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## Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: a randomized controlled trial

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## Abstract

**Objective.** To evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee osteoarthritis (KOA) and comorbidities.

**Method.** In a randomized controlled trial, 126 participants were included with a clinical diagnosis of KOA and at least one of the following target comorbidities: coronary disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease or obesity (body mass index  $\geq 30\text{kg/m}^2$ ), with severity score  $\geq 2$  on the Cumulative Illness Rating Scale. The intervention group received a 20-week, individualized, comorbidity-adapted exercise program consisting of aerobic and strength training. The control group received their current medical care for KOA and were placed on a waiting list for exercise therapy. Primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale physical functioning and 6-minute walking test (6-MWT). Measurements were performed at baseline, after 20 weeks (post-treatment) and at 3 months post-treatment.

**Results.** Statistically significant physical functioning differences over time were found between the intervention and control group (WOMAC;  $B = -7.43$ , 95%CI  $-9.99$  to  $-4.87$ ,  $p < 0.001$  and 6-MWT;  $B = 34.16$ , 95%CI  $17.68$  to  $50.64$ ,  $p < 0.001$ ) in favor of the intervention group. At 3-months follow, the mean improvements in the intervention group were 33% on the WOMAC scale and 15% on the 6-MWT. These improvements are of clinical relevance. No serious adverse events occurred during the intervention.

**Conclusion.** This is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with KOA and severe comorbidities.

Dutch trial registration number: NTR3027

## Significance &amp; Innovations

- Exercise therapy is a key intervention in the management of knee osteoarthritis. Comorbidity is highly prevalent in knee osteoarthritis and interferes with the application of exercise therapy, contributing to nonadherence. This is first RCT investigating the efficacy and safety of exercise therapy tailored to comorbidity.
- The results showed that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with knee osteoarthritis and severe comorbidities. The mean improvements in the intervention group on physical functioning were 33% on the WOMAC scale and 15% on the 6-Minute walking test at 3-months follow-up. These improvements are of clinical relevance. No serious adverse events occurred during the intervention.
- The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee osteoarthritis, even in the presence of severe comorbidity.

## INTRODUCTION

Exercise therapy is a key intervention in the management of knee osteoarthritis (KOA) and recommended in international guidelines on KOA management (1;2). It is an effective intervention to improve physical functioning and to reduce joint pain in patients with KOA (3). However, the presence of comorbid diseases interferes with the application of exercise therapy (4), contributes to nonadherence (5), and may affect the outcome of exercise therapy.

Comorbidity is present in 68 to 85% of patients with osteoarthritis (OA) (6-8). Frequently more than one comorbid disease is present (8). Common comorbidities in KOA are cardiovascular diseases, type 2 diabetes, chronic obstructive pulmonary disease (COPD) and obesity (9). Comorbidity limits exercise tolerance, depending on the type, number and severity of the comorbid disease(s). For example, comorbid heart failure or COPD may limit exercise capacity and may lead to exercise-induced adverse effects, such as decompensation in patients with heart failure, or desaturation in patients with COPD.

The effect of exercise therapy in patients with KOA and severe comorbidity is not known. Patients with unstable medical conditions, precluding safe participation in an exercise program are excluded from clinical trials (10-13), because of the high risk of comorbidity induced adverse events. One study investigated the outcome of exercise therapy in a subgroup of patients with KOA and comorbidity compared to patients without comorbidity (14). Beneficial effects of exercise therapy were found in both groups. However, patients with severe medical conditions such as congestive heart failure or insulin dependent diabetes mellitus were excluded.

Guidelines on KOA do not provide guidance on tailoring exercise therapy to the presence of comorbidity (1;2;18;19). In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy (15). If accepted into an exercise program, both

therapists and patients tend to reduce exercise intensity to a level that is unlikely to be effective, because of fear of aggravating symptoms of the comorbid disease (16;17).

We hypothesize that patients with severe comorbidity can exercise safely if certain precautions are taken and adequate adaptations to the exercise program are made. We have previously developed a treatment protocol to tailor exercise therapy for KOA to comorbid diseases (20). The purpose of the present study was to evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with KOA and comorbidity.

## METHODS

### *Trial design*

This was a single-blind, randomized controlled trial, conducted in a secondary outpatient rehabilitation center. Measurements were performed at baseline, at 10 weeks (midtreatment), 20 weeks (posttreatment) and 32 weeks (3-months posttreatment). The study was conducted in accordance with the Declaration of Helsinki principles (21). The study protocol was approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital; number 1148). All participants gave written informed consent. Dutch trial registration number: NTR3027.

### *Participants*

Participants were recruited from December 2011 to January 2014 through regular referral by general health practitioners, rheumatologists, rehabilitation physicians and orthopedic surgeons, or from advertisements in local newspapers. Participant eligibility was assessed by a short online screening questionnaire, a telephone screening by the researcher (MdR), and subsequently by a rheumatologist and a rehabilitation physician. The final decision on in- or exclusion of a participant was made by the rehabilitation physician.

Inclusion criteria: 1) diagnosis of KOA according to the clinical criteria of the American College of Rheumatology (22); 2) presence of at least one of the target comorbidities (coronary disease, heart failure, type 2 diabetes, COPD or obesity (Body Mass Index (BMI)  $\geq 30\text{kg/m}^2$ )), all diagnosed by a medical specialist, with severity score  $\geq 2$  for the comorbidity on the Cumulative Illness Rating Scale (23) (indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease). Confirmation of the medical diagnosis was obtained by medical history taking and medication prescription. If there was any doubt about the diagnosis the medical specialist or general practitioner was consulted by the rehabilitation physician; and 3) the primary treatment goal was related to KOA (instead of comorbidity related). Exclusion criteria: 1) absolute contraindication for exercise therapy (eg, myocardial infarction within last 3 months); 2) total knee arthroplasty (TKA) or planned TKA in near future; 3) participation in exercise therapy for



KOA within the preceding three months; 4) insufficient comprehension of Dutch language; 5) psychological distress necessitating treatment; 6) dementia (Mini-Mental State Examination score >24); 7) significant physical limitations that would prohibit the participant from following exercise therapy; 8) expected to be lost for follow-up (eg, because of a planned change of residency); and 9) refusal to sign informed consent.

#### *Randomization, treatment allocation and blinding*

Participants were randomly assigned to the intervention group or the control group by the web-based program MagMin (24). This program uses a minimization algorithm based on the Pocock and Simon method (25), balancing the comorbid diseases (coronary disease, heart failure, diabetes type 2, COPD, BMI (BMI >30, BMI 30-35, BMI <35)) and pain severity (NRS score of 1-5, NRS score of 6-10). Comorbid diseases were weighted two, while pain severity was weighted one. Participants were randomized by an independent staff member who had no other involvement in the trial.

Randomization, treatment allocation and statistical analyses were performed blindly. The assessors (in total three) were blinded for treatment allocation. Participants and physiotherapists (PTs) were not blinded for treatment allocation.

#### *Intervention*

**Exercise therapy.** Exercise therapy comprised a 20-week individualized (tailored) KOA exercise program, with two sessions of 30 to 60 minutes a week under supervision of a PT. The exercise therapy provided in the present study was based on the protocol as developed by Knoop et al (12) and consisted of muscle-strength training of the lower limb and aerobic training (1;2;12;19). Flexibility and stability exercises of the lower limb were added on indication. See appendix 1 for an overview of the content of the exercise therapy. Comorbidity-related adaptations were made to the diagnostic phase and the intervention phase (20) (see appendix 2). In the diagnostic phase, comorbidity-related contraindications and restrictions were identified by history taking and physical examination in an extensive one-hour intake procedure. Absolute contraindications were defined as conditions that would

lead to the immediate exclusion of the participant from exercise therapy (eg, unstable angina). Restrictions (or relative contraindications) were defined as impairments which limit the application of exercise therapy (eg, dyspnea in patients with COPD).

In the intervention phase, KOA exercises as described by Knoop et al (12) (see appendix 1) were adapted to the comorbid disease, taking into account restrictions. Exercise therapy was adapted by changing frequency, intensity, timing and type (FITT) factors of the exercises or by adding educational (eg, providing comorbidity-related information on exercise therapy) or coaching strategies (eg, coaching for reducing body weight or coaching for fear of exertion). Third, during every training session, comorbidity-related symptoms and clinical parameters were monitored, and exercise was adapted if required. The specific adaptations to the OA exercises were based on principles described in comorbidity-specific exercise guidelines (eg, cardiac rehabilitation) (26) and were listed in the protocol (20) (see appendix 2). The training intensity was monitored with the Borg Rate of Perceived Exertion (RPE) scale 6-20 (27) and on the heart rate reserve, if indicated (28). In addition to the supervised exercise sessions, education on KOA was provided and participants were encouraged to perform exercises at home for at least five times a week.

*Control intervention.* Participants randomized to the control intervention received their current medical care for KOA and comorbid disease. They were placed on a waiting list for a period of 32 weeks, and thereafter the comorbidity adapted exercise intervention was offered.

#### *Therapists*

Exercise therapy was applied by seven qualified PTs with 3 to 25 years' work experience. The PTs were trained to work with the protocol and to provide treatment in accordance with the protocol. Booster sessions were provided every 12 weeks.

#### *Participant characteristics*

Baseline characteristics were obtained, ie, age, sex, educational level, duration of knee symptoms, BMI, unilateral or bilateral KOA, Kellgren and Lawrence grade (K&L) (29), Cumulative Illness Rating Scale (CIRS) (23), use of pain medication, use of walking devices and mal-alignment of the knee.

### *Outcomes*

*Primary outcome measures.* Physical functioning was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, Dutch translation) - subscale physical function (30) and the 6-minute walk test (6-MWT) (31). An extended description of these measures is available in Appendix 3.

*Secondary outcomes measures.* Serious adverse events related to treatment and testing procedures were reported to the researcher by the treating PT or clinimetric assessors. Knee-pain severity during the last week was scored on a Numeric Rating Scale (NRS) (32) and with the pain subscale of the WOMAC (30). Physical functioning was measured using self-reported physical function questionnaires (subscale of the 36-Item Short-Form Health Survey (SF-36) (33), Patient-Specific Functioning Scale (PSFS) (34), Walking Questionnaire (WQ35) (35), Climbing stairs Questionnaire (CSQ15) (36), Questionnaire Rising and Sitting down (R&SDQS39) (37)) and two physical performance tests (i.e. Get Up and Go test (GUG) (38) and time walking up-down stairs (39)). The LASA Physical Activity Questionnaire (LAPAQ) was used to assess the moderate-intensity physical activity (40). Fatigue was assessed with the NRS scale. Isokinetic muscle strength and proprioceptive accuracy (41) were assessed as described in Appendix 1. Psychological functioning was assessed with the Hospital Anxiety and Depression Scale (HADS) (42). The Evaluative Frailty Index for Physical activity (EFIP) was used to measure the level of frailty (43).

Global perceived effect (GPE) was assessed posttreatment (week 20) in the intervention group, on a 9-point Likert scale, and dichotomized as 'improved' (score 1-4) or

'not improved' (score 5-10) (44). An extended description of the secondary outcome measurements is available in Appendix 3.

For knee-specific variables (K&L grade, muscle strength, proprioceptive accuracy) we used data from one knee per person (index knee). Index knees were determined by the clinical diagnosis of KOA according to ACR-criteria. In case of a clinical diagnosis of KOA in both knees, a knee was chosen at random.

*Process outcome measures.* PTs assessed patient-perceived training intensity on a Borg-scale (27) after each session, and pain severity (NRS) (32) during the preceding week once a week. In addition, PTs completed training diaries and registration forms to record specific adaptations to the exercise program (eg, FITT factors and other adjustments to the exercise program).

#### *Sample size*

The a priori power calculation was based on the WOMAC physical function subscale with an expected effect size of 0.4 between intervention and control group at the 20-week follow-up, four time points of measurement (baseline and three follow-up moments), expected autocorrelation between the repetitions of 0.5, significance level of .05 and desired power of .80. Given these parameters a total sample size of 122 participants was needed. Allowing for a dropout rate of 20% during the study, we aimed to include 154 patients (i.e. 77 patients in each group). However, due to a low dropout rate of only 3% during the study we adjusted our sample size to 126 patients (i.e. 63 patients in each group).

#### *Statistical analyses*

Descriptive statistics for baseline participant characteristics were tabulated as mean (SD) or medians (IQR) or percentages if data did not have a normal distribution. All outcome measures were normally distributed, except for proprioceptive accuracy, GUG test,

stairclimbing test, WQ35, R&SQ39, HADS and LAPAQ. A logarithmic transformation was applied for the non-normally distributed variables: by log10 (for proprioceptive accuracy, GUG test, stairclimbing test, HADS and LAPAQ) or square root (for WQ35, R&SQ39). Comorbidity-related adaptations to the exercise program were described in percentages.

Analyses were based on the intention-to-treat principle (ITT), in which data of all participants were analyzed according to group assignment. Generalized Estimating Equation (GEE) analysis was used to estimate the average group differences over time, and the group differences at the different time points. For the latter, time (treated as a categorical variable and represented by dummy variables) and the interaction between group and time were added to the model. Both analyses were adjusted for the baseline value of the outcome measure (45). Prior to the regression analysis, the assumptions for linear regression were checked. An exchangeable correlation structure was used to account for the within-subject correlations. The between-group standardized mean difference (SMD) was calculated (46). A sensitivity analysis was performed using the participants who fulfilled at least two-thirds of the training sessions *and* with adaptations of the exercise program for FITT factors. P values less than .05 were considered statistically significant. Analyses were performed with SPSS for Windows 22.0 software (SPSS, Chicago, IL).

## RESULTS

### *Participants*

The participants' flow chart is presented in Figure 1. Out of the 344 potential participants, 218 (63%) were not eligible or did not wish to participate. In total, 126 participants were randomized and allocated to the intervention (n=63) or the control group (n=63). One participant of the intervention group and three participants of the control group were lost before the first follow-up measurement.

Baseline characteristics of the intervention and control groups are presented in Table 1. The groups were well balanced and similar on entry to the trial in terms of age, sex, BMI, K&L grade, comorbid diseases and outcome measures. Blinding for treatment allocation was

successful. Group allocation was guessed correctly by the assessor in 64% of the participants (Cohen's kappa= 0.03 p value 0.4).

#### *Compliance and co-interventions*

Fifty-four (86%) of the 63 participants in the intervention group received  $\geq$  two-thirds of the exercise sessions ( $\geq 27$  out of 40 sessions). Of the nine participants who did not complete the program, two participants did not because of severe knee pain and seven participants due to other reasons (unrelated to the intervention). Nine (17%) of the participants performed the exercise program at a low training intensity (Borg scale  $\leq 11$ ), 40 participants (74%) reached a moderate training intensity (Borg scale 12-14) and five participants (9%) reached a high training intensity (Borg scale  $\geq 15$ ). On average, participants performed their home exercises four times a week (SD =1.1) during the trial. In the intervention group, three participants received a corticosteroid injection for their knee symptoms; two of these participants subsequently received a total knee arthroplasty. In the control group two participants received a corticosteroid injection, one participant received a total knee arthroplasty and 11 participants received treatment from a PT (reason for consulting a PT is unknown).

#### *Adaptations to the intervention*

Comorbidity-related adaptations to the exercise program are described in Table 2. In addition to the general adaptations, FITT factors were tailored to the restrictions posed by the comorbid disease in 76% of the participants. In 96% of the participants, additional educational or coaching strategies were provided (eg, coaching on body weight reduction in participants with obesity, or coaching on fear of exertion). For 80% of the participants, a combination of adjustment of FITT factors and education or coaching strategies was provided, while for 17% of the participants only educational or coaching strategies were provided.

#### *Primary outcome*

The WOMAC-pf and 6-MWT outcomes at week 10 (midtreatment), week 20 (directly posttreatment), and week 32 (3-months posttreatment) are illustrated in Figure 2. Significant differences over time between groups were found for WOMAC-pf ( $B = -7.43$  (95%CI -9.99 to -4.87  $p < 0.001$ )) and the 6-MWT ( $B = 34.16$  (95%CI 17.68 to 50.64  $p < 0.001$ )) in favor of the intervention group (see table 3). At each time point, a significant difference between groups was found (see Appendix 4). Directly posttreatment, between-group SMD for the intervention group was 0.9 and 0.6 for WOMAC-pf and 6-MWT, respectively. At three months posttreatment, between-group SMD was 1.0 and 0.7 for WOMAC-pf and 6-MWT, respectively.

### *Secondary outcomes*

No serious adverse events occurred that could be attributed to the exercise therapy provided. We found a significant difference over time between groups in favor of the intervention group for pain and the majority of physical functioning measures (see Table 3), as well as for fatigue, muscle strength, physical activity and frailty (see Appendix 5). No significant differences between groups were found for physical functioning measured with WQ35 and CTQ15 (see Table 3), proprioceptive accuracy, psychological functioning and BMI (see Appendix 5). Ninety-seven percent of the participants in the intervention group reported improvement as a result of the intervention directly posttreatment, and 62.7% still reported improvement at 3-months follow-up (GPE scale).

### *Sensitivity analyses*

The results on the primary outcome measures directly after treatment and at 3-months follow-up were similar when restricted to participants who received less than two-thirds of the training sessions and in whom specific adaptations to the exercise program included adjustments in FITT factors (data not shown). In addition, we performed a subgroup analysis only including patients with obesity ( $BMI \geq 30 \text{ kg/m}^2$ ). Similar results were found as compared to the results of the total group (data not shown).

## Discussion

This is the first study showing that a tailored exercise program for patients with KOA and severe comorbidity is efficacious in improving physical functioning. Statistically significant improvements were found in the intervention group, compared to the control group, directly after treatment and at 3-months follow-up. With respect to physical functioning, the mean improvement in the intervention group was 11.6 points (33%) on the WOMAC-pf and 59 meters (15%) on the 6-MWT at 3-months follow-up. For pain, the mean improvement in the intervention group was 1.7 points (27%) on the NRS pain scale at 3-months follow-up. These improvements are of clinical relevance (47;48). No treatment-related serious adverse events occurred and drop-out during the intervention was low, which suggests that our intervention is safe and feasible. However, we do realize that our sample size, although adequate for measuring the effectiveness of treatment, was small with respect to (serious) adverse events.

In comparison to other exercise trials in patients with knee osteoarthritis and comorbidity we included patients with more severe comorbidity (10;12;13;49). Our study population had more activity limitations at baseline, had on average more pain and had lower muscle strength in comparison to the baseline characteristics of patients in other exercise trials (10;12;13;49). We selected patients if they had a severity score  $\geq 2$  for the comorbidity on the Cumulative Illness Rating Scale (23), indicating that the comorbidity had an impact on daily activities and the patient was receiving regular care for the comorbid disease.

Remarkably, we found a large between-group effect size for self-reported physical functioning (SMD = 0.9) directly after ending treatment, and even further improvement during the following three months (SMD = 1.0). In a recently published Cochrane review, the magnitude of the treatment effect of exercise therapy on physical functioning in patients with



KOA was found to be moderate (SMD =0.5) (immediate posttreatment) to small (SMD =0.15) (two to six months posttreatment) (3). This suggests that tailoring exercise therapy to the comorbid disease is highly effective. The beneficial results of the present study can not only be attributed to the high volume and frequency of the exercise, but also to the several adjustments to the exercise program. First, in order to tailor exercise therapy to the individual patient, an extensive intake procedure was conducted. Second, therapists were encouraged to consult colleagues or medical specialists to discuss the medical condition of the patient, which provided them with the information needed to adapt the exercise program. Third, all patients were scheduled to receive an extended training program of 20 weeks (as opposed to 12 weeks which is regular in our center). Fourth, for more than two-thirds of the patients, exercises were adapted to the comorbid disease by changing FITT factors of the exercises. Fifth, in almost all patients, additional comorbidity-related education or coaching strategies were provided. Last, comorbidity-related symptoms were monitored during each training session, and exercise was adapted if required. We assume that all these factors contributed to exercise adherence in our treatment group.

Some methodological issues should be considered. First, patients in the control group received their current medical care for KOA and comorbid disease and were placed on a waiting list for exercise therapy. We included patients with a comorbidity severity score  $\geq 2$  on the CIRS indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease. Because of an increased risk of comorbidity-related (serious) adverse events, it was considered unethical to provide regular exercise therapy without tailoring to the comorbid disease. Thus, the study contrast concerns tailored exercise therapy versus current medical care. Second, we included patients with various comorbidities. With the current sample size we cannot analyze the outcome of the exercise program in patients with specific comorbidities (except for patients with obesity in whom we observed similar results). Third, we performed an efficacy trial to evaluate the effect of tailored exercise. The treatment was provided in a secondary care setting where PTs have advanced skills in treating patients with complex health conditions and have close collaboration with rehabilitation physicians and rheumatologists. More research is needed to

evaluate the effectiveness of the protocol in primary care. In addition, the effect of tailored exercise in other highly prevalent comorbid diseases in KOA (eg, chronic pain or depression) (9,20,50) should be investigated. Fourth, a limitation of the present study is that we did not investigate the cost-effectiveness of the developed protocols to get insight if the costs outweigh the benefits on health-related outcomes, medication use, hospital care and outpatient care.

In conclusion, this is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and is safe in patients with KOA and severe comorbidities. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with KOA, even in the presence of comorbidity.

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### Legend

Figure 1. Participant flow chart.  
KOA Knee Osteoarthritis

Figure 2. Mean and standard error of WOMAC-pf and 6-Minute Walk Test at baseline (T0), week 10 (T1 midtreatment), week 20 (T2 directly after treatment), and week 32 (T3 3-months posttreatment)



Table 1. Participants characteristics

	Intervention group (n=63)		Control group (n=63)	
	mean ± SD	n (%)	mean ± SD	n (%)
<i>Demographics</i>				
Age (years)	63.2 ± 8.4		63.9 ± 12.4	
Sex (female)		49 (77)		46 (73)
Educational level				
Primary level		12 (19.4)		12 (19)
Secondary level		29 (46.8)		32 (50.8)
College/university		21 (33.9)		19 (30.2)
<i>Clinical variables</i>				
Duration of knee symptoms, years	8.59 ± 8.6		9.4 ± 9.3	
BMI kg/m <sup>2</sup>	36.0 ± 6.8		35.0 ± 7.6	
Clinical diagnosis of KOA				
Unilateral		12 (19)		12 (19)
Bilateral		51 (81)		51 (81)
Radiographic severity of knee				
K/L grade 0/1		26 (41.3)		23 (36.5)
K/L grade 2		19 (30.2)		17 (27.6)
K/L grade 3		10 (15.9)		9 (14.3)
K/L grade 4		8 (12.7)		14 (22.2)
Total number of comorbidities (CIRS score ≥2) (range 0-12)				
1		31 (49.2)		24 (38.1)
2		17 (27.6)		21 (33.3)
≥3		15 (23.8)		18 (28.9)
Comorbidities of inclusion				
Cardiac diseases		24 (38)		21 (33)
Diabetes type 2		10 (15)		9 (14)
COPD		20 (31)		19 (30)
Obesity (BMI ≥30)		41 (65)		36 (57)
Use of pain medication (incl. NSAIDs)		50 (79.4)		48 (76.2)
Use of walking device		23 (36.5)		18 (28.6)
Mal-alignment of knee (≥5° varus or valgus)*		49 (77.8)		43 (68.3)
<i>Physical Functioning</i>				
WOMAC physical functioning (0-68)	35.1 ± 11.9		31.0 ± 12.3	
6-minute walking test (meters)	406.3 ± 107.6		406.4 ± 116.9	
SF 36 physical functioning (0-20)	18.4 ± 4.1		18.8 ± 4.1	
Get Up and Go test (sec) median (IQR)	12.1 (10.4; 14.5)		12.4 (10.4; 15.4)	
Stairclimbing test (sec) median (IQR)				
Ascend	7.5 (5.7; 11.4)		7.7 (6.3; 9.9)	
Descend	8.3 (6.0; 13.2)		8.5 (6.6; 12.5)	
LAPAQ total activity (moderate activity) median (IQR)	57.9 (23.6; 101.4)		45.7 (23.9; 64.3)	
Upper leg muscle strength (Nm/kg)*	0.65 ± 0.29		0.62 ± 0.34	
<i>Pain</i>				
NRS knee pain severity (0-10)	6.4 ± 1.8		5.9 ± 2.1	
WOMAC pain (0-20)	10.1 ± 3.4		9.4 ± 3.5	
<i>Frailty</i>				
EFIP (0-1)	0.3 ± 0.1		0.2 ± 0.1	
<i>Psychological functioning</i>				
HADS Depression and Anxiety (0-21)	11.3 ± 6.6		10.0 ± 6.8	

BMI Body Mass Index. CIRS Cumulative Illness Rating Scale. COPD Chronic Obstructive Pulmonary Disease. EFIP Evaluative Frailty Index for Physical activity. HADS Hospital Anxiety and Depression Scale. K&L Kellgren & Lawrence grade. LAPAQ LASA Physical Activity Questionnaire. NRS Numeric Rating Scale. NSAID Non-Steroidal Anti-Inflammatory Drugs. SD Standard Deviation. SF36 Short Form 36. WOMAC Western Ontario and Mc Master Universities Osteoarthritis Index. \*data from the Index Knee.

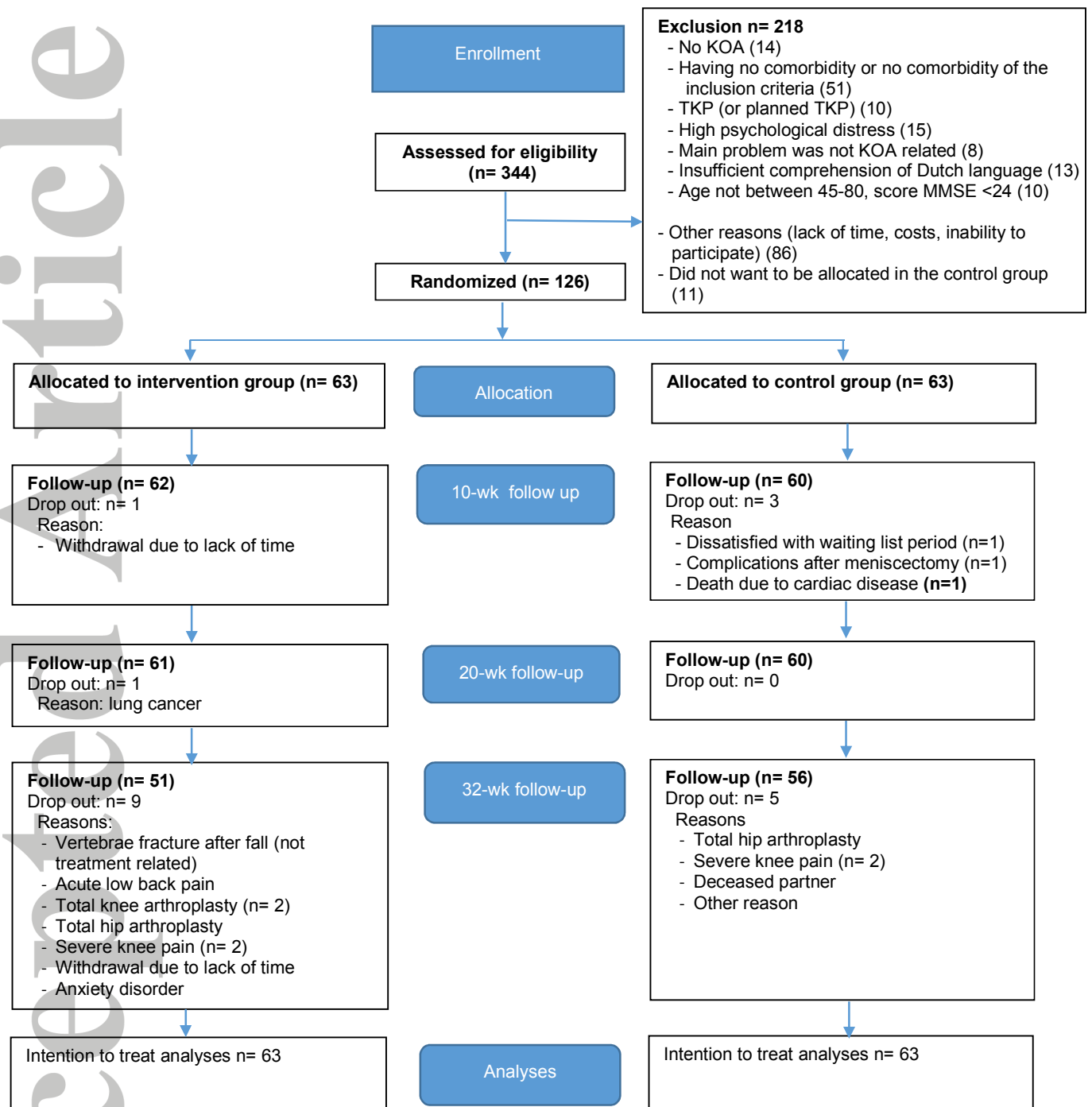
Table 2. Comorbidity-related adaptations to the exercise program

General comorbidity-related adaptations	100%
extended intake procedure: identification of comorbidity related contraindication and restrictions for exercise therapy by history taken and physical examination	
extended training program of 20 weeks (as opposed to 12 weeks which is regular in our center)	
during and after every training session therapists monitored symptoms and clinical parameters related to comorbidity and adapted the exercise program when required	
Exercise program: adaptations of FITT factors	76%
frequency (number of repetition per exercise set)	15%
intensity of exercises (exercise load)	76%
time (duration of exercise session)	17%
type of exercises	52%
Additions to exercise program	96%
coaching on body weight reduction	76%
coaching on fear of exertion	20%
education related to the comorbid disease and exercise	69%
Other adaptations	
consulting a medical specialist or GP about the comorbid disease (eg, medication or high blood pressure or trainability of the patient)	24%
monitoring blood glucose levels before and after the training and in the evening in patients with diabetes	7.4%
postponement of the training session (eg, high blood pressure, pain on the chest, dyspnea)	17%
referred to a dietician	13%
FITT factors: Frequency, Intensity, Time, Type	

Table 3. Outcome measures by group at different time-points (mean ± SD) and group differences over time (ITT)

	Baseline		10-wk FU		20-wk FU		32-wk FU		Group differences over time (10, 20, 32-wk FU) B (95% CI)*
	IG	CG	IG	CG	IG	CG	IG	CG	
<b>Primary outcomes</b>									
WOMAC-pf (0-68)	35.1 ± 11.9 n=63	31.0 ± 12.3 n=63	30.4 ± 11.6 n=60	32.9 ± 11.2 n=55	26.3 ± 12.7 n=59	31.4 ± 13.4 n=59	23.5 ± 13.1 n=51	31.4 ± 12.6 n=56	-7.43 (-9.99, -4.87)‡
6-minute walk test (meters)	406.3 ± 107.6 n=63	406.4±116.9 n=63	440.6 ± 96.7 n=61	423.4± 115.5 n=53	448.0± 102.5 n=56	416.5± 116.9 n=58	465.3± 93.9 n=48	423.0± 114.8 n=55	34.16 (17.68, 50.64)‡
<b>Secondary outcomes</b>									
NRS pain week (0-10)	6.4 ± 1.8 n=63	5.9 ± 2.1 n=63	5.3 ± 1.9 n=60	5.7 ± 2.3 n=55	4.3 ± 2.0 n=59	5.8 ± 2.2 n=59	4.7 ± 1.9 n=51	6.2 ± 2.1 n=56	-1.41 (-1.87, -0.95)‡
WOMAC pain (0-17)	10.1 ± 3.4 n=63	9.4 ± 3.5 n=63	8.4 ± 3.0 n=60	9.1 ± 3.6 n=55	6.9 ±3.4 n=59	8.8 ± 4.2 n=59	6.6 ± 3.6 n=51	8.6 ± 3.6 n=56	-1.78 (-2.65, -0.91)‡
GUG (seconds)	13.6 ± 5.6 n=63	13.5 ± 5.5 n=63	12.0 ± 3.4 n=61	12.9 ± 4.3 n=55	11.9 ± 3.6 n=56	13.0± 4.4 n=58	11.4 ± 3.0 n=48	12.8± 3.7 n=55	-1.35 (-2.16, -0.55)‡#
Stair climbing up (seconds)	10.1 ± 6.9 n=63	9.2 ± 4.7 n=63	8.6 ± 6.7 n=61	11.4 ± 14.7 n=55	7.7 ± 4.3 n=55	8.7± 4.4 n=58	7.4 ± 3.8 n=47	10.0 ± 9.6 n=55	-2.41 (-4.40, -0.43)£#
Stair climbing down (seconds)	10.7 ± 7.2 n=63	11.0 ± 6.6 n=63	9.6 ± 8.0 n=61	11.6 ± 12.5 n=55	8.3 ± 4.4 n=55	9.8 ± 5.5 n=58	7.6 ± 3.8 n=47	9.7 ± 4.9 n=55	-1.64 (-3.18, -0.91)£#
SF36 subscale pf (score 0-20)	18.4 ± 4.1 n=63	18.8 ± 4.1 n=63	n/a	n/a	20.8 ± 4.5 n=59	18.9 ± 5.0 n=59	21.4 ± 4.5 n=50	18.9 ± 4.7 n= 55	2.19 (1.10, 3.28)‡
PSFL (performance of activities 0-10)**	6.7 ± 1.4 n=63	6.6 ± 1.3 n=63	n/a	n/a	4.2 ± 2.1 n=57	5.8 ± 1.7 n=58	4.1 ± 2.2 n=50	5.9 ± 1.8 n=55	-1.59 (-2.19, -0.99)‡
WQ35 (walking, 0-100)	40.2 ± 23.3 n=61	39.76 ± 23.2 n=63	n/a	n/a	30.9 ± 25.2 n=59	38.4 ± 24.1 n=58	29.9 ± 25.4 n=51	34.9 ± 22.5 n=55	-6.84 (-14.94, 1.26)‡#
CTQ15 (stairclimbing, 0-100)	51.4 ± 17.9 n=51	51.2 ± 16.7 n=56	n/a	n/a	42.7 ± 20.3 n=52	48.8 ± 18.2 n=50	40.3 ± 22.6 n=47	48.1 ± 18.1 n=46	-6.10 (-13.41, 1.21)‡
R&SQ39 (rising and sitting down, 0-100)	51.6 ± 27.2 n=56	45.5 ± 22.8 n=61	n/a	n/a	39.2 ± 26.1 n=55	45.9 ± 25.7 n=52	38.5 ± 26.7 n=48	43.8 ± 25.7 n=52	-10.20 (-15.48, -4.92)‡#

CG. Control group. CI confidence interval. GUG Get up and Go. IG Intervention group. ITT Intention to treat. NRS Numeric Rating Scale. n/a not applicable. SD standard deviation. SF36 subscale pf Short Form 36 subscale physical functioning. PSFL Patient specific Functioning List. WOMAC-pf Western Ontario and Mc Master Universities Osteoarthritis Index, subscale physical functioning. \*Adjusted for baseline value of outcome variable difference; # 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 . \*\* average score of 3 activities that were most relevant and problematic for patient; £ p <.05; ‡ p <.001; † p >.05. Overall, a lower score indicates an improvement in physical functioning or pain with exception of the 6-minute walk test and the subscale pf of the SF-36. For all other secondary outcome measures see appendix 3



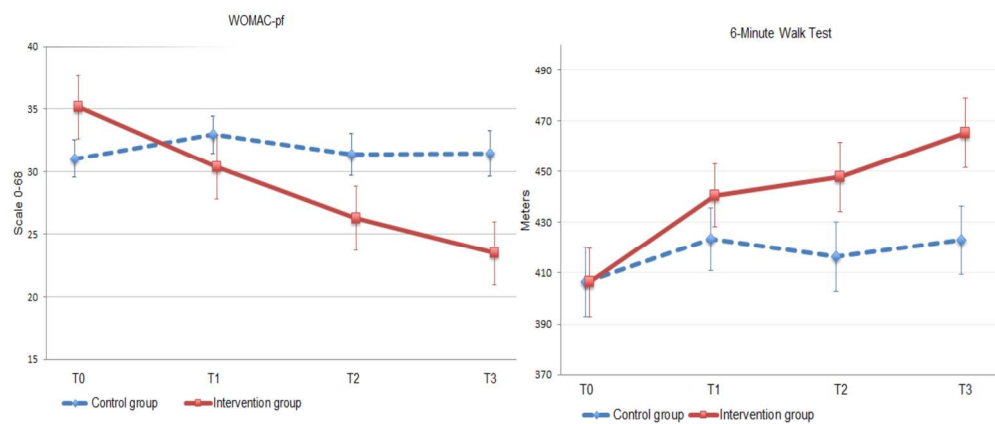


Figure 2. Mean and standard error of WOMAC-pf and 6-Minute Walk Test at baseline (T0), week 10 (T1 midtreatment), week 20 (T2 directly after treatment), and week 32 (T3 3-months posttreatment)

202x90mm (300 x 300 DPI)

Accepted

## Appendix 1 Regular exercises for knee osteoarthritis (OA)

**General information**

- Regular knee OA exercises, based on the protocol as developed by Knoop et al (1).
- The training intensity is monitored with the Borg Rate of Perceived Exertion (RPE) scale 6-20 (2).
- Supervised exercise therapy twice a week and home exercises for five days a week
- Education about OA disease, joint protection and risk factors for functional decline, and advice on self-management are provided.
- Exercise intensity and knee loading are gradually increased every week, to a maximal level that is possible for the patient. When exercise-induced knee pain persists during rest between exercise sets, or for more than one day after exercising, exercise intensity and/or knee loading is decreased in future sessions.
- Stability, flexibility or range of motion exercises of the lower limb are added on indication.
- Functional, patient tailored exercises targeting specific daily activities, which are indicated to be relevant and problematic by the patients themselves are added to the program
- Warming up 5-10 minutes
- Cooling down 5-10 minutes

Type	Intensity	Duration	Exercise (See below)
Aerobic exercise	50-80% of VO <sub>2</sub> max/HRR/HRmax/ maximal workload (moderate intensity) 30-<40% or VO <sub>2</sub> max/HRR/HRmax/ maximal workload (light intensity) is appropriate for individuals with arthritis who are deconditioned	Start with short bouts of 10 min (or less if needed), according individual's pain levels	1, 11, 15, 16, 17, 18, 19, 20
Endurance muscle strength exercise lower limb	40-60% of 1-RM	2-4 sets of 15-20 reps, with rest intervals of 2-3 min between each set of reps	1, 4, 6, 8 9, 11, 14, 16, 18, 20
Maximum muscle power training lower limb	60-80 % of 1RM	The selected resistance should permit the completion of 2-4 sets of 8-12 repetitions, or the number needed to induce muscle fatigue but not exhaustion), rest intervals of 2-3 min between each set of reps	4, 6, 8, 11, 14, 16, 20
Flexibility/range of motion exercises of the lower limb	Stretch to the point of feeling tightness or slight discomfort	2-4 repetitions, 2 or three times per week. Hold a static stretch 10- 30 seconds	2, 3

**Exercise**

1. warming up and cooling down on bicycle ergometer or rowing ergometer
2. stretching of mm. quadriceps femoris, mm. hamstring, m. iliopsoas, m. gastrocnemius, m. soleus
3. isometrically contracting mm. quadriceps femoris while sitting on bench or floor with leg stretched
4. straight leg raising while sitting on bench/floor with leg stretched
5. flexion-extension of the unloaded knee (0-30° knee flexion) while standing in static stride position (weight loading in front knee)
6. squats (progress in angle of knee flexion up to 90° )
7. moving bodyweight from knee to knee, while standing in stride position

8. making a forward lunge step (0-30° up to 0-60° knee flexion)
9. making a forward lunge step under sideways knee load, by using a dynaband (0-30° up to 0-60° knee flexion)
10. making a forward lunge step ending in one leg standing position (0-30° knee flexion)
11. knee flexion –extension while standing on one leg on a step (non-standing foot dropping below step level, sideways)
12. one leg standing (0-30° knee flexion)
13. standing on a balance board, with two or one leg (0-30° knee flexion)
14. leg press workout
15. cycling work out
16. stepping workout
17. cross trainer work out
18. rowing workout
19. tread mill workout
20. training of daily activities like walking on a flat or unstable surfaces, ascending/descending stairs, sitting down/rising up from a chair, or other activities that were reported to be relevant and problematic by patients at baseline

**Treatment goals (ICF-classification)**

21. b620: proprioceptive function (exercise 5, 6, 7, 8, 11, 12)
22. b710: mobility of joint functions (exercise 2, 3, 4, 7)
23. b715: stability of joint functions (exercise 5, 6, 7, 10, 11, 13, 14, 16, 17, 19, 20)
24. b740: muscle endurance functions (exercise 1, 4, 6, 8, 10, 14, 15, 16, 18)
25. b760: control of voluntary movement functions (exercise 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20)
26. b410: heart functions (exercise 1, 15, 16, 17, 18, 19)
27. b445: respiration functions (exercise 1, 15, 17, 18, 19)
28. d450: walking (exercise 19, 20)
29. b730: muscle power functions (exercise 6, 16, 14)
30. b740: muscle endurance functions
31. other daily activities, like stair ascending, stair descending, rising up from a chair, sitting down on chair, or other activities relevant and problematic for a patient (exercise 20)

ICF = International Classification of Functioning, Disability and Health

**Reference**

1. Knoop J, Dekker J, van der Leeden M, Van der Esch M, Thorstensson CA, Gerritsen M et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. *Osteoarthritis Cartilage* 2013;21:1025-34.
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Appendix 2 Adaptations to the exercise program
<p><b>General information</b></p> <ul style="list-style-type: none"><li>• The full protocol provides information regarding the comorbid disease (pathogenesis), medication use, medication use in relation to exercise, history taking, physical examination, and adaptation to the OA exercises. In this appendix we summarize the topics which are addressed.</li><li>• The protocol we previously developed, consists of a diagnostic phase and an intervention phase (1). Each step in the protocol encourages clinical reasoning in order to tailor the diagnostic and intervention phase to the individual person.<ul style="list-style-type: none"><li>- The <i>diagnostic phase</i> (one hour intake procedure) includes an anamnesis, physical examination, establishment of treatment goals, and determination of the treatment strategy. During the anamnesis, OA-related problems, comorbidity-related restrictions and contraindications for exercise therapy are identified. Absolute contraindications are defined as conditions that would lead to the immediate exclusion of the participant from exercise therapy (eg, unstable angina). Restrictions (or relative contraindications) are defined as impairments which limit the application of exercise therapy (eg, dyspnea in patients with COPD) (2). Thereafter, a clinical decision is made as to whether physical examination is possible, or whether the referring physician needs to be consulted because of contraindications for physical examination or the need for further medical information. If there are no contraindications for physical examination, comorbidity-related examination is performed according to the protocol. Subsequently, a decision is made as to whether there are contraindications or restrictions for exercise therapy. In case of a contraindication, referral to a physician is indicated. If there are comorbidity-related restrictions for exercise therapy, a comorbidity-adapted program is indicated. In this phase, the therapist also considers whether referral to professionals in other disciplines (eg, a dietician) is indicated.</li><li>- In the <i>intervention phase</i>, regular knee osteoarthritis exercises, based on the Dutch guideline (3) and described in detail by Knoop et al. (4) (see also appendix A) are adapted to the comorbid disease, taking into account restrictions and contraindications due to the comorbid disease. Exercise therapy is adapted by changing frequency, intensity, timing and type of exercise or by adding educational (eg, providing comorbidity-related information on exercise therapy) or coaching strategies (eg, coaching for reducing body weight or coaching for fear of exertion) (1). The exact adaptations depend on restrictions for exercise therapy identified by the therapist in the diagnostic phase (anamnesis and physical examination). In addition, during every training session, comorbidity-related symptoms and clinical parameters are monitored, and exercise is adapted if required. The specific options for adaptations to OA exercises are listed in the protocol.</li></ul></li><li>• The adaptations to history taking, physical examination and the OA exercises are based on principles described in comorbidity-specific exercise guidelines (eg, cardiac rehabilitation (5)) (6 -15), ACSM guideline (16,18), medical guidelines (19) and expert opinion.</li><li>• Exercise therapy comprised a 20-week individualized (tailored) knee osteoarthritis exercise program, with two sessions of 30 to 60 minutes a week under supervision of a physical therapist.</li><li>• The full protocol is available from the first author. In a previous publication the development of the protocol is described (1).</li></ul>



Cardiac disease
History taking
<ul style="list-style-type: none"> <li>• Medical diagnosis: Myocardial infarction, angina pectoris, heart failure, cardiac arrhythmias, mitral valve disease, other diseases</li> <li>• Year of diagnosis</li> <li>• Other medical diagnoses</li> <li>• Relevant diagnostic and prognostic referral information on patient physical condition</li> <li>• If present settings of Implantable cardiac defibrillator (ICD) (safe heart rate range for exercise) or pacemaker</li> <li>• Is the patient's physical functioning affected by the cardiac disease?</li> <li>• Is the patient's exercise capacity objectively reduced in relation to future functioning?</li> <li>• Results of maximum or symptom limited exercise test</li> <li>• Risk profile (e.g. smoking, alcohol use, physical inactivity, elevated blood cholesterol level, high blood pressure, overweight or obese, diabetes)</li> <li>• All medication (type and dosage)</li> <li>• Fear of exertion</li> <li>• Knowledge of the disease and exercise options</li> </ul>
Specification for heart failure:
<ul style="list-style-type: none"> <li>• Details on the severity of the heart failure (expressed as left ventricular ejection fraction (LEVF) and New York Heart Association (NYHA) class and <math>VO_{2peak}</math> as a percentage of the predicted value)</li> <li>• The remaining left ventricular function (ejection fraction), the severity of any valve disease, and the presence of ischemia and status of the coronary vessels, arrhythmias and conduction defects</li> <li>• Presence or absence of an implantable cardioverter defibrillator (ICD) or (mostly biventricular) pacemaker (type, settings);</li> <li>• Risk of decompensation</li> <li>• Results of maximum or symptom-limited exercise test with gas analysis</li> </ul>
Absolute contraindications for physical examination and participation in the training program include:
<ul style="list-style-type: none"> <li>• Progressive increase in heart failure symptoms</li> <li>• Severe ischemia of the cardiac muscle upon exertion</li> <li>• Respiratory frequency of more than 30 breaths per minute</li> <li>• Heart rate at rest &gt;110 bpm, <math>VO_2</math> max, 10 mL/kg/minute; ventricular tachycardia upon increasing exertion</li> <li>• Fever; acute systemic diseases</li> <li>• Recent pulmonary embolism (&lt;3 months ago) causing severe hemodynamic strain</li> <li>• Thrombophlebitis; acute pericarditis or myocarditis</li> <li>• Hemodynamically serious aortic stenosis or mitral valve stenosis</li> <li>• Presence of unstable angina, for example, pain in the chest at rest or pain that does not react to specific medication</li> </ul>

<ul style="list-style-type: none"><li>• NYHA functional classification class 4</li><li>• Myocardial infarction less than 3 months before the start of the training program</li><li>• Atrial fibrillation with rapid ventricular response at rest (&gt;100 bpm)</li><li>• Weight gain of &gt;2 kg within a few days, whether or not accompanied by increased dyspnea at rest is related to weight gain.</li></ul>	
Physical examination	
<ul style="list-style-type: none"><li>• Check relevant information: The patient’s current physical condition, based on the maximum or symptom-limited exercise test (with gas analysis) (spiro-ergometry) and referral information provided by cardiologist</li><li>• Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test) (20-23)</li><li>• Assess blood pressure (type OMRON M7) in rest and after the exercise test</li><li>• Are there any other factors that could affect the patient’s ability to improve physical condition, such as:<ul style="list-style-type: none"><li>- Medication</li><li>- Dyspnea or fatigue</li><li>- Fear of exertion</li></ul></li></ul>	
Adaptations to the exercise program	
General adaptations	
<ul style="list-style-type: none"><li>• Use the results of a maximum or symptom-limited exercise test to calculate the individual aerobic exercise intensity in patients with cardiac problems. (If the patient is using beta blockers, the exercises should be based on the results of the maximum or symptom-limited exercise test with beta blocker use). The optimized exercise zone can be calculated using the Karvonen formula, which calculates the exercise heart rate as a percentage of the heart rate reserve (the difference between the maximum heart rate and the heart rate at rest), added to the resting heart rate. Patients should start with 2 weeks of exercise at 40%–50% of their VO<sub>2</sub> max then gradually raise the training intensity from 50% to 80% of their VO<sub>2</sub> max or VO<sub>2</sub> reserve.</li><li>• Base the exercise intensity on a percentage of the maximum capacity expressed in watts or METs and/or a Borg RPE-scale (6–20) (24) if the patient’s heart rate does not rise sufficiently during the maximum or symptom-limited exercise test (see Load intensities expressed in various training load measures as reported by the American College of Sports Medicine, Pollock et al 1990 (25)).</li><li>• Continue monitoring and observing of the individual response of the patient and the way they tolerate the exercise load, and check whether the patient shows any signs of excessive strain.</li><li>• Perform interval training for patients in poor physical condition instead of continuous aerobic training.</li><li>• Perform dynamic instead of static strength exercise to prevent high blood pressure</li><li>• Reduce the training intensity in warm climatic conditions.</li></ul>	
Exercise restrictions	Adaptations
Coronary disease <ul style="list-style-type: none"><li>• Pain in the chest during exercise</li></ul>	<ul style="list-style-type: none"><li>• Terminate exercise, ask patient to sit down in chair, wait for reduction of angina. If no reduction: ask if patient uses nitro spray, if yes: apply nitro spray. If no reduction, confer with medical</li></ul>

<ul style="list-style-type: none"> <li>• Cardiac arrhythmias during exercise (high heart frequency disproportionate to the level of exertion, irregular heart rate frequency, changes in known heart arrhythmias), abnormal changes in blood pressure during exercise during exercise (diastolic change <math>\geq 20</math> mmHg); reduction of systolic blood pressure during exercise (<math>&gt;10</math> mmHg), fainting; dizziness; vegetative reactions (eg, excessive perspiring, pallor), shortness of breath disproportionate to exertion, abnormal fatigue disproportionate to exertion</li> <li>• Insufficient knowledge of the disease and exercise options</li> <li>• Fear of exertion</li> </ul> <p>heart failure</p> <ul style="list-style-type: none"> <li>• Known left ventricular ejection fraction of <math>&lt;30\%</math></li> </ul> <ul style="list-style-type: none"> <li>• Level 3 NYHA (New York heart Association Classification)</li> <li>• Reduced recovery capacity</li> </ul>	<p>specialist.</p> <ul style="list-style-type: none"> <li>• Terminate exercise, ask patient to sit down in chair and confer with medical specialist</li> </ul> <ul style="list-style-type: none"> <li>• Provide information about disease and exercise options</li> <li>• Coaching to improve confidence in exercising; i.e. consider starting at lower exercise intensity and give positive rewarding feedback</li> </ul> <ul style="list-style-type: none"> <li>• see coronary disease</li> <li>• Prolong the warming-up and cooling-down sessions to decrease the risk of cardiac decompensation.</li> <li>• Be careful with Valsalva Maneuvers, changing body position such as a supine to standing position because of reduced capacity to adapt blood pressure</li> <li>• Start at lower exercise intensity and consider high intensity interval training (HIIT). Avoid a rapid increase in the peripheral resistance training in patients with heart failure, as this increases the afterload strongly and the risk of decompensation. For improving muscle strength, start with 2 weeks on 30%–40% of 1RM and then gradually increase the resistance from 50% to 70%–80% of 1RM.</li> <li>• Start with resistance training to reduce peripheral blood pressure and cardiac load before aerobic training</li> <li>• Monitor recovery to normal ADL functioning within 3-4 hours after exercise. In case of reduced recovery, reduce training intensity</li> </ul>
<b>Diabetes type 2</b>	
History taking	
<ul style="list-style-type: none"> <li>• Medical diagnose</li> <li>• Year of diagnose</li> <li>• Other medical diagnoses</li> </ul>	

<ul style="list-style-type: none"><li>• Glycemic control:<ul style="list-style-type: none"><li>- Laboratory values (glucose, HbA1c)</li><li>- Medication treatment diabetes (type and dosage):</li><li>- Check if the used Glucose-Lowering Medications interact with the exercise</li></ul></li><li>• Other medication (type and dosage):</li><li>• Risk profile (e.g. smoking, alcohol use, physical inactivity, elevated blood cholesterol level, high blood pressure, overweight or obese, Complications due to diabetes: cardiovascular, neurologic (peripheral and autonomic), nephrologic, retinal</li><li>• Additionally, maximal ergo spirometry testing with ECG monitoring should be done in patients less than 30 years or more than 40 years of age and with the presence of one of the following criteria: diabetes diagnosed more than 10 years previously, hypertension, cigarette smoking, dyslipidemia, retinopathy, or nephropathy. In the case of diagnosed or suspected coronary artery disease, peripheral arterial disease, cerebrovascular disease, autonomic neuropathy, or severe nephropathy (renal failure), such exercise testing also is indicated.</li><li>• Is the patient’s physical functioning affected by diabetes?</li><li>• Knowledge of the disease and exercise options</li><li>• Fear of exertion</li><li>• Refer to physician when: development or worsening of hypertension, angina pectoris, heart rhythm disturbances, development or worsening of resting tachycardia, development or worsening of intermittent claudication, development or worsening of fasting hyperglycemia, frequent hypoglycemic episodes, development or worsening of wounds in lower extremities, cachexia, autonomic neuropathy, or development or worsening of vision disturbances</li></ul>
Absolute contraindications for participation in the training program include
n.a
Physical examination
<ul style="list-style-type: none"><li>• Evaluate of peripheral vascular status: assessment of pain, changes in extremity color, temperature, pulsations of peripheral arteries (dorsalis pedis, tibialis posterior). When a patient complains of having peripheral muscle pain that is provoked by walking and disappears during subsequent recovery, this complaint might indicate intermittent claudication.</li><li>• Check for presence of peripheral neuropathy: Test peripheral sensibility: monofilament (Semmes-Weinstein) (26). During this assessment, use a 10-g monofilament for cutaneous pressure assessment, and a needle to assess pain sensation. Test vibratory sensitivity (8).</li><li>• Check for presence of autonomic neuropathy: Test heart rate in rest (resting (60–100 bpm) and exercise (rate and rhythm) heart rate), blood pressure and symptoms of orthostatic hypotension (a decrease in systolic blood pressure of greater than 30 mm Hg or a decrease in diastolic blood pressure of greater than 10 mm Hg when changing from a supine to standing position). A slowed heart rate recovery after exercise also is typically associated with autonomic neuropathy.</li><li>• Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test) (20-23)</li></ul>

<ul style="list-style-type: none"> <li>Assess blood pressure (type OMRON M7) at start and end of exercise session (140/90 mm Hg). In the case of hypertension (blood pressure &gt;140/90 mm Hg), heart rhythm disturbances, tachycardia (heart rate &gt;100 bpm), and bradycardia (heart rate &lt;60 bpm) with clinical symptoms, such patients should receive further attention and clinical examination.</li> <li>Are there any other factors that could affect the patient's ability to improve physical condition, such as:             <ul style="list-style-type: none"> <li>Medication</li> <li>Dyspnea or fatigue</li> <li>Fear of exertion</li> </ul> </li> </ul>	
Adaptations to the exercise program	
General adaptations <ul style="list-style-type: none"> <li>Ensure adequate hydration and carbohydrate intake before exercise session.</li> <li>Check patients with type 2 diabetes regularly for wounds and sensory defects.</li> <li>Perform interval training for patients in poor physical condition instead of continuous aerobic training</li> <li>Fever: postpone exercise training until body temperature is restored</li> <li>Refer to physician in case of development or worsening of conditions that may be related to diabetes, such as hypertension, angina pectoris, heart rhythm disturbances, resting tachycardia, intermittent claudication, fasting hyperglycemia, frequent hypoglycemic episodes, wounds in lower extremities, cachexia, autonomic neuropathy, or vision disturbances.</li> </ul>	
Exercise restrictions	Adaptations
<ul style="list-style-type: none"> <li>Use of medication which increase in blood insulin level (insulin-dependent patients)</li> <li>Poorly regulated diabetes characterized by a high (&gt;7%) HbA1c and or highly variable blood sugar levels (high or low) and frequent</li> </ul>	<ul style="list-style-type: none"> <li>Monitor blood glucose levels before and after the exercise session and in the evening in case of insulin-dependent diabetes patients. Occurrence of induced hypoglycemia during exercise and up to 48 hours afterwards or 72 hours after intense strength training</li> <li>Lower medication/insulin therapy in case of low blood glucose level (&lt;4.2 mmol/L, &lt;75 mg/dL) or symptoms of hypoglycemia before exercise training</li> <li>Elevate carbohydrate intake in case of low blood glucose level (&lt;5.5 mmol/L, 100 mg/dL) or symptoms of hypoglycemia before exercise training. Adjust training modalities (lower total exercise energy expenditure in case of low blood glucose level or symptoms of hypoglycemia;</li> <li>Postpone exercise training in case of blood glucose values <math>\leq 5</math> and <math>\geq 15</math> mmol/L or signs of hypoglycaemia. Regulation of blood glucose level is necessary (use medication diary).</li> <li>Confer with the medical specialist (internist) about medication use (type, dosage) and exercise. Monitor blood glucose levels before</li> </ul>

<p>hypoglycemia</p> <ul style="list-style-type: none"><li>• Delayed recovery when injured</li><li>• Foot ulcer (as a result of peripheral neuropathy)</li><li>• Sensory deficits (as a result of peripheral neuropathy)</li><li>• Retinopathy</li><li>• Nephropathy</li><li>• Autonomic neuropathy with impaired cardiovascular response to exercise, response to dehydration, thermoregulation, postural hypotension, and /or decreased maximum aerobic activity</li><li>• Insufficient knowledge of the disease, medication and exercise</li><li>• Fear of exertion</li></ul>	<p>and after the exercise session and in the evening. Be aware of signs of hypo/hyperglycemia and complications due to diabetes.</p> <ul style="list-style-type: none"><li>• Start with low exercise intensity and slowly increase</li><li>• Avoid weight bearing exercises when wounds at the feet are present.</li><li>• Refer for foot care if required.</li><li>• Be careful with exercises that require tactile feedback (e.g. balance) and consider providing exercises on machines (patients can have difficulties feeling where e.g. dumbbells are in his hands with the risk of dropping them).</li><li>• Avoid high-intensity training (&gt;80% of maximum oxygen uptake [VO<sub>2</sub>max]) and Valsalva Maneuvers</li><li>• Avoid hypertension (systolic blood pressure &gt; 180 mm Hg) during exercise.</li><li>• Regularly check heart rate and blood pressure in rest and during exercise. The patient's heart rate may not rise or abate sufficiently during or after the training.</li><li>• Provide information about disease and exercise options</li><li>• Coaching to improve confidence in exercising; i.e. consider starting at lower exercise intensity and give positive rewarding feedback</li></ul>
<b>COPD</b>	
History taking	
<ul style="list-style-type: none"><li>• Medical diagnose</li><li>• GOLD stadium: 1, 2, 3, 4</li><li>• Year of diagnose</li><li>• Other medical diagnoses</li><li>• Medication</li><li>• Results of maximum or symptom-limited exercise test with gas analysis</li><li>• Sensations of dyspnea at rest or during exercise</li><li>• Signs of impaired exercise capacity</li><li>• Is the patient's physical functioning affected by COPD?</li><li>• Signs of impaired mucus clearance</li><li>• Natural course of the symptoms and the disorder</li><li>• Recurrent respiratory infections with mucus retention</li></ul>	

<ul style="list-style-type: none"> <li>• Presence of factors that are influencing symptoms and their progression</li> <li>• Fatigue</li> <li>• Fear of exertion or fear of breathlessness</li> </ul>	
Absolute contraindications for participation in the training program include	
<ul style="list-style-type: none"> <li>• Pneumonia and exceptional loss of bodyweight (10% in the past half year or &gt;5% in the past month).</li> </ul>	
Physical examination	
<ul style="list-style-type: none"> <li>• Check relevant information: The patient's current physical condition, based on the maximum or symptom-limited exercise test with gas analysis (spiro-ergometry) and referral information provided by pulmonologist. Typical items in the lung function assessment of these patients are elevated total lung capacity (&gt; 110% of predicted value), functional residual capacity (&gt; 150% of predicted value, reduced Tiffenau index (&lt; 40%) and shape of the forced flow-volume curve.</li> <li>• Assess functional exercise capacity (Shuttle walk Test, Six Minute Walk Test) (20-23)</li> <li>• Assess blood pressure (type OMRON M7)</li> <li>• Clinical inspection (dyspnea, leaning forward position, cyanosis, muscle atrophy, peripheral edema), chest wall configuration (hyperinflation, deformities), respiratory movement (respiratory rate, paradoxical thoracic-abdominal movement at rest and during exercise, accessory respiratory muscle activity, activity of abdominal muscles)</li> <li>• Are there any other factors that could affect the patient's ability to improve physical condition, such as:             <ul style="list-style-type: none"> <li>- Medication</li> <li>- Dyspnea or fatigue</li> <li>- Fear of exertion or fear of breathlessness</li> </ul> </li> </ul>	
Adaptations to the exercise program	
General adaptations	
<ul style="list-style-type: none"> <li>• Use the results of symptom limited exercise test with gas analysis to calculate the individual aerobic exercise intensity.</li> <li>• Start with interval training in patients with COPD with ventilation limitation or impaired oxygen transport in the lungs (hypoxemic [saturation &lt;90%]/hypocapnic [<math>\text{PaCO}_2</math> &gt;55 mmHg] during exercising). Start endurance training if walking on 70% of maximum watts level for at least 10 minutes is possible.</li> <li>• Use the Borg scale (0-10) to measure Dyspnea during exercise (27). A dyspnea rating between 4 and 6 on a scale of 0-10 is the recommended exercise intensity.</li> <li>• Check saturation level: <math>\text{O}_2</math> saturation (<math>\text{SaO}_2</math>) should remain <math>\geq 90\%</math> during exercising (and should not fall by <math>\geq 4\%</math>).</li> <li>• Be aware of poor nutritional status</li> </ul>	
Exercise restrictions	Specific adaptations
<ul style="list-style-type: none"> <li>• Peripheral muscle atrophy and weakness</li> <li>• Reduction of respiratory muscle function</li> </ul>	<ul style="list-style-type: none"> <li>• Pay extra attention to strength training</li> <li>• Add inspiratory muscle training (IMT) if respiratory muscle weakness is present (or consider referral to a specialized therapist)</li> </ul>

<ul style="list-style-type: none"><li>• Insufficient control of respiration and cough techniques</li><li>• Present exacerbation of the disease</li><li>• Severe dyspnea</li><li>• Insufficient knowledge of the use of medication combined with exertion</li><li>• Fear of exertion/fear of breathlessness</li></ul>	<p>for training of pulmonary impairments).</p> <ul style="list-style-type: none"><li>• Teach coughing/huffing/breathing exercise dependent on severity and causes of obstruction. Give advice and exercises targeting body position and breathing if hyperinflation is present. Breathing exercises aimed at reduction of (dynamic) hyperinflation and improvement of gas exchange: pursed lips breathing (PLB), slow and deep breathing, and active expiration.</li><li>• Interval training, resistance training, or transcutaneous neuromuscular electrical stimulation can be used to immediately reactivate patients.</li><li>• Based on evaluation of the exercise limitations: Reduce training intensity or consider interval training and resistance training. It is recommended to use both upper limb and lower limb resistance weight training at an intensity of at least 60% to 80% of the one-repetition maximum. Two to 3 sets of 8 to 12 repetitions per muscle group are preferred. Consider breathing exercise and exercise targeting body position.</li><li>• Provide information about disease and exercise options and medication use</li><li>• Coaching to improve confidence in exercising; i.e. consider starting at lower exercise intensity and give positive rewarding feedback Coach the patient if there is presence of fear of exercising due to breathlessness.</li></ul>
<b>Hypertension</b>	
History taking	
<ul style="list-style-type: none"><li>• Medical diagnose</li><li>• Year of diagnose</li><li>• Medication</li><li>• Blood pressure last time</li><li>• Is the patient’s physical functioning affected by hypertension?</li></ul>	
Contraindications for participation in the training program include	
<ul style="list-style-type: none"><li>• Resting systolic blood pressure of &gt;180 mmHg or diastolic blood pressure of &gt;115 mmHg. Refer to physician.</li></ul>	
Physical examination	
<ul style="list-style-type: none"><li>• Blood pressure assessment (type OMRON M7)</li></ul>	



Adaptations to the exercise program	
<b>General adaptations</b> <ul style="list-style-type: none"> <li>• Be aware that medication to lower blood pressure, like beta blockers, can reduce maximal exercise tolerance and attenuate heart rate response to exercise.</li> <li>• Beta blockers and diuretics may adversely affect thermoregulatory function</li> <li>• Check blood pressure-lowering medication with physician. If adequate but still hypertensive, low-to-moderate intensity strength training should be performed instead of high-intensity strength training.</li> </ul>	
<b>Exercise restrictions</b>	<b>Adaptations</b>
<ul style="list-style-type: none"> <li>• Increased risk of high blood pressure, especially in case of left ventricular hypertrophy</li> <li>• Abnormal changes in blood pressure during exercise during exercise (diastolic change <math>\geq 20</math> mmHg); reduction of systolic blood pressure during exercise (<math>&gt;10</math> mmHg)</li> </ul>	<ul style="list-style-type: none"> <li>• If the plan is to perform moderate (40% <math>&lt; 60\%</math> <math>\text{VO}_2\text{R}</math>) to vigorous intensity (<math>\geq 60\%</math> <math>\text{VO}_2\text{R}</math>) first refer for a symptom-limited exercise test</li> <li>• Terminate exercise and refer to medical specialist</li> </ul>
Obesity	
History taking	
<ul style="list-style-type: none"> <li>• Medical diagnose</li> <li>• Year of diagnose</li> <li>• Other medical diagnoses</li> <li>• Body Weight</li> <li>• Duration of overweight or obesity</li> <li>• Is the patient's physical functioning affected by overweight or obesity?</li> <li>• Experience with body weight reduction/following a diet</li> <li>• Attitude and beliefs about food intake and diet</li> <li>• Food and nutrition related knowledge</li> <li>• Motivation to body weight reduction</li> <li>• Guidance needed to lose body weight (referral to a dietician)</li> </ul>	
Contraindications for participation in the training program include	
n.a.	
Physical examination	
<ul style="list-style-type: none"> <li>• Bodyweight (kg)</li> <li>• Height</li> <li>• Body Mass Index (BMI) = <math>\text{weight}(\text{kg})/\text{height}^2(\text{m}^2)</math>  Underweight = <math>&lt; 18.5</math>  Normal weight = 18.5–24.9  Overweight = 25–29.9 </li> </ul>	

<p>Obesity = BMI of 30 or greater</p> <ul style="list-style-type: none"><li>Assess blood pressure (type OMRON M7)</li></ul>	
Adaptations to the exercise program	
General adaptations	
<ul style="list-style-type: none"><li>Stimulate weight reduction due to overweight or obesity and/or refer to a dietician</li></ul>	
Exercise restrictions	Adaptations
<ul style="list-style-type: none"><li>Increased stress, pressure and pain in weight bearing joint</li><li>Shortness of breath</li><li>Poor thermoregulation during exertion</li><li>Fear of movement</li><li>Lack of motivation for weight reduction</li></ul>	<ul style="list-style-type: none"><li>Reduce weight-bearing exercises because of increase in knee joint pain, consider aquatic based exercise</li><li>Reduce training intensity, consider interval training</li><li>Reduce the training intensity in warm climatic conditions</li><li>Coaching to improve confidence in exercising; i.e. consider starting at lower exercise intensity and give positive rewarding feedback</li><li>Provide information about weight loss and pain relief and exercise options. Stimulate and coach in weight reduction.</li></ul>

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### Appendix 3. Outcome

#### Participant characteristics

Baseline demographics and clinical variables were obtained (ie, age, sex, educational level, duration of knee symptoms, BMI, unilateral or bilateral KOA, Kellgren and Lawrence grade (K&L) (1), Cumulative Illness Rating Scale (CIRS) (2), use of pain medication, use of walking devices and mal-alignment of the knee. Body mass and height were measured in standing position with participants wearing their clothes, but no shoes. Body mass (kg) was measured at baseline, at 10, 20 and 32 weeks respectively. Body mass index was calculated using the standard formula ( $\text{kg/m}^2$ ).

#### Primary outcome measures.

Physical functioning was assessed by self-reported questionnaires and a performance-based measurement. Self-reported physical function was assessed by the Dutch translation of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), subscale physical function (3, 4). The WOMAC is a disease-specific, self-administered questionnaire, developed to study patients with hip osteoarthritis and knee osteoarthritis (KOA). The WOMAC subscale physical functioning consists of 17 questions scaled in a 5-point Likert (LK) scale. The maximum score in the LK scale is 68 points for physical function. Higher scores indicate more limitations in physical function. The WOMAC is widely used in clinical research, and has been shown to be reliable, valid, and responsive for use in patients with OA (3-5). The 6-minute walk test was carried out by patients on a 30 m walkway. Patients were instructed to walk their maximum distance in a 6-minute period of time. The total distance covered in meters during 6-minutes of walking was scored (6).

#### Secondary outcomes

*Serious adverse events.* Serious adverse events related to treatment and testing procedures were reported to the researcher by the treating PT or clinimetric assessors.

*Pain.* Knee pain severity during the last week was scored on an NRS ranging from 0 to 10 (0= no pain; 10= worst pain imaginable) (7). In addition, pain was also assessed with a subscale of the WOMAC (3, 4). The WOMAC subscale pain consists of 5 questions scaled in a 5-point Likert (LK) scale. The maximum score in the LK scale is 20 points for pain. Higher scores indicate more pain.

*Physical Functioning.* Physical functioning was measured using self-reported physical function questionnaires (ie subscale of the 36-Item Short-Form Health Survey (SF-36) (8), Patient-Specific Functioning Scale (PSFS) (9,10), Walking Questionnaire (WQ35) (11), Climbing stairs (CTQ15) (12), Questionnaire Rising and Sitting down (QR&S39)) (13) and two physical performance tests (ie Get Up and Go test (GUG) (14) and time to descend and ascend stairs) (15).

The subscale physical functioning of the SF-36 (8) was used to measure physical function (score 0-20), with a higher score indicating an improvement in physical functioning. The SF-36 is a widely applied generic instrument for measuring health status. The reliability (median reliability coefficient 0.85 for all subscales) for the SF-36 has been established (16, 17), and its validity has been shown in an elderly population, in which the instrument distinguished between those with and without poor health (18).

The PSFS was used to evaluate limitations in activities of the individual patient (9, 10). Participants were asked "Which activities do you perceive as important and were hampered by knee pain during the last week?". A list of activity suggestions was offered to support recall, and patients were allowed to provide other limited activities that were not on the list. Of these activities, the patient selected three main activities and ranked them in order of importance. The difficulty of performance of the main activities were scored by self-assessment on a numeric rating scale ([NRS from 0-10]: 0= no problems to perform the activity, 10= impossible to perform the activity). The PSFS is an efficient and valid measure for assessing limitations in activities and change in limitations in persons with knee dysfunction (10).

The Walking Questionnaire (WQ35) (11), Climbing stairs (CSQ15) (12), Questionnaire Rising and Sitting down (R&SQ39) (13) were used to assess specific lower-extremity related limitations in daily activities and have been validated in OA patients.

The Get Up and Go test (14) was performed with participants seated on a high standard chair (seat height 49 cm). The participants were instructed to stand up without the help of the

arms on the command “go”, and walk 15 m along an unobstructed corridor as fast as possible without running. The chronometer was stopped when they reached the 15 m mark on the floor. All subjects wore walking shoes. Participants who normally used walking devices were allowed to use them during the test. A longer time taken to perform the test was considered a higher activity limitation.

The stair-climb test was performed. Participants were instructed to climb 12 stairs without using the hand-rail (if possible), ascending one stair at the time as fast as possible, without running. Once they reached the top, the chronometer was stopped while they turned around. Subsequently, and following the same instructions, after a signal the chronometer was started again and the subject descended the stairs. Both times (in seconds) were recorded independently and added together to calculate the time for the whole task. All participants were wearing walking shoes. A longer time performing the test was considered a higher activity limitation. The intraclass correlation coefficient (ICC) for intratester and intertester reliability were both 0.98 (15).

*Physical activity.* The LASA Physical Activity Questionnaire (LAPAQ) (19) was used to measure the level of moderate intensity physical activity in minutes per day. The LAPAQ is a reliable and valid instrument specifically developed for older adults. The LAPAQ is a comprehensive questionnaire on diverse (physical) activities of daily living including walking, riding a bicycle, gardening, light household chores, heavy household chores and sporting activities. Based on the results of this questionnaire, the average amount of moderate physical activity in minutes per day was computed (including all domains of the LAPAQ except light household chores (ie cooking, doing dishes)).

*Fatigue.* Fatigue was measured with the NRS scale (0-10).

*Muscle strength.* Muscle strength was assessed for flexion and extension of the knee using an isokinetic dynamometer (EnKnee; Enraf-Nonius B.V., Rotterdam, the Netherlands) (20). Quadriceps and hamstring strength were measured isokinetically at 60°/s. Participants performed a maximum of three test repetitions to measure the strength of the quadriceps and hamstrings for each knee. Mean muscle strength per leg was calculated to obtain a measure of overall leg muscle strength (in Nm). Subsequently, mean muscle strength was divided by the participant's



weight to control for the correlation between muscle strength and weight. This measure (in Nm/kg) was used for the analyses. Excellent intrarater reliability (intraclass correlation coefficient 0.93) has been reported for this measure in KOA patients (21).

*Proprioceptive accuracy.* Proprioceptive accuracy (motion sense) was assessed using a knee joint motion detection threshold (JMDT) (20). In a sitting position (semi-reclined), both lower legs were supported on two separate level arms and moved to a starting position of 30° flexion. A constant angular motion of one knee at a time was initiated at a velocity of 0.3°/s in the extension direction. The participant was instructed to push the right-hand button after detecting motion of the right knee, or the left-hand button after detecting motion of the left knee. The order of the leg being tested was randomly selected. Interference of additional visual-auditory stimuli, and clues such as cutaneous tension, pressure or vibration, were minimized. JMDT for the knee joint was measured as the difference in degrees between the original joint position, and the position in which the participant pushed the button indicating detection of knee motion. The mean of 3 measurements was calculated for each knee. Intrarater and interrater reliability (ICC 0.91) for measuring motion detection in patients with KOA was found to be excellent (20).

*Psychological functioning.* Psychological functioning was assessed with the Hospital Anxiety and Depression Scale (HADS) (22). The HADS is a self-reported questionnaire with 14 items rated on a 4-point LK scale (range: 0–3). It is designed to measure anxiety and depression (seven items for each subscale). The total score is the sum of the 14 items, and, for each subscale, the score is the sum of the respective seven items (ranging from 0 to 21). The HADS is widely used in clinical research and has been shown to be reliable, valid, and responsive for use as a screening tool in patients with OA (23).

*Level of frailty.* The Evaluative Frailty Index for Physical activity (EFIP) was used to measure the level of frailty (24). The EFIP is a 50-item questionnaire based on deficit accumulation (symptoms, signs, disabilities) in multiple domains (physical, psychological, social and general health status). The score on this questionnaire is expressed as the ratio of deficits present to the total number of deficits considered. The score ranges from 0 to 1, with 0 indicating no frailty and 1 indicating maximum frailty.

Global perceived effect (GPE) was assessed on a 9-point Likert scale (ranging from 1= much better, 5= no change, to 9 = much worse) and dichotomized as 'improved' (score 1-4) or not improved (score 5-9) (25).

For knee-specific variables (K&L grade, muscle strength, proprioceptive accuracy) we used data from one knee per person (Index Knee). Index knees were determined by the clinical diagnosis of KOA according to ACR-criteria, and in case of a clinical diagnosis of KOA in both knees, a knee was chosen at random.

*Process outcome measures.* Therapists assessed patient-perceived training intensity on a Borg-scale (26) after each session, and pain severity (NRS) (7) during the preceding week once a week. In addition, therapist filled in training diaries and registration forms to record specific adaptations to the exercise program (eg FITT factors and other adjustments to the program).

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## Appendix 4. Group differences at different time points (ITT)

	Group difference at different time points B (95% CI)*		
	10-wk FU	20-wk FU	32-wk FU
<b>Primary outcomes</b>			
WOMAC-pf (0-68)	-5.70 (-8.41, -3.00)‡	-7.81 (-11.05, -4.57)‡	-9.30 (-12.79, -5.82)‡
6-minute walk test (meters)	25.85 (10.86, 40.85)‡	39.41 (17.08, 61.74)‡	39.53 (17.55, 61.51)‡
<b>Secondary outcomes</b>			
NRS pain week (0-10)	-0.82 (-1.39, -0.245)‡	-1.83 (-2.49, -1.215)‡	-1.59 (-1.59, -0.98)‡
WOMAC pain (0-17)	-1.19 (-2.14, -0.25)‡	-2.28 (-3.37, -1.20)‡	-1.97 (-3.14, -0.80)‡
GUG (seconds)	-1.26 (-2.07, -0.45)£#	-1.38 (-2.37, -0.40)£#	-1.50 (-2.35, -0.66)‡#
Stair climbing up (seconds)	-3.23 (-7.26, 0.80)‡#	-1.49 (-2.55, -0.42)£#	-2.78 (-5.23, -0.34)£#
Stair climbing down (seconds)	-1.95 (-5.50, 1.61)‡#	1.44 (-2.67, -0.22)£#	-1.83 (-3.15, -0.51)£#
SF36 subscale pf (score 0-20)	n/a	2.23 (1.01, 3.45)‡	2.12 (0.91, 3.34)‡
PSFL (performance of activities 0-10)**	n/a	-1.47 (-2.16, -0.79)‡	-1.72 (-2.48, -0.96)‡
WQ35 (walking, 0-100)	n/a	-8.85 (-17.38, -0.32)£#	-4.51 (-13.40, 4.37)‡#
CTQ15 (stairclimbing, 0-100)	n/a	-4.49 (-12.56, 3.57)‡	-8.12 (-16.18, -0.06)£
R&SQ39 (rising and sitting down, 0-100)	n/a	-12.48 (-18.48, -6.47)‡#	-7.52 (-13.47, -1.58)£#

CI confidence interval. GUG Get up and Go. ITT Intention to treat. NRS Numeric Rating Scale. n/a not applicable. SD standard deviation. SF36 subscale pf Short Form 36 subscale physical functioning. PSFL Patient specific Functioning List. WOMAC-pf Western Ontario and Mc Master Universities Osteoarthritis Index, subscale physical functioning. \*Adjusted for baseline value of outcome variable difference; # 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. \*\* average score of 3 activities that were most relevant and problematic for patient; £ p <.05; ‡ p <.001; ‡ p >.05. Overall, a lower score indicates an improvement in physical functioning or pain with exception of the 6-minute walk test and the subscale pf of the SF-36

Appendix 5. Secondary outcome measures by group at different time-points (mean ± SD) and group differences over time (ITT)

	Baseline		10-wk FU		20-wk FU		32-wk FU		Group differences over time (10, 20, 32-wk FU) B (95% CI)*	Group difference at different time points B (95% CI)*		
	IG	CG	IG	CG	IG	CG	IG	CG		10-wk FU	20-wk FU	32-wk FU
LAPAQ moderate activities (minutes per day)	70.4 ± 33.8 n=63	50.7 ± 33.8 n=63	n/a	n/a	80.0 ± 62.4 n=56	62.5 ± 61.3 n=58	82.4 ± 55.4 n=49	59.0 ± 47.1 n=55	0.12 (0.02, 0.231) £#	n/a	0.115 (-0.00, 0.23) ]#	0.13 (0.01, 0.26) £#
NRS fatigue (0-10)	6.6 ± 1.9 n=63	6.1 ± 2.2 n=63	5.2 ± 1.8 n=60	5.8 ± 2.5 n=55	4.4 ± 2.2 n=59	6.0 ± 2.6 n=59	4.5 ± 2.2 n=51	6.4 ± 2.2 n=55	-0.68 (-1.24, -0.12) ‡	0.49 (-1.19, 0.21) ]	-0.91 (-1.66, -0.71) ‡	-0.59 (-1.41, 0.23) ]
Muscle strength (Nm/kg) (Index Knee)	0.65 ± 0.29 n=62	0.63 ± 0.34 n=63	0.77 ± 0.29 n=61	0.69 ± 0.35 n=55	0.78 ± 0.30 n=55	0.66 ± 0.33 n=58	0.81 ± 0.28 n=47	0.67 ± 0.31 n=55	0.08 (0.02, 0.13) ‡	0.05 (-0.01, 0.11) ]	0.09 (0.02, 0.15) ‡	0.11 (0.04, 0.18) ‡
Knee joint Proprioception (degrees) (Index Knee)	3.71 ± 3.80 n=63	3.72 ± 2.83 n=63	3.12 ± 2.46 n=61	3.50 ± 3.57 n=55	2.74 ± 1.55 n=53	2.84 ± 1.84 n=58	2.54 ± 1.35 n=48	3.56 ± 3.73 n=54	-0.46 (-1.17, 0.25) ]#	-0.37 (-1.44, 0.70) ]#	0.066 (-0.65, 0.52) ]#	-1.12 (-2.13, -0.11) £#
HADS (0-21)	11.3 ± 6.6 n=62	10.0 ± 6.8 n=63	n/a	n/a	10.2 ± 6.3 n= 59	8.2 ± 5.5 n=57	9.6 ± 6.5 n=51	8.0 ± 6.7 n=55	0.92 (-0.77, 2.62) ]#	n/a	0.86 (-0.87, 2.58) ]#	0.98 (-1.04, 3.01) ]#
EFIP (0-1)	0.27 ± 0.09 n=63	0.23 ± 0.09 n=63	n/a	n/a	0.24 ± 0.09 n=58	0.24 ± 0.09 n=56	0.24 ± 0.10 n=48	0.24 ± 0.09 n=55	-0.19 (-0.037, 6.18E-5) £	n/a	-0.021 (-0.04, -0.00) £	-0.02 (-0.04, 0.01) ]
BMI (kg/m <sup>2</sup> )	36.0 ± 6.8 n=63	35.0 ± 7.6 n=63	35.5 ± 6.3 n=61	36.4 ± 8.4 n=55	35.4 ± 6.3 n=56	34.7 ± 7.2 n=58	35.9 ± 6.1 n=48	34.7 ± 7.5 n=55	-0.03 (-0.61, 0.56) ]	-0.66 (-2.00, 0.68) ]	0.148 (-0.30, 0.60) ]	0.43 (-0.11, 0.96) ]

BMI Body Mass Index. CI confidence interval. CG. Control group. EFIP Evaluative Frailty Index for Physical activity. FU Follow up. HADS Hospital Anxiety and Depression Scale. IG. Intervention group. ITT Intention to treat. LAPAQ LASA Physical Activity Questionnaire. NRS Numeric Rating Scale. SD Standard Deviation. PSFL Patient specific Functioning List. \*Adjusted for baseline value of outcome variable difference. # 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 with exception of the LAPAQ moderate activities. £ p <.05; ‡ p <.01; ] p >.05