Stratified exercise therapy does not improve outcomes compared with usual exercise therapy in people with knee osteoarthritis (OCTOPuS study) a cluster randomised trial

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Research

Stratified exercise therapy does not improve outcomes compared with usual exercise therapy in people with knee osteoarthritis (OCTOPuS study): a cluster randomised trial

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KEY WORDS

Knee osteoarthritis
Exercise therapy
Dietary intervention
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Stratified care

ABSTRACT

Question: In people with knee osteoarthritis, how much more effective is stratified exercise therapy that distinguishes three subgroups (high muscle strength subgroup, low muscle strength subgroup, obesity subgroup) in reducing knee pain and improving physical function than usual exercise therapy? **Design:** Pragmatic cluster randomised controlled trial in a primary care setting. **Participants:** A total of 335 people with knee osteoarthritis: 153 in an experimental arm and 182 in a control arm. **Intervention:** Physiotherapy practices were randomised into an experimental arm providing stratified exercise therapy (supplemented by a dietary intervention from a dietician for the obesity subgroup) or a control arm providing usual, non-stratified exercise therapy. **Outcome measures:** Primary outcomes were knee pain severity (numerical rating scale for pain, 0 to 10) and physical function (Knee Injury and Osteoarthritis Outcome Score subscale activities of daily living, 0 to 100). Measurements were performed at baseline, 3 months (primary endpoint) and 6 and 12 months (follow-up). Intention-to-treat, multilevel, regression analysis was performed. **Results:** Negligible differences were found between the experimental and control groups in knee pain (mean adjusted difference 0.2, 95% CI −0.4 to 0.7) and physical function (−0.8, 95% CI −4.3 to 2.6) at 3 months. Similar effects between groups were also found for each subgroup separately, as well as at other time points and for nearly all secondary outcome measures. **Conclusion:** This pragmatic trial demonstrated no added value regarding clinical outcomes of the model of stratified exercise therapy compared with usual exercise therapy. This could be attributed to the experimental arm therapists facing difficulty in effectively applying the model (especially in the obesity subgroup) and to elements of stratified exercise therapy possibly being applied in the control arm. **Registration:** Netherlands National Trial Register NL7463. **[Knoop J, Dekker J, van Dongen JM, van der Leeden M, de Rooij M, Peter WFH, de Joode W, van Bodegom-Vos L, Lopuhaä N, Bennell KL, Lems WF, van der Esch M, Vliet Vlieland TPM, Ostelo RWJG (2022) Stratified exercise therapy does not improve outcomes compared with usual exercise therapy in people with knee osteoarthritis (OCTOPuS study): a cluster randomised trial. *Journal of Physiotherapy* 68:182–190]**

Introduction

Osteoarthritis (OA) is a common chronic health condition and a leading cause of pain and disability among adults.[1] Knee OA is a highly heterogeneous disease but is likely to consist of homogeneous phenotypes or subgroups.[2,3] Exercise therapy is recommended as a first-step treatment, next to pain medication and diet.[4] There is strong, high-quality evidence for the effectiveness of exercise therapy on knee pain and physical function compared with no exercise therapy.[5] These effects have been found in mild OA and also in severe OA.[6,7] However, although effective, the average standardised effect size of exercise therapy compared with no exercise therapy is only moderate (approximately 0.5).[5] This may be attributed to the current 'one-size-fits-all' exercise approach. A stratification into subgroups

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that receive specifically tailored interventions may yield superior clinical and economic outcomes.[8] Randomised trials are needed to determine the added value of such a stratified approach of exercise therapy.

Five phenotypes or subgroups of knee OA patients were recently identified in one cohort[9] and this finding was replicated in a second cohort.[10] Subsequently, a model of stratified exercise therapy was developed based on three of the identified subgroups that are aligned with well-accepted OA phenotypes: a 'low muscle strength subgroup' (LMS) ('age-induced phenotype[3]), a 'high muscle strength subgroup' (HMS) ('post-traumatic phenotype[3]), and an 'obesity subgroup' (OS) ('metabolic phenotype[3]). For each subgroup, a subgroup-specific exercise therapy intervention was developed, based on existing exercise therapy interventions,[11,12] supplemented by a dietary intervention for the OS. These interventions, together with a simple stratification algorithm to allocate patients into one of the subgroups, were pilot tested for feasibility and further optimisation.[13] Moreover, it was found that the construct validity of the final stratification algorithm was adequate, as it consistently aligned these subgroups with their proposed phenotype.[14]

It was then hypothesised that this model of stratified exercise therapy – in which the HMS, LMS and OS subgroups receive subgroup-specific exercise therapy, supplemented by a dietary intervention for the OS – would be more effective in reducing pain and improving physical function in patients with knee OA compared with usual, 'non-stratified' exercise therapy.

Therefore, the study question for this cluster randomised trial was:

> In patients with knee osteoarthritis, how much more effective is stratified exercise therapy that distinguishes three subgroups ('high muscle strength subgroup', 'low muscle strength subgroup' and 'obesity subgroup') in reducing knee pain and improving physical function than usual exercise therapy?

Method

Study design

A pragmatic, parallel, two-group, cluster randomised controlled trial in primary care was performed – the Optimisation of exerCise Therapy in patients with knee Osteoarthritis in a Primary care Setting (OCTOPuS) study – which was accompanied by a qualitative process evaluation[15] and economic evaluation (under review). Detailed description of the trial methods has been published.[16] This trial is reported according to the CONSORT 2010 checklist for cluster randomised controlled trials (Appendix 1 on the eAddenda).[17]

In line with current recommendations for pragmatic cluster randomised controlled trials,[18] patients were blinded for treatment allocation (ie, only informed about their own intervention). Blinding experimental arm physiotherapists or dieticians was not possible, but control arm physiotherapists were blinded for the content of the experimental intervention. Blinding of researchers responsible for the study logistics was not possible. However, an independent researcher who was blinded for treatment allocation performed the randomisation of physiotherapy practices and primary analyses.

Physiotherapists screened patients for eligibility at their first consultation. After providing informed consent, eligible patients were included and asked to complete questionnaires at baseline (T0), 3 months follow-up (T3), 6 months follow-up (T6), and 12 months follow-up (T12). All physiotherapists and dieticians registered treatment fidelity parameters for each session. As this was a pragmatic trial, patients from both groups were allowed to receive any additional usual care and this was monitored in the follow-up questionnaires. The design of the study is presented in Figure 1.

Physiotherapists

Physiotherapists were considered eligible if there were at least two physiotherapists working in one practice, they were located within 50 km of one of the two study centres, they had exercise therapy facilities and they were treating on average at least one new patient with knee OA per month.

A total of 55 practices with 126 physiotherapists were randomly allocated (1:2 ratio) to the experimental arm (19 practices, 46 physiotherapists) or control-arm (36 practices, 80 physiotherapists), by using a web-based randomisation program, with random sequence generation and concealment of randomisation guaranteed. The 1:2 ratio was chosen to reduce the number of participants needed for each control-arm physiotherapist, thereby minimising their burden, as physiotherapists expressed interest in this study primarily because of the experimental intervention. Because of low participant inclusion rates in the experimental arm, a second wave was added to recruit physiotherapists with a 2:1 instead of 1:2 randomisation (in order to include more experimental-arm than control-arm physiotherapists) and without the criterion of at least two participating physiotherapists per practice. This second wave resulted in four practices with eight physiotherapists being allocated to the experimental arm and two practices with three physiotherapists to the control arm. Each of the experimental-arm physiotherapy practices were instructed to nominate a dietician with whom they already collaborated for the diet intervention in the OS.

Participants

Participants were recruited by participating physiotherapists in primary care, and tested for eligibility with the following eligibility criteria. The inclusion criteria were: the presence of knee pain with a duration $\geq$ 3 months and severity during walking $\geq$ 2/10 on the pain numerical rating scale; and a clinical knee OA diagnosis.[19] The exclusion criteria were: age $<$ 40 or $>$ 85 years; pain severity during walking $\geq$ 9/10 on the pain numerical rating scale; physical or mental comorbidity severely affecting daily life and contra-indicating exercise therapy; suspicion of chronic widespread pain; (planned) total knee arthroplasty; other reasons for knee pain (eg, rheumatoid arthritis, gout); physiotherapy or intra-articular injections for knee pain in past 6 months; and insufficient Dutch language comprehension.

Intervention

Experimental arm

Physiotherapists were trained to provide treatment according to the model of stratified exercise therapy, which consisted of: subgroup allocation by physiotherapists through a simple, stratification algorithm (Figure 2); and subgroup-specific, protocolised exercise therapy interventions (see Table 1 for a summary and Appendix 2 on the eAddenda for detailed information).

Dieticians were instructed to deliver a dietary intervention according to the current Dutch guideline[20] to participants in the OS (see Table 1 for summary and Appendix 3 on the eAddenda for detailed information).

Control arm

Physiotherapists were instructed to provide their usual care (ie, standard, 'non-stratified' exercise therapy, according to the guideline[21]).

Outcome measures

Patient-reported outcome measures were administered at T0, T3 (primary end-point), T6 and T12, while the three physical tests were applied at T0 and T3 (by physiotherapist) and T12 (by physiotherapist or researcher team member).

Primary outcome measures

Average knee pain severity during walking in the past week: assessed by a numerical rating scale (score 0 = no pain; 10 = worst pain imaginable).[22]

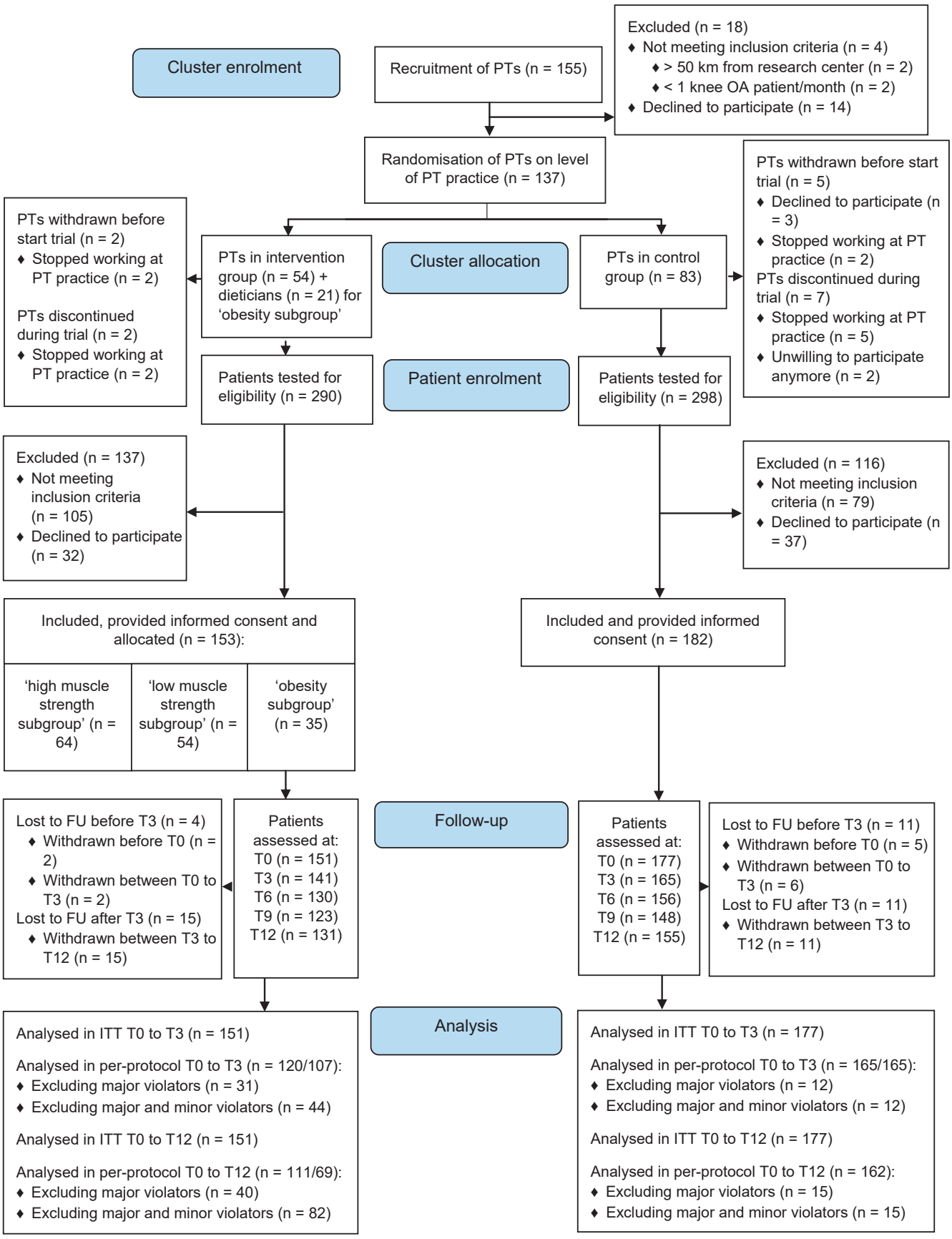

Figure 1. Flow diagram.
FU = follow-up, ITT = intention to treat, OA = osteoarthritis, PT = physiotherapist, T = time point.

Physical functioning: assessed by subscale function in daily living (activities of daily living) of the Dutch translation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (score 0 = maximal problems; 100 = no problem).[23,24]

Secondary outcome measures

Global perceived effect: measuring the participant's subjective global change using a 7-point scale ranging from 'worse than ever' to 'completely recovered'. This was dichotomised as follows: recovered

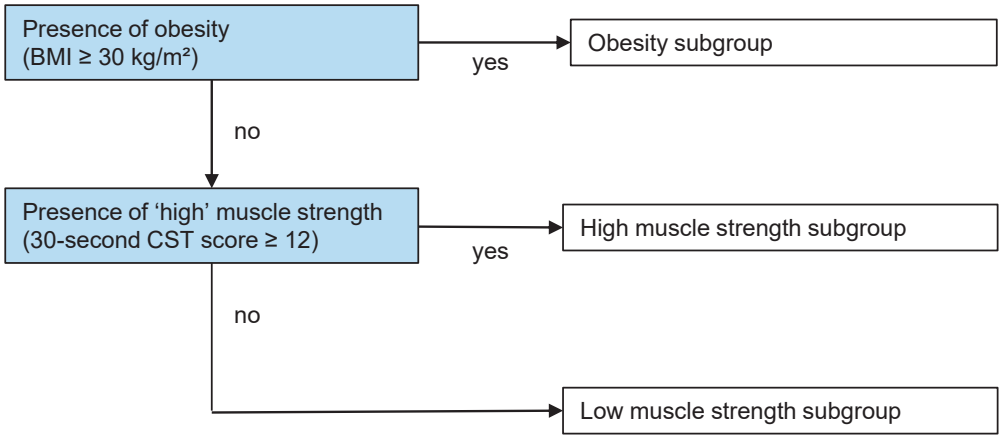

Figure 2. Stratification algorithm.
BMI = body mass index, CST = chair stand test.

('completely recovered' and 'much recovered') versus not recovered (all other responses).

Physical functioning: assessed by the short version of the Dutch translation of the KOOS questionnaire (0 = maximal problems; 100 = no problem).[23,24]

Pain interference: assessed by the short version of the Patient Reported Outcomes Measurement Information System (PROMIS) (4 = best score; 20 = worst score).[25]

Fatigue: assessed by the short version of PROMIS (4 = best score; 20 = worst score).[25]

Patient-reported knee instability: assessed by frequency of episodes of knee instability in the past 3 months, and severity of impact of knee instability on daily living.[26]

Upper leg muscle strength: assessed by the 30-second chair stand test, as a measure of lower body strength and physical functioning.[27]

Body mass index (BMI): body weight (in kilograms) divided by squared body height (in metres).

Waist circumference: distance around the abdomen in the horizontal plane midway between the lowest rib and iliac crest.

Treatment fidelity measures

The treatment fidelity measures were: number of sessions (physiotherapy and dietary intervention); intervention modalities (physiotherapy and dietary intervention); adverse events (physiotherapy and dietary intervention); training intensity on 6-to-20 Borg scale[28] as perceived by the patient (physiotherapy intervention); and patient-reported adherence to home exercises and (moderate and vigorous) physical activities (physiotherapy intervention).

Healthcare utilisation

At baseline and every follow-up time point, participants registered in the questionnaires the number of received consults of any other healthcare in the past 3 months. Healthcare utilisation was subdivided into general practitioner, other primary care (eg, occupational therapist), secondary care (eg, orthopaedic surgeon) and alternative care (eg, acupuncturist).

Additional baseline measures

General participant characteristics (age, gender, duration of knee symptoms, left/right knee, history of knee surgery, comorbidity) and physiotherapist characteristics (age, gender, years employed, years of experience treating knee OA patients, number of knee OA patients treated monthly, education level and additional OA-related education) were collected through questionnaires.

Data analysis

A between-group difference of 0.5 on the 0 to 10 pain numerical rating scale was a priori expected, based on the effectiveness of usual exercise therapy[5], the pilot study[13] and a previous study[29] comparing stratified exercise therapy versus usual care in low back pain. With an estimated standard deviation (SD) of 1.4, $\alpha = 0.05$ (two-sided testing), power = 90% and design effect of 1.05, 346 participants were needed. With a 15% drop-out rate, the sample size was 408 participants (204 per group).

All data were analysed according to the intention-to-treat principle. In a deviation to the statistical analysis plan, multiple

Table 1
Summary[a] of description of subgroup-specific, protocolised exercise therapy interventions.

High muscle strength subgroup	Low muscle strength subgroup	Obesity subgroup
Exercise therapy from physiotherapist Number of sessions: - 3 to 5 individual sessions in a 12-wk treatment period - 1 'booster' session in the post-treatment period Content: a) subgroup-specific education/advice b) home exercises	Exercise therapy from physiotherapist Number of sessions: - 8 to 12 individual sessions in a 12-wk treatment period - 1 to 2 'booster' sessions in the post-treatment period Content: a) subgroup-specific education/advice b) supervised exercise therapy, primarily targeting upper leg muscle strength c) home exercises	Exercise therapy from physiotherapist Number of sessions: - 12 to 18 individual sessions in a 12-wk treatment period - 2 to 3 'booster' sessions in the post-treatment period Content: a) subgroup-specific education/advice b) supervised exercise therapy adapted to obesity, targeting upper leg muscle strength, aerobic capacity and weight loss c) home exercises Dietary intervention from dietician Number of sessions: - 5 to 8 individual sessions, of 150 minutes in total Content: - advising and monitoring healthy diet and active lifestyle, aiming at ≥ 10% weight loss Interprofessional consultation between physiotherapist and dietician - at least one consultation after 3 to 4 wks of treatment to agree on an approach to achieve sustainable lifestyle change

[a] Detailed information provided at Appendices 1 (physiotherapy intervention) and 2 (diet intervention) on the eAddenda.

imputation was used instead of maximum likelihood estimation for missing values, due to the number of missing data.

A multilevel, regression analysis – with levels of physiotherapy practice, patient and time point – was performed for the primary outcomes. The primary end-point was T3, with the other time points and the overall effect for the total follow-up period as secondary time points. Analyses were adjusted for the baseline value of the outcome variable, and of the presumed effect modifiers (ie, pain severity, upper leg muscle strength and BMI). Similar analyses for secondary outcome measures were performed with continuous scales, while logistic multilevel analysis was performed for the dichotomous secondary outcome measures. Subgroup analyses were also performed comparing the two trial arms separately for each of the three subgroups. Sensitivity analyses were performed: excluding all cases with a major protocol violation; and excluding all cases with any protocol violation (per-protocol analyses), with all a priori formulated protocol violations described in Appendix 4 on the eAddenda. The intended sensitivity analysis accounting for the number of participating physiotherapists within each physiotherapy practice (as a fourth level alongside physiotherapy practice, patient and time point) could not be performed due to small numbers. Finally, we calculated relative improvements (%), number of responders (based on currently accepted cut-off points for minimally clinically important change) and within-group and between-group Cohen's effect sizes.

StataSE software[a] was used for multilevel regression analyses. IBM software[b] was used for description of baseline, treatment fidelity and healthcare utilisation characteristics.

Results

Flow of participants through the study

Figure 1 shows the flow of physiotherapists and participants through the trial. A total of 137 physiotherapists were randomised to the experimental arm (n = 54) and control arm (n = 83). In addition, 21 dieticians were recruited for the diet intervention of the OS. Patients were enrolled between January 2019 and May 2020, and enrolment was stopped at 335 participants (ie, 82% of the intended 408) due to a COVID-19 lock-down that obstructed any further inclusion for a substantial period. The intention-to-treat analysis included 328 participants, which was 95% of the 346 that were needed based on the sample size calculation.

Baseline characteristics of the study participants

The baseline characteristics of participants from the experimental arm (n = 151) and control arm (n = 177), and of the physiotherapists are described in Table 2. In the experimental arm, 42% were allocated to HMS, 35% to LMS and 23% to OS. No stratification algorithm was used in the control arm, but based on baseline characteristics, 38% would have been allocated to HMS, 31% to LMS and 31% to OS.

Table 2
Baseline characteristics.

	Exp (n = 151)	Con (n = 177)
General patient characteristics		
Age *(years)*, mean (SD)	66 (9)	64 (9)
Gender *(female)*, number (%)	95 (63)	114 (64)
Duration of knee symptoms *(yr)*, mean (SD)	9 (10)	7 (8)
History of knee surgery *(yes)*, n (%)	50 (33)	55 (31)
Using pain medication *(yes)*, n (%)	63 (42)	86 (49)
Comorbidity, n (%)		
present	90 (60)	103 (58)
present and affecting daily life	32 (21)	31 (18)
Work status, n (%)		
paid work	54 (36)	75 (42)
no work, but not retired	16 (11)	16 (9)
retired	79 (52)	85 (48)
unknown	2 (1)	1 (1)
Sick leave in past 3 mths, n (%)	10 (7)	13 (7)
Allocation to subgroup, n (%)		
High muscle strength subgroup	63 (42)	65 (37)[a]
Low muscle strength subgroup	54 (35)	53 (30)[a]
Obesity subgroup	34 (23)	53 (30)[a]
Unknown		6 (3)[a]
Clinical variables		
Knee pain severity *(NRS, 0 to 10)*, mean (SD)	5.1 (2.1)	5.3 (2.1)
Physical function *(0 to 100)*, mean (SD)		
KOOS ADL	68 (19)	65 (18)
KOOS Short form	55 (22)	51 (20)
Pain interference *(PROMIS, 4 to 20)*, mean (SD)	10.1 (3.5)	10.5 (3.4)
Fatigue *(PROMIS, 4 to 20)*, mean (SD)	8.0 (3.7)	8.1 (3.7)
Knee instability, n (%)		
in past 3 mths	111 (74)	137 (77)
affecting daily life	65 (43)	84 (47)
30-s chair stand test *(reps)*, mean (SD)	11.7 (3.1)	11.5 (3.7)
Body mass index *(kg/m^2)*, mean (SD)	27.1 (4.0)	28.6 (4.9)
Waist circumference *(cm)*, mean (SD)	97.9 (11.4)	100.7 (13.5)
General physiotherapist characteristics	Exp (n = 54)	Con (n = 80)
Age *(yr)*, mean (SD)	34 (11)	39 (11)
Gender *(female)*, n (%)	26 (48)	37 (45)
Years working as physiotherapist, mean (SD)	10 (9)	14 (11)

ADL = activities of daily living, Con = control group, Exp = experimental group, KOOS = Knee Injury and Osteoarthritis Outcome Score, NRS = numerical rating scale, PROMIS = the Patient Reported Outcomes Measurement Information System.
[a] Control arm was unaware of and did not use stratification algorithm for subgroup allocation.

Clinical outcomes

The adjusted mean differences between the experimental and control arms on the primary outcomes knee pain (numerical rating scale) and physical function (KOOS ADL) at T3 were 0.2 (95% CI –0.4 to 0.7) and –0.8 (95% CI –4.3 to 2.6), respectively (see Table 3, and Appendix 5a on the eAddenda). These differences can be considered negligible. Subgroup analyses in which the experimental and control groups were compared in each of the three subgroups separately resulted in similar results of negligible differences between arms (see Appendix 5b to 5d and Appendix 6 on the eAddenda).

Negligible differences were also found between arms for the secondary outcome measures. Small effects were found favouring the experimental arm for pain interference (PROMIS; at T3, T12 and for overall effect) and upper leg muscle strength (30-second chair stand test; for overall effect only), but these were all too small to be of clinical relevance. Per-protocol analyses yielded similar findings (data not shown). Both arms showed comparable average relative improvements at T3 and T12 (ie, 20 to 30% for knee pain and 10 to 20% for physical function), which only slightly varied across subgroups (see Table 4). Finally, the two arms showed comparable responder rates (ie, 65% responders for knee pain; 42% and 45% responders in experimental and control arm, respectively, for physical function) and comparable within-group effect sizes (ie, 0.5 to 0.7 for knee pain; 0.3 to 0.6 for physical function) (see Appendix 7 on the eAddenda). Individual participant data are presented in Table 5 on the eAddenda.

Treatment fidelity

The mean number of physiotherapy sessions was 8.4 (SD 4.7) in the experimental arm and 9.6 (SD 4.8) in the control arm (Table 6). The mean number of sessions in the experimental arm differed across subgroups, as instructed (5.3 for HMS, 9.6 for LMS, 12.2 for OS), while they were similar across subgroups in the control arm (9.9 for HMS, 9.4 for LMS, 9.9 for OS). The OS participants from the experimental arm additionally received on average 3.2 sessions (SD 1.8) from a dietician. The mean training intensity was marginally higher in the experimental arm – Borg score (scale 6 to 20) of 13.1 (SD 2.0) versus 12.3 (SD 2.0) – based on 2,021 registered sessions. Home exercises were performed for on average 3 days/week throughout the 12-month follow-up period in both groups. In 61% and 58% of the participants, the intended level of physical activity (ie, 150 minutes/week of at least moderately intense activities) was reached at 12-months follow-up, in the experimental and control groups, respectively.

Table 3
Primary and secondary outcomes.

	Scores[a]		Estimated mean difference (MD) between arms	
	Exp (n = 151)	Con (n = 177)	Crude analyses	Adjusted analyses[b]
			MD (95% CI)	MD (95% CI)
Primary outcomes				
Knee pain severity *(NRS, 0 to 10)*				
Baseline	5.1 (0.17)	5.3 (0.16)	n/a	n/a
3 mths follow-up	4.1 (0.19)	4.1 (0.20)	0.1 (−0.5 to 0.6)	0.2 (−0.4 to 0.7)
6 mths follow-up	4.1 (0.20)	4.0 (0.20)	0.1 (−0.5 to 0.7)	0.3 (−0.3 to 0.8)
12 mths follow-up	3.6 (0.19)	3.9 (0.18)	−0.2 (−0.8 to 0.4)	−0.2 (−0.7 to 0.4)
Overall	n/a	n/a	0.0 (−0.5 to 0.5)	0.1 (−0.3 to 0.5)
Physical function *(KOOS ADL, 0 to 100)* [c]				
Baseline	68 (1.6)	65 (1.4)	n/a	n/a
3 mths follow-up	74 (1.4)	73 (1.5)	1.1 (−2.9 to 5.1)	−0.8 (−4.3 to 2.6)
6 mths follow-up	76 (1.6)	74 (1.5)	1.4 (−2.7 to 5.6)	−0.5 (−4.1 to 3.1)
12 mths follow-up	77 (1.4)	76 (1.4)	0.8 (−3.2 to 4.8)	−0.6 (−4.0 to 2.8)
Overall	n/a	n/a	1.1 (−2.4 to 4.6)	−0.7 (−3.5 to 2.2)
Secondary outcomes				
Global perceived effect *(at least 'much improved')*				
3 mths follow-up	48 (32%)	60 (34%)	0.9 (0.4 to 1.9)[d]	0.9 (0.4 to 1.8)[d]
6 mths follow-up	54 (36%)	67 (38%)	0.9 (0.4 to 1.9)[d]	0.8 (0.4 to 1.8)[d]
12 mths follow-up	65 (43%)	73 (41%)	1.1 (0.5 to 2.6)[d]	1.1 (0.5 to 2.5)[d]
Overall	n/a	n/a	1.0 (0.5 to 1.7)[d]	0.9 (0.5 to 1.7)[d]
Physical function *(KOOS short form, 0 to 100)* [c]				
Baseline	55 (1.8)	51 (1.5)	n/a	n/a
3 mths follow-up	60 (1.6)	58 (1.6)	1.3 (−3.2 to 5.8)	−1.08 (−4.9 to 3.0)
6 mths follow-up	63 (1.8)	61 (1.7)	2.0 (−2.8 to 6.7)	−0.3 (−4.6 to 4.0)
12 mths follow-up	63 (1.8)	63 (1.9)	0.2 (−5.4 to 5.7)	−2.1 (−7.2 to 3.0)
Overall	n/a	n/a	1.2 (−2.9 to 5.3)	−1.1 (−4.6 to 2.3)
Pain interference *(PROMIS, 4 to 20)*				
Baseline	10.1 (0.28)	10.5 (0.26)	n/a	n/a
3 mths follow-up	8.0 (0.24)	9.0 (0.30)	−0.9 (−1.8 to −0.1)	−0.7 (−1.4 to −0.1)
6 mths follow-up	7.9 (0.30)	8.4 (0.26)	−0.5 (−1.3 to 0.4)	−0.3 (−0.9 to 0.4)
12 mths follow-up	7.3 (0.27)	8.3 (0.28)	−1.0 (−1.8 to −0.1)	−0.8 (−1.5 to 0.0)
Overall	n/a	n/a	−0.8 (−1.5 to −0.1)	−0.6 (−1.1 to −0.1)
Fatigue *(PROMIS, 4 to 20)*				
Baseline	8.1 (0.30)	8.1 (0.28)	n/a	n/a
3 mths follow-up	7.7 (0.27)	7.4 (0.26)	0.2 (−0.8 to 1.1)	0.3 (−0.3 to 1.0)
6 mths follow-up	7.4 (0.32)	7.9 (0.30)	−0.6 (−1.6 to 0.5)	−0.4 (−1.2 to 0.4)
12 mths follow-up	7.2 (0.27)	7.5 (0.28)	−0.3 (−1.3 to 0.6)	−0.2 (−0.8 to 0.5)
Overall	n/a	n/a	−0.2 (−1.4 to 0.7)	−0.1 (−0.6 to 0.5)
Knee instability in past 3 mths				
Baseline	112 (74%)	136 (77%)	n/a	n/a
3 mths follow-up	122 (81%)	149 (84%)	0.8 (0.3 to 2.2)[d]	0.9 (0.4 to 2.3)[d]
6 mths follow-up	110 (73%)	140 (79%)	0.7 (0.3 to 1.6)[d]	0.7 (0.3 to 1.7)[d]
12 mths follow-up	104 (69%)	120 (68%)	1.1 (0.5 to 2.6)[d]	1.3 (0.6 to 2.7)[d]
Overall	n/a	n/a	0.9 (0.5 to 1.7)[d]	1.0 (0.6 to 1.7)[d]
Knee instability affecting daily life				
Baseline	65 (43%)	85 (48%)	n/a	n/a
3 mths follow-up	59 (39%)	76 (43%)	0.7 (0.3 to 1.8)[d]	0.9 (0.4 to 1.9)[d]
6 mths follow-up	56 (37%)	64 (36%)	1.0 (0.4 to 2.5)[d]	1.2 (0.5 to 2.8)[d]
12 mths follow-up	45 (30%)	62 (35%)	0.7 (0.3 to 1.8)[d]	0.8 (0.3 to 2.0)[d]
Overall	n/a	n/a	0.81 (0.40 to 1.63)[d]	0.96 (0.53 to 1.76)[d]
Upper leg muscle strength *(30-s CST, repetitions)*				
Baseline	11.7 (0.26)	11.4 (0.28)	n/a	n/a
3 mths follow-up	14.9 (0.28)	14.0 (0.36)	0.9 (−0.3 to 2.0)	0.8 (−0.1 to 1.7)
12 mths follow-up	15.3 (0.68)	14.3 (0.38)	0.9 (−0.4 to 2.2)	0.8 (−0.4 to 2.0)
Overall	n/a	n/a	0.9 (−0.1 to 1.9)	0.8 (0.1 to 1.5)
Body mass index *(kg/m^2)*				
Baseline	27.1 (0.33)	28.6 (0.37)	n/a	n/a
3 mths follow-up	26.9 (0.32)	28.4 (0.35)	−1.5 (−2.6 to −0.5)	−0.2 (−0.7 to 0.2)
12 mths follow-up	27.1 (0.32)	28.5 (0.40)	−1.4 (−2.5 to −0.3)	−0.1 (−0.6 to 0.4)
Overall	n/a	n/a	−1.5 (−2.5 to −0.4)	−0.2 (−0.6 to 0.2)
Waist circumference *(cm)*				
Baseline	97.7 (0.93)	100.9 (1.03)	n/a	n/a
3 mths follow-up	96.6 (0.90)	99.5 (0.98)	−3.0 (−6.2 to 0.2)	−0.2 (−1.6 to 1.3)
12 mths follow-up	96.3 (1.04)	99.5 (1.05)	−3.3 (−6.9 to 0.2)	−0.5 (−3.0 to 1.9)
Overall	n/a	n/a	−3.2 (−6.3 to 0.0)	−0.4 (−1.8 to 1.1)

ADL = activities of daily living, BMI = body mass index, Con = control group, CST = chair stand test, Exp = experimental group, KOOS = Knee Injury and Osteoarthritis Outcome Score, NRS = numerical rating scale, PROMIS = the Patient Reported Outcomes Measurement Information System.

[a] Mean (standard error) for continuous outcomes; % for dichotomous outcomes.

[b] Adjusted for baseline value of outcome measure, in addition to baseline values of NRS pain, 30-s chair stand test and BMI.

[c] Level of physiotherapist practice could not be added.

[d] Odds ratio.

Table 4
Relative improvements in primary outcome measures for each arm and subgroup.

	Exp (n = 151)				Con (n = 177)[a]			
	Total (n = 151)	HMS (n = 63)	LMS (n = 54)	OS (n = 34)	Total (n = 171)	HMS (n = 65)[b]	LMS (n = 53)[b]	OS (n = 53)[b]
Knee pain severity (NRS)								
3 mths follow-up	−20%	−19%	−23%	−14%	−23%	−30%	−13%	−26%
12 mths follow-up	−29%	−26%	−34%	−30%	−26%	−30%	−29%	−21%
Physical function (KOOS ADL)								
3 mths follow-up	+19%	+6%	+9%	+17%	+11%	+11%	+8%	+13%
12 mths follow-up	+14%	+8%	+17%	+22%	+17%	+14%	+14%	+20%

ADL = activities of daily living, Con = control group, Exp = experimental group, HMS = high muscle strength subgroup, KOOS = Knee Injury and Osteoarthritis Outcome Score, LMS = low muscle strength subgroup, NRS = numerical rating scale, OS = obesity subgroup.
[a] subgroup allocation was unknown for six participants in control arm.
[b] control arm was unaware and did not use stratification algorithm for subgroup allocation.

Major protocol violations were identified in 34 (23%) and 11 (6%) in the experimental and control arm, respectively (see Appendix 8 on the eAddenda). The most frequently reported major protocol violation in the experimental arm was 'too few physiotherapy sessions' (with minimum number of sessions differing across subgroups) (n = 30) and 'less than two physiotherapy sessions' (n = 5) in the control arm. Minor protocol violations were identified in 52 (34%) participants in the experimental arm, mostly due to 'no booster session provided' (n = 47). No minor protocol deviations were defined in the control arm. No adverse events were reported.

Other healthcare utilisation

During the 12-month follow-up period, 101 participants (67%) in the experimental arm received general practitioner care (median number of consults 1, IQR 0 to 3), 30 (20%) received primary care (other than experimental intervention) (median 0, IQR 0 to 0), 71 (47%) received secondary care (median 0, IQR 0 to 2) and 15 (10%) received alternative care (median 0, IQR 0 to 0). In the control arm, this was 122 (69%) (median 2, IQR 0 to 3) for general practitioner, 33 (19%) (median 0, IQR 0 to 0) for primary care (other than the control intervention), 87 (49%) (median 0, IQR 0 to 2) for secondary care and 14 (8%) (median 0, IQR 0 to 0) for alternative care.

Discussion

In this large, pragmatic cluster randomised controlled trial in a primary care setting, the clinical effectiveness of a new model of stratified exercise therapy for an HMS, LMS and OS (supplemented by a dietary intervention for the OS) was evaluated in people with knee OA. This model of stratified exercise therapy was based on effective exercise programs,[11,12] well-accepted[3] and empirically observed phenotypes,[9,10] and a valid stratification algorithm.[14] In contrast to the hypothesis, the promising results in a pilot study[13] and the model being perceived by patients and therapists as highly applicable,[15] it showed no added value regarding clinical outcomes compared with usual exercise therapy, neither in the total sample nor in any of the three subgroups. Although the study estimated effects on two secondary outcome measures in favour of the experimental arm, these were clearly too small to be clinically important.

Table 6
Treatment fidelity.

	Exp (n = 151)				Con (n = 171)[a]			
	Total (n = 151)	HMS (n = 63)	LMS (n = 54)	OS (n = 34)	Total (n = 171)	HMS (n = 65)[b]	LMS (n = 53)[b]	OS (n = 53)[b]
Physiotherapy treatment								
Physiotherapy sessions								
Number of sessions (12-mth period), mean (SD)	8.4 (4.7)	5.3 (3.1)	9.6 (3.6)	12.2 (5.1)	9.6 (4.8)	9.9 (5.0)	9.4 (4.4)	9.9 (4.7)
Fewer sessions than recommended, n (%)	30 (20)	3 (5)	12 (22)	15 (44)	n/a	n/a	n/a	n/a
More sessions than recommended, n (%)	15 (10)	9 (14)	2 (4)	4 (12)	n/a	n/a	n/a	n/a
Type of physiotherapy interventions, n (%)								
Patient education	141 (95)	56 (92)	51 (94)	34 (100)	141 (84)	50 (81)	47 (89)	42 (84)
Home exercises	137 (91)	56 (92)	48 (89)	33 (97)	135 (80)	50 (81)	42 (79)	41 (82)
Exercise therapy (any)	132 (89)	46 (75)	52 (96)	34 (100)	168 (96)	59 (95)	51 (96)	49 (98)
Strength training	129 (87)	43 (71)	52 (96)	34 (100)	155 (92)	57 (92)	49 (93)	47 (94)
Aerobic training	78 (52)	14 (23)	36 (67)	28 (82)	105 (63)	36 (58)	62 (33)	35 (70)
Functional training	90 (60)	27 (44)	38 (70)	25 (74)	100 (60)	40 (65)	31 (59)	29 (58)
Balance/ stabilisation training	92 (62)	27 (44)	37 (69)	28 (82)	135 (80)	50 (81)	43 (81)	41 (82)
Other interventions (any)	33 (22)	13 (21)	11 (20)	9 (27)	63 (38)	22 (36)	20 (38)	20 (40)
Active/passive mobilisation	27 (18)	10 (16)	11 (20)	6 (18)	44 (26)	13 (21)	13 (25)	17 (34)
Massage	9 (6)	3 (5)	2 (4)	4 (12)	18 (11)	9 (15)	5 (9)	3 (6)
Taping	2 (1)	0 (0)	1 (2)	1 (3)	15 (9)	6 (10)	7 (13)	2 (4)
TENS	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	1 (2)	2 (4)
Dry needling	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (2)
Dietary intervention								
Number of sessions (12-mth period), mean (SD)	n/a	n/a	n/a	3.2 (1.8)	n/a	n/a	n/a	n/a
Total minutes, mean (SD)	n/a	n/a	n/a	105 (5)	n/a	n/a	n/a	n/a
Fewer sessions than recommended, n (%)	n/a	n/a	n/a	10 (29)	n/a	n/a	n/a	n/a
More sessions than recommended, n (%)	n/a	n/a	n/a	0 (0)	n/a	n/a	n/a	n/a

Con = control group, Exp = experimental group, HMS = high muscle strength subgroup, LMS = low muscle strength subgroup, OS = obesity subgroup, TKA = total knee arthroplasty.
[a] subgroup allocation was unknown for six participants in the control arm.
[b] control arm was unaware and did not use stratification algorithm for subgroup allocation.

Stratified care is considered to have major potential to optimise current treatment effects in knee OA and is a research priority in the field.[8,30] It is believed that this is the first study to perform a randomised controlled trial evaluating a stratified approach to exercise therapy in knee OA. The results align with trials in other musculoskeletal patient groups where stratified care appeared to have no[31–34] to minimal[29] added value over usual care. Results from ongoing trials[35–37] on stratified exercise therapy are expected soon. A slightly different approach, namely a stepped care approach, has recently been tested in knee OA, demonstrating an unclear effect.[38] This means that the evidence underlying stratified exercise therapy in musculoskeletal patient groups is currently very limited.

The lack of difference in effects in this study can be attributed to the contrast between both interventions being smaller than intended for two reasons. First, the experimental intervention seemed to not have been provided fully as planned, especially in the OS. In this subgroup, a substantial proportion (ie, 44% regarding physiotherapy sessions, 29% regarding dietary sessions) received too few sessions. This may have impeded the potential of the intervention, thereby reducing the contrast with the control arm. In addition, the qualitative evaluation[15] revealed several barriers in applying the stratified care model, which is in line with qualitative evaluations regarding the most-applied other stratified care model (ie, STarT BACK approach in low back pain).[39,40] Again, especially in the OS, multiple barriers were observed, namely physiotherapists being hesitant to address obesity, and both physiotherapists and dieticians reporting barriers regarding their interprofessional collaboration. These barriers, in addition to the lower number of provided sessions, might have been responsible for the fact that, in contrast with other studies combining exercise with diet (eg,[41]), no participant in the OS reached the intended 10% weight loss and clinical effects in this subgroup were lower than expected. It should be noted that participants in the current trial initially consulted their physiotherapist for their knee symptoms, with no intention of additionally following a diet intervention from a dietician. It was also found that across all subgroups, a large number of participants (31%) did not receive the recommended booster session(s), due to a lack of perceived necessity by the physiotherapists.[15] The concise training of physiotherapists (ie, e-learning course on the physiotherapy guideline and a 4-hour training course on the experimental intervention, supplemented by online videos and site visits by the researcher) may have been insufficient. By addressing the barriers more extensively in this training of physiotherapists, and by providing tools and resources that support physiotherapists and dieticians, the effectiveness of the experimental intervention might improve.

A second reason for the smaller contrast is that it is possible that elements of the stratified model were already integrated in usual care. In contrast to our hypothesis, physiotherapists no longer seem to apply a 'one-size-fits-all' but a personalised approach, meaning that the treatment is tailored to the person-specific rather than subgroup-specific patient factors, needs and preferences. Such a personalised approach could make a stratified, subgroup-specific approach redundant. Moreover, especially in physiotherapy, considering the wide range of factors that should be taken into account, a stratified approach with only two factors seems to be too simplistic and could even hinder the process of personalisation and clinical reasoning by limiting physiotherapists in their treatment options. Therefore, this stratified approach may only be of added value in physiotherapy for only a few specific purposes, such as for deciding for which patient minimal supervision is sufficient and for which patient other healthcare professionals (eg, dietician) need to be consulted. It is also possible that in this process of personalisation, physiotherapists in the control arm tailored their treatment to the two stratification factors of the model (ie, upper leg muscle strength and BMI), which further minimised the contrast between arms. It should be noted that the control-arm physiotherapists, who were very keen to participate in this trial, may have had more expertise in providing knee OA treatments and were therefore not fully generalisable compared with physiotherapists outside the study.

Based on these results and recent other trials,[29,31–34] it was concluded that the potential of stratified, subgroup-specific exercise therapy is not as high as proposed, with usual exercise therapy already being the best available treatment option. Therefore, further research on stratified approaches of exercise therapy seems to be less relevant. Instead, it is recommended that future research focuses on optimising clinical reasoning process and applying a personalised approach by physiotherapists, such as tailoring exercise therapy to the major comorbidity.[42]

This trial demonstrated no added value regarding clinical outcomes of the model of stratified exercise therapy compared with usual exercise therapy. This could be attributed to the experimental-arm therapists facing difficulty in effectively applying the model (especially in the OS) and to elements of the model possibly being applied in the control arm.

What was already known on this topic: There is strong, high-quality evidence for the effectiveness of exercise therapy on knee pain and physical function. The population of people with knee osteoarthritis is heterogeneous but it contains homogeneous phenotypes or subgroups.
What this study adds: Stratification of exercise therapy so that it is tailored to subgroups with well-preserved muscle strength, low muscle strength or obesity does not substantially improve clinical outcomes in people with knee osteoarthritis.

Footnotes: [a] StataSE 16, StataCorp, College Station, TX, USA.
[b] IBM SPSS statistics 27, IBM Corp., Armonk, USA.

eAddenda: Table 5 and Appendices 1 to 8 can be found online at https://doi.org/10.1016/j.jphys.2022.06.005

Ethics approval: This study was approved by the Medical Ethical Committee of the VU University Medical Centre (2018.563). This study was conducted in agreement with the Declaration of Helsinki (2013), in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO), and the General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming, AVG). Written informed consent was obtained from each subject, after an information letter had been provided. The researchers made sure that the participants were given complete, adequate, written and oral information regarding the nature, aims, possible risks and benefits of the study. The participants were informed that they were free to interrupt their participation in the study at any moment without any consequence, and that they were able to receive a digital copy of their personal data. Participants received a copy of the information sheet and informed consent form. An independent expert was appointed to provide participants with the opportunity to ask questions about the study to someone not related to the study.

Competing interests: RWJG Ostelo is member of the editorial board of *Journal of Physiotherapy*. He was also member of the Scientific Board Physical Therapy of the Royal Dutch Society for Physical Therapy until March 2021, which is the funder of this project. All other authors declare that they have no competing interests.

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