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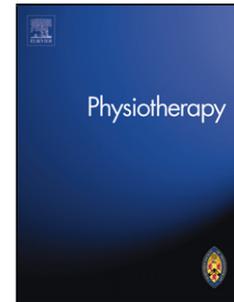
## Accepted Manuscript

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**Is a model of stratified exercise therapy by physical therapists in primary care feasible in patients with knee osteoarthritis?**

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**Objectives.** To explore the feasibility of a newly developed model of stratified exercise therapy in primary care for patients with knee osteoarthritis (OA).

**Design.** Mixed method design (process, outcome and qualitative evaluation).

**Setting.** Six physical therapy practices in primary care around Amsterdam.

**Participants.** Fifty eligible patients with knee OA, visiting one of the participating physical therapists (PTs).

**Intervention.** Patients were allocated to a subgroup based on a simple stratification tool and received subgroup-specific, protocolized, 4-month, exercise therapy.

**Main outcome measures.** Feasibility of this model of stratified exercise therapy was explored by multiple process parameters, outcome measures (physical functioning and knee pain; at baseline and 4-months follow-up) and experiences from patients and PTs.

**Results.** From 97 potentially eligible patients, fifty patients were included and allocated to the 'high muscle strength subgroup' (n=17), 'depression subgroup' (n=4), 'obesity subgroup' (n=6) or 'low muscle strength subgroup' (n=23). Three patients dropped out during the study period. PTs provided relatively low numbers of sessions (on average 10 sessions), although exceedance of the recommended maximum number of sessions did occur frequently. We found clinically relevant improvements on physical functioning and knee pain ( $p < 0.001$  for both) for the total group. In general, the model of stratified exercise therapy was considered to be easily applicable and of added value for daily practice.

**Conclusions.** Our model of stratified exercise therapy seems to be feasible in primary care, although a number of limitations were reported. Future research should determine the (cost-)effectiveness of an adapted model, compared to usual, non-stratified exercise therapy.

**KEY WORDS**

Knee osteoarthritis

Exercise therapy

Phenotypes

Subgroups

Feasibility

Physical therapy

**INTRODUCTION**

Osteoarthritis (OA) is one of the most common chronic health conditions and a leading cause of pain and disability among adults [1]. Knee OA is a highly heterogeneous disease, with large differences between patients in disease onset and course, symptoms, and treatment response, and may need to be differentiated in multiple clinically relevant phenotypes [2-6]. Exercise therapy by a physical therapist (PT) is recommended as a first-step, conservative treatment for patients with knee OA [7-9], based on strong, high-quality evidence for its effect on physical functioning and knee pain, compared to no exercise therapy [10]. Nonetheless, the clinical effects of exercise therapy are only modest [10-11], which may be attributed to a generic, ‘one-size-fits-all’ approach of exercise therapy, as illustrated by non-specific recommendations to provide exercise therapy in current guidelines [7-9]. Because of the large heterogeneity of knee OA, a stratified approach in exercise therapy, meaning that patients are allocated to subgroups and receive a subgroup-specific exercise therapy intervention, may be superior over usual exercise therapy. The added value of stratified exercise therapy has been proven in low back

pain patients [12-14], but has not been tested in other patient groups. As far as we know, no model of stratified exercise therapy has yet been developed for patients with knee OA.

Recently, we were able to identify five phenotypes of knee OA patients based on clinically relevant and easily obtainable patient characteristics (i.e., upper leg muscle strength, body mass index, depressive mood and radiographic OA severity) and replicated this finding to a large degree in a second cohort as well [15,16]. In these two studies, we identified a ‘minimal joint disease phenotype’ (16%-28% of the patients), ‘strong muscle phenotype’ (21-22%), ‘severe radiographic phenotype’ (21-31%), ‘obese phenotype’ (15-20%) and ‘depressive phenotype’ (10-16%). The replication indicates that these phenotypes can be considered as stable, valid and clinically relevant, and potentially useful for treatment stratification (e.g., stratified exercise therapy). Based on these phenotypes, we developed a model of stratified exercise therapy, as described more in detail in the Methods. In short, in this model, patients are allocated into the ‘high muscle strength subgroup’, ‘low muscle strength subgroup’ (combination of ‘minimal joint disease phenotype’ and ‘severe radiographic phenotype’), ‘obesity subgroup’ or the ‘depression subgroup’, and treated according to the subgroup-specific exercise therapy intervention.

We hypothesize that a model of stratified exercise therapy based on these phenotypes, is superior over usual, ‘non-stratified’ exercise therapy in patients with knee OA. In the present study, we aim to explore the feasibility of a newly developed model of stratified exercise therapy in primary care, using an process, outcome and qualitative evaluation.

## **METHODS**

### *Design*

A mixed method design based on Reelick et al [17] was used, combining (i) a process evaluation of multiple process parameters, (ii) an uncontrolled, pretest-posttest design for outcome measurements, and (iii) a qualitative approach with semi-structured interviews and a focus group meeting.

*Model of stratified exercise therapy.*

In the preparatory phase, we developed a model of stratified exercise therapy, consisting of a simple stratification tool and subgroup-specific interventions. Draft versions of this model were discussed with PTs from both primary and secondary care, and with our research group in which multiple relevant disciplines are embedded.

Subgroups. From the five previously identified phenotypes [15,16] (as described in the Introduction), we decided to develop a model of stratified care with four subgroups. First, a ‘high muscle strength subgroup’ that is characterized by relatively high upper leg muscle strength and moderate to severe knee joint damage, and presumed to be mostly male, having a history of knee trauma and/or surgery (‘post-traumatic knee OA’) and a high level of physical activity. Second, a ‘low muscle strength subgroup’ that is characterized by upper leg muscle weakness and minimal to severe knee joint damage. This subgroup is a combination of the previously identified ‘minimal joint disease phenotype’ and ‘severe radiographic phenotype’, as both phenotypes were characterized by upper leg muscle weakness and only differed in radiographic OA severity. As radiographic severity has been found to be unrelated to the effect of exercise therapy [18,19] and the content of the exercise therapy is recommended to be irrespective of radiographic severity [7-9], the two phenotypes can receive the same intervention and can therefore be combined in one subgroup. Third, an ‘obesity subgroup’ that is characterized by (severe) obesity, upper leg muscle weakness and high symptom levels.

Fourth and final, a ‘depressive subgroup’ that is characterized by a depressive mood, upper leg muscle weakness and high symptom levels.

Stratification tool. Based on the characteristics of the original phenotypes [15,16], we developed a simple stratification tool with cut-off values in order to allocate patients with knee OA into one of the four subgroups (see **Figure 1**). By using this tool, patients are first allocated to the ‘high muscle strength subgroup’ if quadriceps strength is 0.85 Nm/kg or higher. The decision for quadriceps strength as the first variable for stratification was based on existing literature suggesting that beneficial effects of exercise therapy are primarily driven by improvements in quadriceps strength [20-22], implying that above a certain value of quadriceps strength, exercise therapy is unlikely to be beneficial. The cut-off value was based on previous research by our group on a threshold in the relationship between upper leg muscle strength and physical functioning. This threshold suggests that in patients with muscle strength above this threshold, an increase in muscle strength is not likely to improve physical functioning, whereas in patients with levels of muscle strength below this threshold, an increase in muscle strength is likely to improve physical function [23]. Second, patients with quadriceps strength lower than 0.85 Nm/kg are allocated to the ‘depression subgroup’ if the score on the depression questionnaire (Hospital Anxiety and Depression Scale; HADS) was equal or higher than 8 (i.e., indicative for a possible depressive mood) [24]. Third and final, from all remaining patients, those with BMI equal or higher than 35 kg/m<sup>2</sup> (i.e., severe obesity) are allocated to the ‘obesity subgroup’ and all others to the ‘low muscle strength subgroup’. This tool allocates each patient into only one subgroup.

Subgroup-specific exercise therapy. Based on exercise programs that were previously developed and proven to be effective by our research groups [25-27], we developed protocols

of exercise therapy interventions that were matched to each of the four subgroups (see **Table 1**).

For the ‘high muscle strength subgroup’, the intervention was minimal and comprised 3-4 sessions, consisting of (i) patient education and advice focusing on self-management and avoidance of knee overloading, and (ii) instructions to perform home exercises to sustain adequate level of muscle strength and physical activity.

For the ‘depression subgroup’, the intervention comprised 12-18 sessions, consisting of (i) patient education and advice focusing on pain behavior and active lifestyle, (ii) supervised exercise therapy focusing on improving upper leg muscle strength, aerobic capacity and performance of daily activities, and (iii) instructions to perform home exercises. The exercise therapy was specifically adapted to depressive knee OA patients (e.g., by integrating behavioral graded activity and incorporating elements of pain coping skills training), based on the depression-protocol from the COOA-study (COmorbidity and OsteoArthritis), which has been found to be feasible [26] in this subgroup. In addition, (iv) patients were advised to visit their general practitioner to consider additional care for their possible depressive mood.

For the ‘obesity subgroup’, the intervention comprised 12-18 sessions, consisting of (i) patient education and advice focusing on active lifestyle (especially physical activities that lead to fat loss) and avoiding knee overloading, (ii) supervised exercise therapy focusing on upper leg muscle strength, aerobic capacity and daily activities, and (iii) instructions to perform home exercises. The exercise therapy was specifically adapted to the presence of (severe) obesity (e.g., by initially performing non-weight bearing exercises and providing a slow gradual increase in training intensity), based on the obesity-protocol from the COOA-study, which has been found to be feasible [26] and effective [27] in this subgroup. In addition, (iv) patients were advised to visit a dietician for diet advice.

For the ‘low muscle strength subgroup’, the intervention comprised 8-12 sessions, consisting of (i) patient education and advice focusing on active lifestyle, (ii) instructions to perform home exercises focusing on upper leg muscle strengthening, and (iii) supervised exercise therapy focusing on upper leg muscle strengthening, aerobic capacity and daily activities. This intervention is based on the protocol from the Stability-study, which was been found to be effective [25], irrespective of severity of MRI-detected knee joint damage [18].

In general, PTs could individualize the treatment, based on patient’s symptoms and preferences. All sessions were individually provided in 30-minute sessions. PTs were instructed to use the following exercise intensity and volume, with a weekly gradual increase if possible: 3 series of 10 repetitions in 60 to 80% of 1RM (1 repetition maximum) for strengthening exercises, 3 series of 10 repetitions for functional exercises, and 60 to 80% of maximal heart rate for aerobic exercises. Patients were additionally instructed to perform at least three of these exercises at home on three days a week.

### *Participants*

Fourteen PTs from six practices in primary care around Amsterdam, with specific expertise in rheumatic diseases and regularly treating patients with knee OA were recruited and trained. Study eligibility was evaluated by the PTs during intake. Patients with persistent knee pain (> 3 months) as a reason to visit the PT, age  $\leq$  80 years, meeting American College for Rheumatology (ACR) criteria for knee OA [28] and providing informed consent were included. Exclusion criteria were other reasons for knee pain than knee OA (e.g. rheumatoid arthritis, gout), severe knee pain in past week (i.e., Numeric Rating Scale (NRS) > 8/10), physical or mental comorbidity severely affecting daily life, suspicion of chronic widespread pain based on

ACR-criteria for fibromyalgia [29], total knee arthroplasty (TKA) or on waiting list for TKA for most painful knee, and insufficient comprehension of Dutch language. All participants provided written informed consent. We aimed at including 50 eligible patients in total, based on an a priori power calculation.

### *Measurements*

Process evaluation. The process evaluation aimed at collecting information on (i) inclusion and follow-up, (ii) subgroup allocation; and (iii) treatment fidelity, as recommended by Reelick et al [17]. The researcher (JK) continuously documented process parameters (i.e., number of participants from eligible patients, number of excluded patients and drop-outs, allocation, reasons for exclusion and drop-out). PTs registered number of attended sessions and protocol violations (i.e., referral, additional PT-interventions) in the electronic patient files.

Outcome evaluation. Outcome variables were assessed at baseline and 4-months follow-up. Primary outcome variables were: (i) physical functioning, assessed by the Dutch translation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire subscale function in daily living (ADL; score between 0 and 100; 0= maximal problems; 100= no problem) [30,31] and (ii) knee pain severity, assessed by a NRS for knee pain on average during walking in the past week (score between 0 and 10; 0= no pain; 10= worst pain imaginable) [32].

Secondary outcome variables were all other KOOS subscales, NRS knee pain severity on average in the past week and at the moment and global perceived effect (GPE; 7-item scale). In addition, secondary outcome variables included subgroup variables (knee extension strength, depressive mood and BMI) as well. Isometric knee extension strength of the most painful knee was measured by the PT using a hand-held dynamometer (MicroFET 2; Hoggan Health Industries Inc., USA/ Biometrics Motion BV, Netherlands). To decrease the measurement error, a frame that was based on the 'dynajig' from Fleeton et al [33] was used to fix the dynamometer

against the wall instead of the assessor's hand. Participants were seated with the tested knee at 60 degrees flexion and their lower leg positioned at 90 degrees to the axis of this frame, crossed their arms over their chest, and then performed three attempts of maximal, isometric knee extension. The distance between the knee anterior joint line and the center of the point of application of the hand-held dynamometer (approximately 10 centimeters above malleolus) was measured in meters. The best of three attempts, which were conducted in approximately two minutes in total, was recorded and expressed in Newton meters (Nm) standardized for body mass (Nm/kg). Depressive mood was assessed by the Dutch translation of the HADS questionnaire subscale depression, which consists of 7 items on a 4-point scale, resulting in a total score between 0 and 21 [24,34]. BMI was calculated by dividing body weight (in kilogram; measured by the PT) by squared body length (in meters; measured by the PT).

Finally, general patient characteristics (i.e., age, gender, duration of knee symptoms, history of knee surgery, presence of comorbidities and use of pain medication and health care in past 4 months) were assessed by self-report at baseline. Use of pain medication and health care in the past 4 months were also assessed at 4-months follow-up.

Qualitative evaluation. Post-treatment, semi-structured interviews (with all participating patients and those PTs who included at least two patients) were performed by the researcher to collect qualitative information on experiences with the model of stratified care, as recommended by Reelick et al [17]. A topic list was used to structure the interviews. In addition, a focus group meeting with participating PTs was organized to discuss the study results and to reach consensus on the suggested adaptations in the model.

### *Statistical analysis*

Process parameters, qualitative information and baseline patient characteristics were analyzed descriptively. In addition, ANOVA-tests were performed to determine baseline differences in patient characteristics between subgroups. Primary and secondary outcome measures were analyzed using paired sample t-tests and within-group effect sizes (i.e., mean difference between baseline score and follow-up score, divided by the standard deviation of baseline score) for all patients included in the study (n=50), as well as for each subgroup. In addition, number of patients with a minimal clinically important difference (MCID) were calculated for the primary outcome variables (i.e., improvement  $\geq 10$  points for KOOS [35]; reduction  $\geq 2$  points or  $\geq 33\%$  on NRS pain [36]). For drop-outs, missing data at follow-up were replaced by baseline score. Sensitivity analyses were performed with only those patients who completed the intervention and those without any protocol deviation. As our study was not powered for this purpose, we did not perform between-group analyses. All analyses were performed using SPSS software, version 18.0 (SPSS, Chicago, IL), with statistical significance accepted at p-values of less than 0.05.

## RESULTS

### *Process evaluation*

Inclusion and follow-up. In a period of twelve months, 97 patients visited a participating PT because of knee complaints and were screened for eligibility, of which 50 patients (52%) could be included. Reasons for not being included were: unwilling to participate (n=16), knee complaints < 3 months (n=8), age > 80 year (n=7), absence of clinical diagnosis of knee OA (n=5), insufficient comprehension of Dutch language (n=4), TKA planned (n=3), suspicion of chronic widespread pain (n=2), severe comorbidity (n=1) and pain severity > 8 (n=1). Three

out of 50 participants dropped out of the study, as they decided to quit the intervention due to insufficient pain relief (n=2) or illness of partner (n=1).

Subgroup allocation. Based on our stratification tool, patients were allocated to a subgroup as follows: 46% to the ‘low muscle strength subgroup’, 34% to the ‘high muscle strength subgroup’, 12% to the ‘obesity subgroup’, and 8% to the ‘depression subgroup’. The subgroups significantly differed from each other on each of the three subgroup variables and on history of knee surgery (i.e., higher prevalence in ‘high muscle strength subgroup’) (see **Table 2**).

Treatment fidelity. The number of treatment sessions was on average 10, ranging from on average 6 sessions for the ‘high muscle strength subgroup’ (recommended number of sessions: 3 to 4), 12 for the ‘low muscle strength subgroup’ (8 to 12), 13 for the ‘obesity subgroup’ (12 to 18) and 16 for the ‘depression subgroup’ (12 to 18). In addition to the supervised sessions, patients performed home exercises on 4 days a week on average (SD: 2) and physical activities like walking, bicycling, or sports on 4 days a week as well (SD: 2). Protocol deviations were reported in 28 patients, mainly consisting of exceedance of the recommended maximum number of sessions in the ‘high muscle strength subgroup’ (n=10) or in the ‘low muscle strength subgroup’ (n=9). Additional interventions from the PT (dry needling; n=2) or from other health care professionals (intra-articular injection; n=1) were hardly reported (see **Table 3**).

#### *Outcome evaluation*

Physical functioning (KOOS-ADL) improved from 61 at baseline to 74 at 4-months follow-up ( $p<0.001$ ; within-group effect size: 0.7), whereas knee pain severity during walking (NRS) reduced from 5.7 at baseline to 3.6 at 4-months follow-up ( $p<0.001$ ; within-group effect size: 1.1) (see **Table 4 and 5**). Based on MCID’s for KOOS<sup>32</sup> and NRS pain<sup>33</sup>, 54% and 67% of the participants improved on physical functioning and knee pain, respectively. Statistically

significant improvements were also found on all secondary outcome variables, except for BMI. Pain medication usage in the past 4 months reduced from 38% of the patients at baseline to 30% at 4 months follow-up. During the treatment period, orthopedic surgeons were consulted by 21% of the patients, GPs by 21% and other health professionals by 10%.

### *Qualitative evaluation*

Interviews with 48 out of 50 patients and 9 out of 14 PTs and a focus group meeting with participating PTs revealed that our model of stratified care was considered to be easy to apply and to have added value for daily practice, in general.

Experiences with the stratification tool were highly positive, with two exceptions. First, the isometric strength measurement by a hand-held dynamometer was reported to be difficult to perform adequately by patients and difficult to test reliably by PTs. On the other hand, most of the PTs did consider this test as valuable, especially to demonstrate to patients their (change in) level of strength over the course of the treatment. Second, PTs reported that a limitation of the stratification tool was that not all patients with (severe) obesity were allocated to the ‘obesity subgroup’.

Experiences with the subgroup-specific interventions were positive as well. Patients were specifically positive about the tailored patient education and easy-to-perform exercises. PTs appreciated the applicability of the treatment protocols, but reported three limitations. First, the maximum number of four sessions for the ‘high muscle strength subgroup’ was considered too low in many patients. Second, PTs reported that the behavioral approach in exercise therapy and advice to visit a GP for the ‘depression subgroup’ were considered unnecessary in most of the patients within this subgroup, as the depressive mood hardly affected patient’s daily life. Third, PTs reported that the interdisciplinary consult with a dietician for the ‘obesity subgroup’

could not always take place because of problems with contacting a dietician, while 3 out of 5 patients from this subgroup refused to visit a dietician.

## DISCUSSION

Because of the high and further increasing prevalence of and costs related to knee OA, it is of key importance to optimize the content and usage of exercise therapy. A stratified approach may optimize overall effectiveness of exercise therapy, as proven for low back pain [12-14]. Our model of stratified exercise therapy, which is the first one developed for knee OA, seems to be feasible in primary care. In general, patients and PTs were positive about the applicability and added value of the model. Furthermore, clinically relevant improvements on physical functioning and knee pain and low numbers of treatment sessions provided by PTs were found. The present study also revealed several limitations of the model, which needs to be acknowledged in an adapted version of the model.

Three of our four subgroups (i.e., ‘high muscle strength subgroup’, ‘depression subgroup’ and ‘low muscle strength subgroup’) improved substantially in physical functioning and knee pain. In comparison to previously reported mean improvements of exercise therapy compared to ‘no exercise’ in knee OA (i.e., 10 points on 0-100 scale for physical function and 1.2 points on 0-10 scale for knee pain [10]), the mean improvements in our study are higher (12.5 points on 0-100 scale for physical function and 2.1 points on 0-10 scale for knee pain). This suggests that our stratified approach could optimize current exercise interventions, but this will need to be confirmed in a future randomized controlled trial (RCT). Remarkably, for the ‘depression subgroup’, exercise therapy was not only effective in physical functioning and knee pain, but also in depressive mood. This is even more surprising as PTs reported that in most

patients from this subgroup, depressive mood was only mildly present, therefore adaptations to the exercise therapy as described in the protocol (i.e., behavioral approach, advice to visit GP) were considered unnecessary. In contrast, treatment effects were substantially lower in the ‘obesity subgroup’, with no effect at all on BMI. This suggests that obesity-adapted exercise therapy combined with advice to visit a dietician, being ignored by three of the five patients, is probably insufficient. Possibly, a more extensive intervention, aiming at weight loss and active lifestyle, with a stronger collaboration between PT and dietician, is necessary in this subgroup. Recent studies from the group of Messier et al [37,38] provided evidence for effects of such an extensive (18-month), combined intervention on clinical symptoms, body weight and inflammatory markers. However, to implement such an intervention in primary care, access to dieticians and interdisciplinary collaboration between PTs and dieticians may need to further improved.

Our subgroup-specific exercise therapy interventions were based on exercise programs that we previously developed [25,26] and were proven to be effective in clinical trials [25, 27]. We also followed the training intensity parameters for strength training (i.e., at 60-80% of one-repetition maximum) and aerobic training (i.e., at 60-80% of maximal heart rate) as recommended in the American College of Sports Medicine (ACSM) guideline [39]. In addition, patients were instructed to perform at least three home exercises on three days a week, in addition to the supervised exercise sessions, as recommended in the ACSM guideline [39] as well. Therefore, we are convinced that our subgroup-specific interventions are adequately designed to achieve training effects as large as possible.

Unexpectedly, the process evaluation revealed that from our study group, only a small minority could be allocated to the ‘obesity subgroup’ (12%) or the ‘depression subgroup’ (8%). This finding is in contrast to the proportions in our previous phenotype-studies [15,16], and

may indicate that these patients do not visit a PT in primary care, prefer a specialized treatment in secondary care, or do not visit any health care professional at all. These low proportions can also be partly attributed to the order of subgroup variables in our stratification tool. This order resulted in four out of ten patients with severe obesity being allocated to other subgroups than the ‘obesity subgroup’, and two out of six patients with possible depressive mood allocated to other subgroups than the ‘depression subgroup’. Second, our process evaluation revealed mixed results on treatment fidelity. On the one hand, usage of other (not recommended) interventions than exercise therapy was almost absent and average number of sessions was generally within the recommended range. On the other hand, exceedance of the recommended maximal number of sessions did occur regularly, especially in the ‘high muscle strength subgroup’ (in 10 out of 17 patients). Apparently, many PTs preferred to provide some additional supervised sessions, in order to ensure adequate exercise performance and to increase exercise adherence. Nevertheless, the overall average number of treatment sessions remained substantially lower than the nationwide average as provided by Dutch PTs in OA patients (10 vs. 17 sessions [40]), which suggests that health care costs could be saved by using our model.

This preliminary study identified several limitations of our model that should be acknowledged in an adapted version, as agreed by our participating PTs in our final focus group meeting. First, because of the reported limitations by both patients and PTs of the handheld dynamometer for measuring muscle strength, we will replace it for a functional strength measurement, namely the 30-second chair stand test (30s-CST). This test is recommended by the OARSI as a core outcome measurement in OA [41] and strongly correlated to isometric muscle strength [42], and in contrast to the handheld dynamometer, the 30s-CST is more easy to perform in daily practice and costless. Second, to avoid obese patients being allocated to subgroups other than the ‘obesity subgroup’, we will change the order of allocating patients to

subgroups (i.e., BMI as first step in the stratification tool) and reduce the cut-off value on BMI for allocation to the ‘obesity subgroup’ from 35 to 30. Third and final, because of the low prevalence of patients allocated to the ‘depression subgroup’, the low level of depressive mood and minor (behavioral) adaptations in applying exercise therapy in this subgroup, this subgroup could be removed from our model. Thereby, an adapted model will differentiate patients into three large subgroups, that should receive minimal (‘high muscle strength subgroup’), average (‘low muscle strength subgroup’) or extensive exercise therapy combined with a diet/weight loss intervention (‘obesity subgroup’). Patients with severe somatic or psychological comorbidities will not be included in our model, as they should be referred to specialized PTs or multidisciplinary care. This adapted model can be expected to be superior in clinical effectiveness with a reduced number of treatment sessions, compared to usual, non-stratified exercise therapy. If so, this model might be included in clinical guidelines, in order to better specify the current (‘generic’) recommendations on the usage of exercise therapy in knee OA.

This preliminary study has some methodological limitations that needs to be addressed. First, as we used an uncontrolled design without a control group in a relatively low sample size, our results should be interpreted with caution. Second, as we only included PTs with specific expertise in knee OA and patients that fulfilled our study criteria, our results are only applicable to this group. Third, we lacked information on the content of the dietician-delivered (in ‘obesity subgroup’) and GP-delivered treatment (in ‘depression subgroup’). Fourth, because this was a pilot-study to explore feasibility, we used a short follow-up period (i.e., directly post-treatment) and a relatively small set of measurements including only one physical test. In a planned large-scale RCT, we will evaluate the (cost-)effectiveness of our (adapted) model of stratified exercise therapy compared to usual exercise therapy, using a longer follow-up period (i.e., one year) and a larger set of both physical and self-reported measurements.

To conclude, our model of stratified exercise therapy, which is the first one developed for knee OA, seems to be feasible in primary care, based on a process, outcome and qualitative evaluation, although a number of limitations of the model were reported. Future research using a fully powered RCT should determine the (cost-) effectiveness of an adapted version of our model, in which the reported limitations have been acknowledged, compared to usual, non-stratified exercise therapy.

### **CONTRIBUTION OF THE PAPER**

- This preliminary study revealed promising results of a new, phenotype-based, stratified approach of exercise therapy for patients with knee OA, suggesting that by using this intervention, the current modest effects of exercise therapy can be optimized with potential cost-savings.
- We also revealed some limitations of our model of stratified care, based on both quantitative and qualitative information, which needs to be acknowledged in an adapted version of the model.
- Future research using a fully powered randomized controlled trial (RCT) should determine the (cost-)effectiveness of our (adapted) model, compared to usual, non-stratified exercise therapy.

### **CONFLICT OF INTEREST**

None declared.

### **ETHICAL APPROVAL**

This accredited Ethics Committee of Slotervaart Hospital and Reade reviewed this study and determined, based on the Dutch Medical Research Involving Human Subjects Act (Dutch

acronym: WMO), that the research activities meet the requirements for exemption from METC review under the WMO (reference number: P1615). All participant provided written informed consent.

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**REFERENCES**

- [1] Allen KD, Golightly YM. State of the evidence. *Curr Opin Rheumatol*. 2015 May;27(3):276-83.
- [2] Felson DT. Identifying different osteoarthritis phenotypes through epidemiology. *Osteoarthritis Cartilage*. 2010 May;18(5):601-4.
- [3] Driban JB, Sitler MR, Barbe MF, Balasubramanian E. Is osteoarthritis a heterogeneous disease that can be stratified into subsets? *Clin Rheumatol*. 2010 Feb;29(2):123-31.
- [4] Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377(9783):2115-2126.
- [5] Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC Musculoskelet Disord*. 2016 Oct 12;17(1):425.
- [6] Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. *Osteoarthritis Cartilage*. 2017 Dec;25(12):1926-1941.
- [7] 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): 476-499.
- [8] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012 Apr;64(4):465-74.

- [9] National Clinical Guideline Centre (UK). Osteoarthritis: Care and Management in Adults. London: National Institute for Health and Care Excellence (UK); 2014 Feb (PubMed PMID: 25340227).
- [10] Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2015 Jan 9;1:CD004376.
- [11] Fitzgerald GK, Fritz JM, Childs JD, Brennan GP, Talisa V, Gil AB, et al. Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. *Osteoarthritis Cartilage*. 2016 Aug;24.
- [12] Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet*. 2011 Oct 29;378(9802):1560-71.
- [13] Fritz JM, Lindsay W, Matheson JW, Brennan GP, Hunter SJ, Moffit SD, et al. Is there a subgroup of patients with low back pain likely to benefit from mechanical traction? Results of a randomized clinical trial and subgrouping analysis. *Spine (Phila Pa 1976)*. 2007 Dec 15;32(26):E793-800.
- [14] Brennan GP, Fritz JM, Hunter SJ, Thackeray A, Delitto A, Erhard RE. Identifying subgroups of patients with acute/subacute "nonspecific" low back pain: results of a randomized clinical trial. *Spine (Phila Pa 1976)*. 2006 Mar 15;31(6):623-31.
- [15] Knoop J, van der Leeden M, Thorstensson CA, Roorda LD, Lems WF, Knol DL, et al. Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2011;63(11):1535-1542.
- [16] van der Esch M, Knoop J, van der Leeden M, Roorda LD, Lems WF, Knol DL, et al. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. *Osteoarthritis Cartilage*. 2015 Apr;23(4):544-9.

- [17] Reelick MF, Faes MC, Esselink RA, Kessels RP, Olde Rikkert MG. How to perform a preplanned process evaluation for complex interventions in geriatric medicine: exemplified with the process evaluation of a complex falls-prevention program for community-dwelling frail older fallers. *J Am Med Dir Assoc*. 2011 Jun;12(5):331-6.
- [18] Knoop J, Dekker J, van der Leeden M, van der Esch M, Klein JP, Hunter DJ, et al. Is the severity of knee osteoarthritis on MRI associated with outcome of exercise therapy? *Arthritis Care Res (Hoboken)* 2013;66(1):63-8.
- [19] Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014 Mar;66(3):622-36.
- [20] Runhaar J, Luijsterburg P, Dekker J, Bierma-Zeinstra SM. Identifying potential working mechanisms behind the positive effects of exercise therapy on pain and function in osteoarthritis; a systematic review. *Osteoarthritis Cartilage*. 2015 Jul;23(7):1071-82.
- [21] Knoop J, Steultjens MP, Roorda LD, Lems WF, van der Esch M, Thorstensson CA, et al. Improvement in upper leg muscle strength underlies beneficial effects of exercise therapy in knee osteoarthritis: secondary analysis from a randomised controlled trial. *Physiotherapy*. 2015 Jun;101(2):171-7.
- [22] Bartholdy C, Juhl C, Christensen R, Lund H, Zhang W, Henriksen M. The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and meta-regression analysis of randomized trials. *Semin Arthritis Rheum*. 2017 Aug;47(1):9-21.
- [23] Edelaar LM, van Dieën JH, van der Esch M, Roorda LD, Dekker J, Lems WF, et al. Nonlinear relationship between isokinetic muscle strength and activity limitations in patients with knee osteoarthritis: Results of the Amsterdam-Osteoarthritis cohort. *J Rehabil Med*. 2017 Jul 7;49(7):598-605.

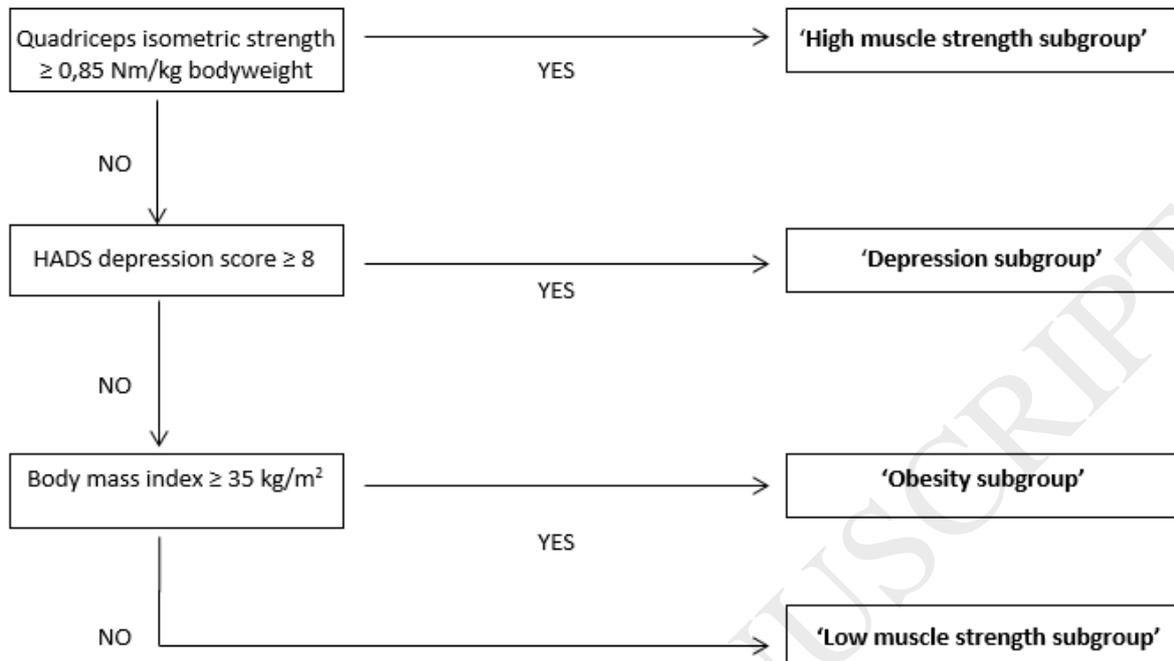
- [24] Zigmund AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.
- [25] Knoop J, Dekker J, van der Leeden M, van der Esch M, Thorstensson CA, Gerritsen M, et al. Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. *Osteoarthritis Cartilage* 2013;21(8):1025-34.
- [26] de Rooij M, van der Leeden M, Avezaat E, Häkkinen A, Klaver R, Maas T, et al. Development of comorbidity-adapted exercise protocols for patients with knee osteoarthritis. *Clin Interv Aging* 2014 May 14;9:829-42.
- [27] de Rooij M, van der Leeden M, Cheung J, van der Esch M, Häkkinen A, Haverkamp D, et al. Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)*. 2017 Jun;69(6):807-816.
- [28] 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. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*. 1986 Aug;29(8):1039-49.
- [29] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990 Feb;33(2):160-72.
- [30] Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998 Aug;28(2):88-96.
- [31] de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes*. 2008 Feb 26;6:16.

- [32] McCaffery M, Pasero C (2001) Using the 0-to-10 pain rating scale. *Am J Nurs* 101:81-82.
- [33] Fleeton G, Harmer AR, Nairn L, Crosbie J, March L, Crawford R, et al. Self-reported knee instability before and after total knee replacement surgery. *Arthritis Care Res (Hoboken)*. 2015 Aug 28.
- [34] Van Hemert B, Ormel J. Nederlandse versie van de Hospital Anxiety and Depression scale (HADS). Vragenlijst en regels voor scoring. 1996.
- [35] Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003 Nov 3;1:64.
- [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 Aug;8(4):283-91.
- [37] Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA*. 2013 Sep 25;310(12):1263-73.
- [38] Loeser RF, Beavers DP, Bay-Jensen AC, Karsdal MA, Nicklas BJ, Guermazi A, et al. Effects of dietary weight loss with and without exercise on interstitial matrix turnover and tissue inflammation biomarkers in adults with knee osteoarthritis: the Intensive Diet and Exercise for Arthritis trial (IDEA). *Osteoarthritis Cartilage*. 2017 Nov;25(11):1822-1828.
- [39] ACSM's Guidelines for Exercise Testing and Prescription 10<sup>th</sup> ed. Philadelphia (PA): Wolters Kluwer Health 2018.
- [40] Leemrijse CJ, Barten JA, Kooijman MK, Verberne LDM, Veenhof C, Swinkels ICS. Omvang en kenmerken fysiotherapeutische zorg bij patiënten met artrose. [www.nivel.nl/node/4376](http://www.nivel.nl/node/4376). Published: 04-03-2016; Accessed: 03-10-2017.

- [41] Dobson F, Hinman RS, Hall M, Marshall CJ, Sayer T, Anderson C, et al. Reliability and measurement error of the Osteoarthritis Research Society International (OARSI) recommended performance-based tests of physical function in people with hip and knee osteoarthritis. *Osteoarthritis Cartilage*. 2017 Jun 22. pii: S1063-4584(17)31053-1.
- [42] Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport*. 1999;70(2):113-9.

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## FIGURES



HADS = Hospital Anxiety and Depression Scale

**FIGURE 1. Stratification tool**

**TABLE 1: Subgroup-specific exercise therapy**

	<b>High muscle strength subgroup</b>	<b>Depression subgroup</b>	<b>Obesity subgroup</b>	<b>Low muscle strength subgroup</b>
<b>A. Exercise therapy by PT:</b>				
i. patient education	X	X	X	X
ii. home exercises	X	X	X	X
iii. supervised exercise program		X <sup>1</sup>	X <sup>2</sup>	X <sup>3</sup>
Recommended number of sessions	3-4	12-18	12-18	8-12
<b>B. Advice to visit GP</b>		X		
<b>C. Advice to visit dietician</b>			X	

<sup>1</sup> based on COOA/depression-protocol [26]; <sup>2</sup> based on COOA/obesity-protocol [27]; <sup>3</sup> based on Stability-protocol [25]

**TABLE 2. Baseline characteristics of study sample**

	<b>Total group (n=50)</b>	<b>High muscle strength (n=17)</b>	<b>Depression (n=4)</b>	<b>Obese (n=6)</b>
<b>General patient characteristics:</b>				
Female, n (%)	29 (58%)	8 (47%)	2 (50%)	3 (50%)
Age (years), mean (SD)	64 (9)	62 (9)	60 (7)	64 (9)
Duration of knee symptoms (years), mean (SD)	7 (10)	11 (12)	3 (5)	5 (4)
History of knee surgery, n (%)	18 (36%)	10 (59%)	1 (25%)	0 (0%)
Presence of comorbidity, n (%)	31 (62%)	9 (53%)	2 (50%)	5 (83%)
Use of pain medication, n (%)	19 (38%)	5 (29%)	2 (50%)	3 (50%)
<b>Subgroup variables:</b>				
Isometric quadriceps muscle strength (Nm/kg), mean (SD)	0.84 (0.34)	1.22 (0.29)	0.64 (0.16)	0.68 (0.16)
BMI, mean (SD)	29.3 (5.6)	29.5 (5.4)	30.2 (3.8)	38.6 (5.6)
Presence of severe obesity (BMI $\geq$ 35), n (%)	10 (20%)	3 (18%)	1 (25%)	6 (100%)
HADS depression (0-21), mean (SD)	3.4 (3.1)	3.5 (3.3)	10.3 (2.2)	3.2 (2.2)
Presence of possible depressive mood ( $\geq$ 8), n (%)	6 (12%)	2 (12%)	4 (100%)	0 (0%)
<b>Primary outcome variables:</b>				
KOOS ADL (0-100), mean (SD)	61.1 (18.2)	62.3 (17.9)	46.3 (18.0)	61.0 (18.2)
NRS pain severity during walking (0-10), mean (SD)	5.7 (1.9)	5.6 (2.2)	5.8 (1.7)	6.7 (1.9)

SD = standard deviation; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; NRS = numeric rating scale.

**TABLE 3: Treatment fidelity for each subgroup**

	<b>Total group (n=50)</b>	<b>High muscle strength (n=17)</b>	<b>Depression (n=4)</b>	<b>Obesity (n=6)</b>	<b>Low muscle strength (n=23)</b>
Sessions, mean (min, max)	10 (2-24)	6 (3-19)	16 (8-24)	13 (8-21)	12 (2-24)
Protocol deviations, total (n)	28/47	11/17	2/4	4/5	11/21
More than max. no. of sessions (n)	21/47	10/17	1/4	1/5	9/21
Less than min. no. of sessions (n)	2/47	0/17	0/4	1/5	1/21
Other PT-interventions (n)	2/47	0/17	0/4	1/5	1/21
Refused to visit dietician (n)	3/47	n/a	n/a	3/5	n/a
Refused to visit GP (n)	2/47	n/a	2/4	n/a	n/a
Other interventions (n)	1/47	0/17	0/4	0/5	1/21
Drop-outs, n	3/50	0/17	0/4	1/6	2/23

**TABLE 4. Changes in outcome during 4-month treatment period (n=50)**

	Baseline mean (SD)	4-month FU mean (SD)	Mean difference mean (95% CI)	P-value	Effect size*	% change
<b>Primary outcome variables:</b>						
KOOS ADL, 100-0	61.1 (18.2)	73.6 (19.2)	12.5 (7.2 to 17.7)	<0.001	0.7	+20%
NRS, pain during walking in past week, 0-10	5.7 (1.9)	3.6 (2.5)	-2.1 (-2.8 to 1.3)	<0.001	1.1	-37%
<b>Secondary outcome variables:</b>						
KOOS, 100-0						
Symptoms	60.7 (19.5)	67.8 (18.9)	7.1 (1.4 to 12.9)	0.016	0.4	+12%
Pain	55.0 (16.6)	68.1 (19.1)	13.1 (7.2 to 18.9)	<0.001	0.8	+24%
Sports and recreation	23.0 (18.8)	35.1 (24.8)	12.1 (5.1 to 19.2)	0.001	0.6	+53%
Quality of life	42.6 (13.9)	51.6 (19.2)	9.0 (4.7 to 13.3)	<0.001	0.6	+21%
NRS, pain in past week, 0-10	5.5 (2.0)	3.4 (2.3)	-2.1 (-2.8 to -1.3)	<0.001	1.1	-37%
NRS, pain at the moment, 0-10	4.9 (2.4)	2.9 (2.7)	-1.9 (-2.8 to -1.1)	<0.001	0.8	-41%
GPE, number (%)**	n/a		n/a	n/a	n/a	n/a
Very much improved		7 (15%)				
Much improved		15 (32%)				
Slightly improved		18 (38%)				
No difference		5 (11%)				
Slightly worsened		1 (2%)				
Much worsened		1 (2%)				
Very much worsened		0 (0%)				
<b>Subgroup variables:</b>						
Isometric quadriceps muscle strength, Nm/kg	0.84 (0.34)	1.12 (0.41)	0.29 (0.20 to 0.37)	<0.001	0.9	+33%
BMI, kg/m <sup>2</sup>	29.3 (5.6)	29.2 (5.6)	-0.1 (-0.4 to 0.1)	0.213	0.0	0%
HADS depression, 0-21	3.4 (3.1)	2.4 (2.5)	-1.0 (-1.6 to 0.4)	0.002	0.3	-29%

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\* within-group effect sizes ( $t_0 - t_1 / SD$  at  $t_0$ ); \*\* n=47; SD = standard deviation; CI = confidence interval; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = function in daily living; NRS = numeric rating scale; GPE = global perceived effect; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale.

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**TABLE 5. Changes in outcome for each subgroup during 4-month treatment period (n=50)**

	High muscle strength (n=17)		Depression (n=4)		Obesity (n=6)		Low muscle strength (n=23)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
<b>Primary outcome variables:</b>								
KOOS ADL, 100-0	13.3 (18.7)	+21%	18.8 (15.7)	+41%	3.4 (22.7)	-6%	14.9 (16.6)	+24%
MCID <sup>1</sup> , n (5)	9 (53%)		3 (75%)		3 (50%)		12 (52%)	
NRS, pain during walking in past week, 0-10	-2.1 (3.1)	-37%	-2.0 (3.4)	-35%	-1.0 (2.6)	-15%	-2.4 (2.2)	-45%
MCID <sup>2</sup> , n (%)	11 (65%)		3 (75%)		2 (33%)		17 (74%)	
<b>Subgroup variables:</b>								
Isometric quadriceps muscle strength, Nm/kg	0.24 (0.36)	+20%	0.33 (0.17)	+48%	0.18 (0.16)	+26%	0.34 (0.32)	+56%
HADS depression, 0-21	-1.0 (2.1)	-32%	-4.3 (5.1)	-42%	-0.7 (0.8)	-22%	-0.4 (1.1)	-18%
BMI, kg/m <sup>2</sup>	-0.3 (0.5)	-1%	-0.7 (1.3)	-2%	0.1 (0.8)	0%	0.0 (0.7)	0%

<sup>1</sup> Improvement  $\geq 10$  points on 0-100 scale (based on Roos & Lohmander [35]).

<sup>2</sup> Reduction  $\geq 2$  points on 0-10 scale or  $\geq 33\%$  (based on Salaffi et al [36]).

SD = standard deviation; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = function in daily living; MCID = minimally clinically important difference; NRS = numeric rating scale; HADS = Hospital Anxiety and Depression Scale; BMI = body mass index.