (QR&S39)[30] were used to assess specific lower-extremity related limitations in daily activities and have been validated in OA patients. In addition, baseline demographics were obtained.

For knee-specific variables we used data from one knee per person (index knee). Index knees were determined as follows: (1) knee with clinical diagnosis of knee OA according to ACR-criteria; (2) in case of clinical diagnosis of knee OA in both knees, knee that fulfilled criteria for biomechanically assessed knee instability (based on cut-off points for muscle weakness in combination with impaired proprioceptive accuracy and/or high laxity; see *Participants*); (3) in case of biomechanically assessed knee instability in both knees or none at all, knee that fulfilled criteria for self-reported knee instability; (4) in case of self-reported knee instability in both knees or none at all, a knee was randomly chosen.

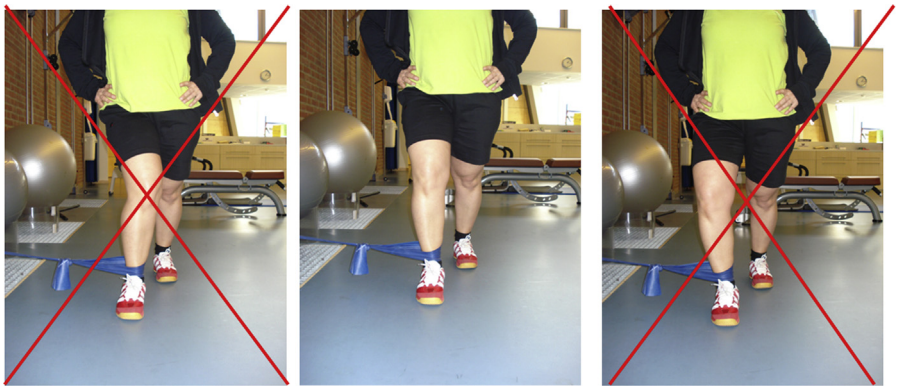

Fig. 2. Example of knee stabilization exercise. Exercise: forward lunge step under sideways knee load by use of dyna band, emphasizing on neutral alignment of the knee: no valgus position (left photo) or varus position (right photo), but knee position in line with hip and ankle (centered photo).

All measurements were performed by one blinded assessor (SR), at baseline and at three follow-up (FU) points: at 6-week FU (mid treatment), 12-week FU (directly post-treatment) and 38-week FU (6 months post-treatment). Serious adverse events, defined as falls, injuries or severe illness during exercising were collected by the researcher. Therapists assessed patient-perceived training intensity on a Borg-scale[31] after each session, and pain severity (NRS) during the past week, which could be used for individual adaptations of the exercise protocol. In addition, at 38-week FU, GPE in comparison to directly post-treatment, adherence to the home exercises, level of physical activity and use of health care during 6-months FU period were assessed.

Blinding

Randomization, treatment allocation and statistical analyses were performed blindly. The assessor (SR), who measured all participants, was blinded for treatment allocation. Allocation of each participant was guessed by the assessor at the 12-week FU measurement to check blinding. Due to the nature of the interventions, neither the patients nor the therapists could be blinded. However, no information was given to the patients on the hypothesized most beneficial treatment.

Sample size

The a priori power calculation was based on a significance level of $\alpha = 0.05$, an expected autocorrelation between the repetitions of 0.60, a desired power $(1 - \beta)$ of 0.90 and a cautious estimate of 0.3 as the minimally expected difference in effect size between experimental and control group at 12-week FU. Given these parameters, a total sample size of 108 patients was needed. Allowing for an attrition rate of 10% during the study, we aimed to include at least 120 patients (i.e., two groups of 60 patients).

Statistical analyses

Data were analyzed using PASW Statistics 18.0 (SPSS Inc, Chicago, IL). Baseline descriptives were compared between groups. Generalized Estimating Equation (GEE) analysis, a longitudinal regression analysis technique analyzing all time points (i.e., 6-week, 12-week and 38-week FU) at once with adjustments for dependence of repeated measures within individual participants[32], was performed (using exchangeable correlation matrix). Group differences on average over time and interactions between group and time were estimated, adjusting for baseline value of outcome measure and relevant baseline variables that were different between groups (i.e., varus knee alignment, proprioceptive accuracy and self-reported knee instability affecting daily functioning; see Table I). Prior to analysis, outcome measures were checked for normality. All outcomes measures were considered normally

Table I
Baseline characteristics of experimental and control group

	Experimental group ($n = 80$)		Control group ($n = 79$)	
	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)
Age (years)	62.1 ± 7.6		61.8 ± 6.6	
Gender (female)		53 (66)		44 (56)
Duration of knee symptoms	10.8 ± 9.7		10.7 ± 8.8	
BMI (kg/m^2)	28.8 ± 4.8		28.3 ± 4.5	
Clinical knee OA (according to ACR-criteria)				
Unilateral		21 (26)		19 (24)
Bilateral		59 (74)		60 (76)
Radiographic severity of knee*				
K/L grade 0/1		31 (39)		25 (32)
K/L grade 2		23 (29)		21 (27)
K/L grade 3		18 (23)		23 (29)
K/L grade 4		8 (10)		10 (13)
Education level				
Primary		1 (1)		2 (3)
Secondary		55 (69)		57 (72)
College/university		24 (30)		20 (25)
Comorbidity score (CIRS, 0–52)	3.7 ± 4.5		3.7 ± 4.7	
Use of pain medication (including NSAIDs)		35 (44)		37 (47)
Use of walking device (like brace, cane)		16 (20)		10 (13)
Alignment of knee*				
Varus malalignment (≥5° varus)		14 (18)		24 (30)
No varus malalignment		66 (82)		55 (70)
Upper leg muscle strength (Nm/kg)*	0.83 ± 0.35		0.85 ± 0.43	
Proprioceptive accuracy of knee (degrees)*	2.7 ± 2.2		3.7 ± 2.6	
Varus–valgus laxity of knee (degrees)*	7.0 ± 3.1		7.1 ± 4.5	
WOMAC (physical function, 0–68)	25.2 ± 11.8		27.1 ± 12.7	
NRS (knee pain severity, 0–10)	4.8 ± 2.2		5.2 ± 2.0	
Knee instability, self-reported				
≥One episode in past six weeks, yes		67 (84)		65 (82)
Resulting in activity limitations, yes		39 (49)		53 (67)

SD = standard deviation; BMI = body mass index; K/L = Kellgren/Lawrence; CIRS = cumulative illness rating scale; NSAID = non-steroidal anti-inflammatory drug.

* Data from index knee.

distributed, except for secondary outcome measures proprioceptive accuracy, WQ35 and QR&S, which were therefore transformed by log10 (for proprioceptive accuracy) or square root (for WQ35 and QR&S).

Primary analyses were based on intention-to-treat (ITT) approach, in which data of all patients were analyzed according to group assignment. Standardized mean differences (SMD)[33,34] were calculated for the differences between interventions (between-group effect size) and for each intervention separately (within-group effect sizes). Additionally, relative changes (%) and treatment response, based on minimal clinically important differences (MCID)[26,27,35,36] were calculated. Secondary analyses included sensitivity analyses with a 'last observation carried forward' imputation method for missings and per-protocol analyses, excluding protocol violators (i.e., patients discontinued treatment, missing more than eight out of 24 sessions or undergone knee surgery during study period). P values less than 0.05 were considered statistically significant.

Results

Participant's flow chart is presented in Fig. 3. From a total of 539 potential candidates, 380 were excluded, mostly because of refusal/inability to participate (e.g., costs, time restrictions) ($n = 197$). Therefore, 159 participants were included, of which 70% fulfilled criteria for self-reported knee instability only, 6% criteria for biomechanically assessed knee instability only, and 23% both criteria. Eighty people were allocated to experimental group, 79 to control group. One person from the experimental group (reason: lack of time) and four from the control group (reasons: health problems unrelated to OA ($n = 3$) and lack of time ($n = 1$)) were lost before the first FU measurement, meaning that data from 154 participants were available for the ITT analysis. Thirteen participants (eight from experimental group; five from control group) were considered protocol violators and excluded from per-protocol analyses.

Baseline characteristics of the experimental and control group are presented in Table I. Participants attended 21 out of 24 sessions and performed home exercises during the exercise program for 4 days a week on average, similarly in both groups. In both groups, perceived training intensity, reported by patient on Borg-scale, gradually increased during the 12-week program and was on average similar between groups (11.8 ± 1.0 and 11.7 ± 1.1 for experimental and control group, respectively; $P = 0.33$). However, course of training intensity slightly differed between groups, as perceived intensity in experimental group was significantly higher

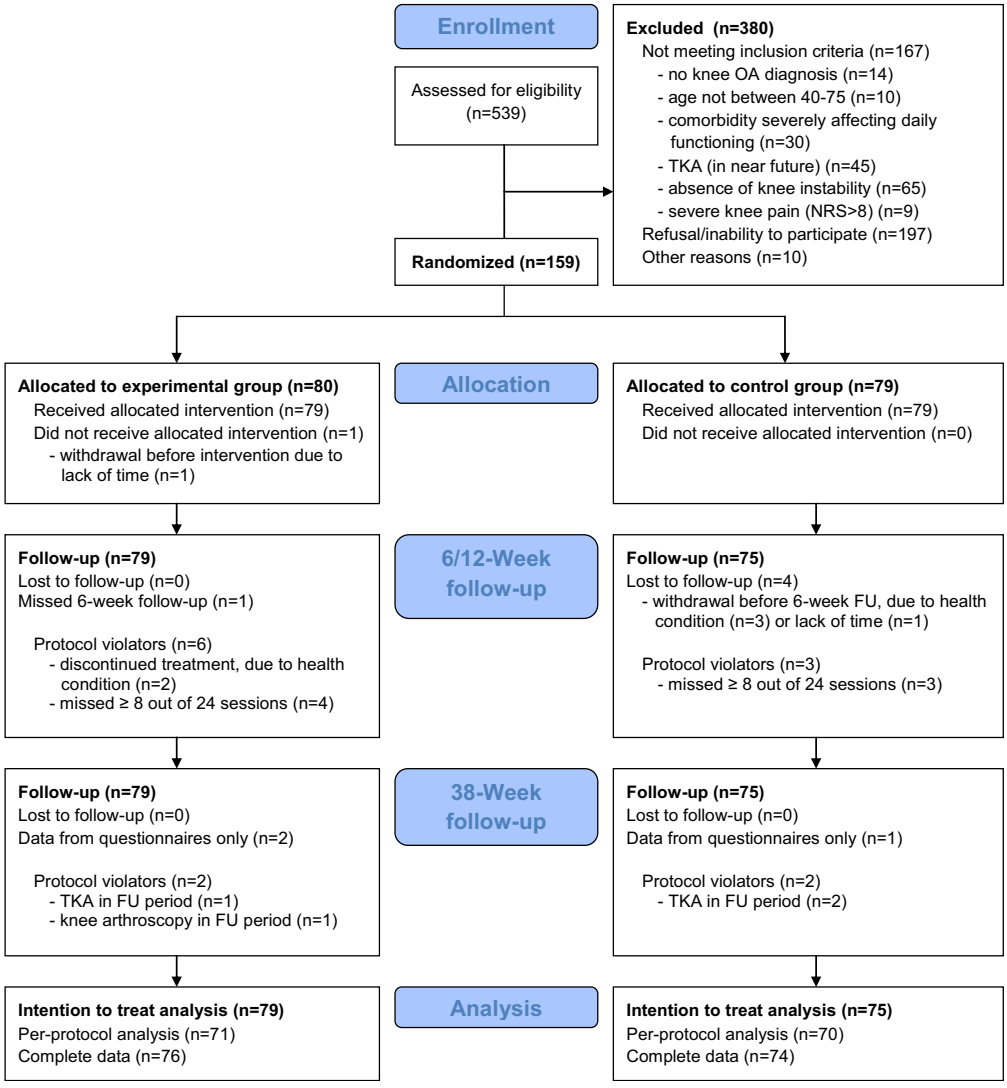

Fig. 3. Flow chart.

in the first 4 weeks as compared to control group (10.3 ± 1.5 vs 9.8 ± 1.7; $P = 0.03$), while significantly lower in the last 4 weeks (12.9 ± 1.3 vs 13.5 ± 1.4; $P = 0.01$) (see Fig. 4). No serious adverse events had been reported. Group allocation was guessed correctly by the assessor in 59% of the participants ($\kappa = 0.18$).

No significant group differences on average over time or interactions between group and time were found on primary outcome WOMAC physical function or on secondary outcomes, except for a significantly higher GPE in the experimental group directly post-treatment (87% vs 73% in control group; OR (95% CI) = 2.4 (1.0–5.8)) (see Table II). Per-protocol analyses did not lead to different study results, although all outcomes slightly changed in favor of the experimental group.

As shown by Table III, both interventions were found to be effective on each outcome measure. Approximately two third of the participants demonstrated clinically relevant improvements on activity limitations and pain, based on MCID, which were sustained 6 months later [see also Fig. 5(a and b)]. Furthermore, a large majority of the participants (78% and 77% in experimental and control group, respectively) indicated their symptoms remained stable or even improved during the 6-month period post-treatment.

No difference in effectiveness between treatments could be demonstrated, as between-group effect size of 0.06 for WOMAC physical function and 0.09 for NRS pain severity were found. Within-group effect size for the experimental treatment were 0.77 (WOMAC physical function) and 0.91 (NRS pain), and for the control treatment 0.72 and 0.93, respectively.

Discussion

In this study, we determined the additional effect of initial knee joint stabilization training, prior to strength training and training of daily activities, in persons with knee OA suffering from knee instability. We could not confirm our hypothesis that specific knee joint stabilization training has additional value in this targeted subgroup of patients, as both treatment groups demonstrated similarly large and clinically relevant improvements on activity limitations, pain and knee instability. Only on one secondary outcome measure (i.e., GPE), we found a significant difference, in favor of the experimental group.

In recent years, two studies[37,38] have already been conducted in knee OA patients to determine the effect of knee stabilization training in addition to strength training. The first was a small non-randomized study[37] in 60 female knee OA patients, demonstrating significant but small effects of 'kinesthetic (i.e., proprioceptive) and balance training' in addition to strengthening exercises, compared to strengthening exercises only. However, because of a higher training intensity of the experimental program[39], a high drop-out rate (32%) and the lack of randomization, evidence for an additional effect of knee stabilization training was not provided. The second study was a large randomized controlled trial[38] in 183 knee OA patients, focusing on the additional effect of agility and perturbation exercises, which exposes patients to challenges in balance, in addition to strengthening exercises. Again, no additional effect could be demonstrated. Unlike these two studies, we selected participants based on the presence of knee instability, as particularly these patients were presumed to benefit from an exercise program that specifically targets knee stabilization. Surprisingly, we were also unable to demonstrate an additional effect of knee stabilization training.

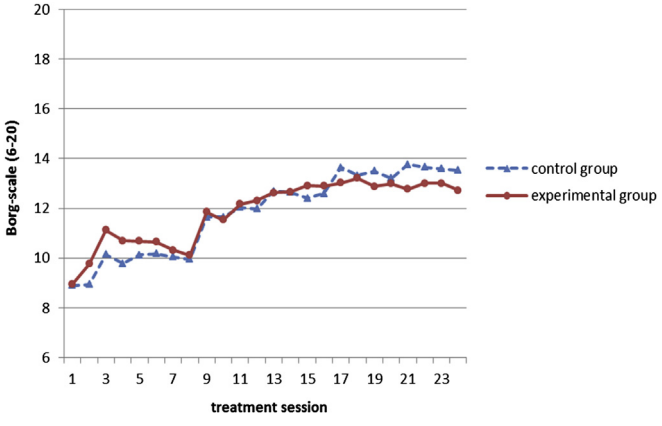

Fig. 4. Patient-perceived training intensity (Borg-scale[31]) for control and experimental group separately.

Our study results, along with the studies from Diracoglu *et al.*[37] and Fitzgerald *et al.*[38], may imply that knee stability can be improved through strength training, without necessarily adding specific knee stabilization training. Multiple studies[37,40–42] in knee OA patients showed that proprioception can be improved through exercises. We found improvements of ~30% in proprioceptive accuracy and reductions of ~30% in self-reported knee instability in both groups, while Diracoglu *et al.*[37] reported even larger proprioceptive improvements in patients receiving strength training with and without additional proprioceptive training. These effects of strength training could be attributed to an increase in amount[43] and sensitivity[13] of muscle spindles, which are considered the most important sources of proprioceptive stimuli[44], and to a decrease in muscle fatigue[45] and level of muscle contraction, relative to maximum level[46], which may all positively influence proprioceptive accuracy and knee stability[43]. In addition, we demonstrated in a previous study[11] that low muscle strength of the upper leg was strongly related to the presence of self-reported knee instability in a knee OA cohort, while unexpectedly, impaired proprioceptive accuracy and high laxity were not. These results consistently indicate that the role of upper leg muscles in knee stabilization seem to be dominant over other biomechanical factors involved in the knee joint stabilization process.

We revealed large within-group effect sizes of 0.8 for activity limitations and 0.9 for pain severity, which are at the higher end of within-group effects previously reported for exercise programs in large knee OA studies[38,47–50]. Moreover, clinically relevant improvements were found in two out of every three participants. These large effects presumably indicate a well-chosen content of our programs, including strengthening, aerobic and functional exercises plus education, as well as an adequate gradual increase in training intensity, all according to recent guidelines[2–4]. Furthermore, exercises were linked to daily activities like walking, stair-climbing and rising from a chair into our exercises, which may be important to reduce activity limitations. Finally, no adverse events (e.g., pain flares, knee injuries) occurred during the interventions, which is possibly attributable to the low intensity and minimal knee loading of exercises in the first phase, with gradual increase during the program, as illustrated in Fig. 4.

In contrast to previous studies[5,51], treatment effects in the present study hardly changed 6 months after the intervention. Crucial factors for long-term effects have been found to be adherence to home exercises and being physically active in daily life[51]. Our participants were highly adherent, both during the exercise program (i.e., 21 out of 24 treatment sessions were attended on average) and post-treatment (i.e., 78% of the participants continued performing home exercises after the intervention), and a majority of the participants (53%) increased their physical activity level, compared to baseline. These results may possibly be ascribed to the feasibility of the exercises, a strong link between exercises and daily activities and adequate education, which included self-management advice.

Table II
Outcome measures by group at different time-points (mean ± SD unless otherwise stated) and group differences over time (ITT-analysis)

	Baseline		6-Wk FU (mid treatment)		12-Wk FU (directly post-treatment)		38-Wk FU (6 months post-treatment)		Group differences over time (6-, 12- and 38-wk FU)*	
	Exp.	Con.	Exp.	Con.	Exp.	Con.	Exp.	Con.	B (95% CI)	*P*
Primary outcome										
WOMAC (physical function, 0–68)	25.2 ± 11.8	27.1 ± 12.7	21.5 ± 11.6	21.8 ± 10.4	17.4 ± 11.6	19.3 ± 11.4	18.9 ± 13.3	19.2 ± 13.2	−0.01 (−2.58 to 2.57)	0.99
Secondary outcomes										
NRS (knee pain severity, 0–10)	4.8 ± 2.2	5.2 ± 2.0	3.7 ± 2.1	3.9 ± 1.9	2.8 ± 2.1	3.3 ± 2.1	3.1 ± 2.5	3.7 ± 2.4	−0.26 (−0.76 to 0.23)	0.30
GPE†, *n* (%)	*n/a*	*n/a*	*n/a*	*n/a*	69 (87)	55 (73)	*n/a*	*n/a*	2.44 (1.02–5.84)‖·¶	0.04
Knee instability, self-reported										
≥One episode in past 6 weeks, *n* (%)	67 (84)	65 (84)	53 (68)	54 (72)	41 (52)	41 (55)	41 (51)	30 (40)	1.07 (0.64–1.67)‖	0.80
Resulting in activity limitations, *n* (%)	39 (49)	53 (67)	27 (35)	27 (36)	18 (23)	24 (32)	22 (28)	29 (39)	0.93 (0.54–1.58)‖	0.79
Upper leg muscle strength (Nm/kg)‡	0.83 ± 0.35	0.85 ± 0.43	0.92 ± 0.35	0.94 ± 0.39	0.97 ± 0.32	1.01 ± 0.42	1.00 ± 0.36	1.04 ± 0.40	−0.01 (−0.06 to 0.05)	0.79
Proprioceptive accuracy (degrees)‡	2.7 ± 2.2	3.7 ± 2.6	2.4 ± 1.9	2.5 ± 1.6	2.0 ± 1.6	2.5 ± 1.8	1.9 ± 1.4	2.2 ± 1.4	0.07 (−0.26 to 0.39)#	0.69
GUG-test (seconds)	10.6 ± 1.8	10.8 ± 2.5	10.2 ± 1.8	10.1 ± 2.7	10.1 ± 1.5	9.7 ± 2.0	10.0 ± 1.6	9.9 ± 2.0	0.26 (−0.07 to 0.53)	0.08
PSFL (performance of activities, 0–100)§	53.7 ± 16.4	56.2 ± 17.7	*n/a*	*n/a*	29.5 ± 18.1	34.4 ± 19.8	31.3 ± 22.1	34.6 ± 20.3	−1.01 (−6.53 to 4.51)	0.72
WQ35 (walking, 0–100)	23.9 ± 18.1	27.7 ± 22.6	19.8 ± 16.8	24.1 ± 20.6	14.6 ± 15.4	19.4 ± 20.3	17.7 ± 20.4	19.2 ± 20.7	−1.15 (−5.43 to 3.12)#	0.60
CStQ15 (stair climbing, 0–100)	37.4 ± 20.2	39.4 ± 20.6	32.2 ± 20.4	36.2 ± 21.8	25.3 ± 19.1	27.4 ± 18.8	28.3 ± 22.7	30.8 ± 22.0	0.19 (−3.93 to 4.30)	0.93
QR&S39 (rising and sitting down, 0–100)	35.0 ± 22.3	38.4 ± 25.7	31.4 ± 22.9	32.2 ± 25.5	24.6 ± 20.3	26.6 ± 23.1	29.2 ± 25.3	26.9 ± 24.6	2.07 (−2.00 to 6.14)#	0.32

Exp. = experimental group; Con. = control group; CI = confidence interval; ; PSFL = patient specific functioning list; *n/a* = not assessed.
* Adjusted for baseline value of outcome variable, presence of self-reported instability affecting daily functioning at baseline, proprioceptive accuracy at baseline and presence of varus malalignment at baseline.
† Perceived improvement vs no perceived improvement (reference).
‡ Data from index knee.
§ Average score of three activities that were most relevant and problematic for patient.
‖ Odds ratio (95% CI).
¶ Group difference at 12-wk FU.
# Although outcome measure was not optimally distributed, analysis of non-transformed data reported, as this is more easily interpretable and yielded similar results as analysis with transformed data.

Major strengths of the present study are a large study population ($n = 159$), our selection of patients that were presumed to benefit from targeted knee joint stabilization training, low drop-out rate (3%), high patient adherence, consistent study results from multiple (both global and specific) outcome measures and the contrast between treatment arms, which enabled us to determine the isolated effect of initial knee joint stabilization training. A limitation of the study might be the non-optimal blinding of the assessor, who correctly guessed participant's group allocation in 59%. A second limitation could be a small but significant difference in training intensity in the last treatment phase in favor of the control treatment, which could be explained by the instructions to perform exercises in a controlled manner, only provided in the experimental group, thereby possibly hindering a larger increase in training intensity.

In conclusion, both exercise programs were highly effective in reducing activity limitations and pain and restoring knee stability in knee OA patients with instability of the knee. In knee OA patients suffering from knee instability, specific knee joint stabilization training, in addition to strength training and training of daily activities, does not seem to have any additional value.

Table III
Relative change and treatment response by group from baseline to 12-week FU and baseline to 38-week FU ($n = 154$)

	Δ Baseline-12-week FU				Δ Baseline-38-week FU			
	Experimental		Control		Experimental		Control	
	% Δ	Responders, *n* (%)*	% Δ	Responders, *n* (%)*	% Δ	Responders, *n* (%)*	% Δ	Responders, *n* (%)*
Primary outcome								
WOMAC (physical function)	−31%	52 (66%)	−27%	47 (63%)	−25%	49 (62%)	−28%	46 (61%)
Secondary outcomes:								
NRS (knee pain severity)	−41%	55 (70%)	−36%	54 (72%)	−35%	57 (72%)	−28%	43 (57%)
GUG-test	−5%	19 (24%)	−9%	29 (39%)	−6%	16 (21%)	−8%	25 (34%)
PSFL (performance of daily activities)†	−45%	50 (63%)	−37%	38 (51%)	−42%	43 (56%)	−37%	33 (45%)
Upper leg muscle strength‡	+18%	–	+19%	–	+22%	–	+23%	–
Proprioceptive accuracy‡	−28%	–	−31%	–	−30%	–	−40%	–
WQ35 (walking)	−40%	–	−28%	–	−27%	–	−29%	–
CStQ15 (stair climbing)	−33%	–	−29%	–	−25%	–	−20%	–
QR&S39 (rising and sitting down)	−30%	–	−29%	–	−17%	–	−28%	–

* Based on MCID of 12% for WOMAC[35], 15% for NRS pain[36], and 20 mm for PSFL[27], and minimal detectable change (MDC) of 1.2 s for GUG-test[26].
† Average score of three activities that were most relevant and problematic for patient.
‡ Data from index knee.

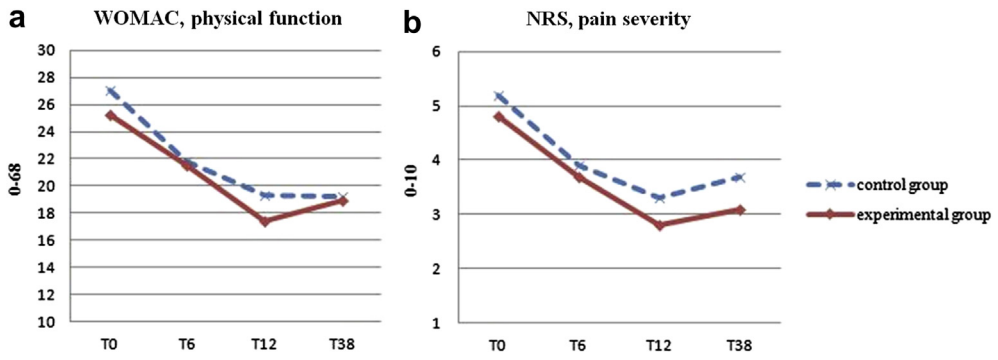

Fig. 5. Outcomes on WOMAC, physical function (a) and NRS, pain severity (b) during study period for control and experimental group separately.

Author contribution

Conception and design of the study: Knoop, Dekker, van der Leeden, van der Esch, Thorstensson, Gerritsen, Voorneman, Peter, de Rooij, Romviel, Lems, Roorda, Steultjens.

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Competing interest statement

The authors do not have any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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Supplementary data

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References

1. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al.* The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84(3):351–8.
2. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, *et al.* Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133(9):726–37.
3. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010;18(4):476–99.
4. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, *et al.* EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62(12):1145–55.
5. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2008;4:CD004376.
6. Lange AK, Vanwanseele B, Fiatarone Singh MA. Strength training for treatment of osteoarthritis of the knee: a systematic review. Arthritis Rheum 2008;59(10):1488–94.
7. Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. J Physiother 2011;57(1):11–20.
8. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991;9(1):113–9.
9. Fitzgerald GK, Piva SR, Irrgang JJ. Reports of joint instability in knee osteoarthritis: its prevalence and relationship to physical function. Arthritis Rheum 2004;51(6):941–6.
10. van der Esch M, Knoop J, van der Leeden M, Voorneman R, Gerritsen M, Reiding D, *et al.* Self-reported knee instability and activity limitations in patients with knee osteoarthritis: results of the Amsterdam Osteoarthritis Cohort. Clin Rheumatol 2012;31(10):1505–10.
11. Knoop J, van der Leeden M, van der Esch M, Thorstensson CA, Gerritsen M, Voorneman RE, *et al.* Association of lower muscle strength with self-reported knee instability in osteoarthritis of the knee: results from the Amsterdam Osteoarthritis Cohort. Arthritis Care Res (Hoboken) 2012;64(1):38–45.
12. Schmitt LC, Fitzgerald GK, Reisman AS, Rudolph KS. Instability, laxity, and physical function in patients with medial knee osteoarthritis. Phys Ther 2008;88(12):1506–16.
13. Knoop J, Steultjens MP, van der Leeden M, van der Esch M, Thorstensson CA, Roorda LD, *et al.* Proprioception in knee osteoarthritis: a narrative review. Osteoarthritis Cartilage 2011;19(4):381–8.
14. Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. Curr Opin Rheumatol 2009;21(5):520–4.

15. van der Esch M, Steultjens M, Harlaar J, Knol D, Lems W, Dekker J. Joint proprioception, muscle strength, and functional ability in patients with osteoarthritis of the knee. Arthritis Rheum 2007;57(5):787–93.
16. Holla JFM, van der Leeden M, Peter WFH, Roorda LD, van der Esch M, Lems WF, *et al*. Proprioception, laxity, muscle strength and activity limitations in early symptomatic knee osteoarthritis: results from the CHECK cohort. J Rehabil Med 2012;44(10):862–8.
17. van der Esch M, Steultjens M, Knol DL, Dinant H, Dekker J. Joint laxity and the relationship between muscle strength and functional ability in patients with osteoarthritis of the knee. Arthritis Rheum 2006;55(6):953–9.
18. van der Esch M, Steultjens M, Harlaar J, Wolterbeek N, Knol D, Dekker J. Varus–valgus motion and functional ability in patients with knee osteoarthritis. Ann Rheum Dis 2008;67(4):471–7.
19. Ageberg E, Link A, Roos EM. 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.
20. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
21. Felson DT, Niu J, McClennan C, Sack B, Aliabadi P, Hunter DJ, *et al*. Knee buckling: prevalence, risk factors, and associated limitations in function. Ann Intern Med 2007;147(8):534–40.
22. Williams GN, Chmielewski T, Rudolph K, Buchanan TS, Snyder-Mackler L. Dynamic knee stability: current theory and implications for clinicians and scientists. J Orthop Sports Phys Ther 2001;31(10):546–66.
23. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. 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(12):1833–40.
24. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, *et al*. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004;63(1):36–42.
25. Turk DC, Melzack R. Handbook of Pain Assessment. 2nd edn. New York: Guilford Press; 2001.
26. Piva SR, Fitzgerald GK, Irrgang JJ, Bouzubar F, Starz TW. Get up and go test in patients with knee osteoarthritis. Arch Phys Med Rehabil 2004;85(2):284–9.
27. Beurskens AJ, de Vet HC, Koke AJ. Responsiveness of functional status in low back pain: a comparison of different instruments. Pain 1996;65(1):71–6.
28. Roorda LD, Roebroeck ME, van Tilburg T, Molenaar IW, Lankhorst GJ, Bouter LM, *et al*. Measuring activity limitations in walking: development of a hierarchical scale for patients with lower-extremity disorders who live at home. Arch Phys Med Rehabil 2005;86(12):2277–83.
29. Roorda LD, Roebroeck ME, van Tilburg T, Lankhorst GJ, Bouter LM. Measuring activity limitations in climbing stairs: development of a hierarchical scale for patients with lower-extremity disorders living at home. Arch Phys Med Rehabil 2004;85(6):967–71.
30. Roorda LD, Molenaar IW, Lankhorst GJ, Bouter LM. Improvement of a questionnaire measuring activity limitations in rising and sitting down in patients with lower-extremity disorders living at home. Arch Phys Med Rehabil 2005;86(11):2204–10.
31. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2(2):92–8.
32. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology; a Practical Guide. 1st edn. Cambridge, UK: Cambridge University Press; 2003.
33. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, NJ: Erlbaum; 1988.
34. French HP, Fitzpatrick M, FitzGerald O. Responsiveness of physical function outcomes following physiotherapy intervention for osteoarthritis of the knee: an outcome comparison study. Physiotherapy 2011;97(4):302–8.
35. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384–91.
36. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004;8(4):283–91.
37. Diracoglu D, Aydin R, Baskent A, Celik A. Effects of kinesthesia and balance exercises in knee osteoarthritis. J Clin Rheumatol 2005;11(6):303–10.
38. Fitzgerald GK, Piva SR, Gil AB, Wisniewski SR, Oddis CV, Irrgang JJ. 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(4):452–69.
39. Diracoglu D, Baskent A, Celik A, Issever H, Aydin R. Long-term effects of kinesthesia/balance and strengthening exercises on patients with knee osteoarthritis: a one-year follow-up study. J Back Musculoskelet Rehabil 2008;21(4):253–62.
40. Hurley MV, Scott DL. Improvements in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. Br J Rheumatol 1998;37(11):1181–7.
41. Lin DH, Lin CH, Lin YF, Jan MH. Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a randomized clinical trial. J Orthop Sports Phys Ther 2009;39(6):450–7.
42. Jan MH, Lin CH, Lin YF, Lin JJ, Lin DH. Effects of weight-bearing versus nonweight-bearing exercise on function, walking speed, and position sense in participants with knee osteoarthritis: a randomized controlled trial. Arch Phys Med Rehabil 2009;90(6):897–904.
43. Butler AA, Lord SR, Rogers MW, Fitzpatrick RC. Muscle weakness impairs the proprioceptive control of human standing. Brain Res 2008;1242:244–51.
44. Solomonow M, D'Ambrosia R. Neural reflex arcs and muscle control of knee stability and motion. In: Scott WN, Ed. The Knee 1994:107–20. St. Louis.
45. Givoni NJ, Pham T, Allen TJ, Proske U. The effect of quadriceps muscle fatigue on position matching at the knee. J Physiol 2007;584(Pt 1):111–9.
46. Wise AK, Gregory JE, Proske U. Detection of movements of the human forearm during and after co-contractions of muscles acting at the elbow joint. J Physiol 1998;508(Pt 1):325–30.
47. van Baar ME, Dekker J, Oostendorp RA, Bijl D, Voorn TB, Lemmens JA, *et al*. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. J Rheumatol 1998;25(12):2432–9.
48. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. Ann Rheum Dis 1999;58(1):15–9.

49. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, *et al*. Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: a randomized clinical trial. Arthritis Rheum 2006;55(6):925–34.
50. Farr JN, Going SB, McKnight PE, Kasle S, Cussler EC, Cornett M. Progressive resistance training improves overall physical activity levels in patients with early osteoarthritis of the knee: a randomized controlled trial. Phys Ther 2010;90(3):356–66.
51. Pisters MF, Veenhof C, van Meeteren NL, Ostelo RW, de Bakker DH, Schellevis FG, *et al*. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. Arthritis Rheum 2007;57(7):1245–53.