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Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial

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SUMMARY

Objective: To assess the effectiveness of exercise therapy added to general practitioner (GP) care compared with GP care alone, in patients with hip osteoarthritis (OA) during 12 months follow-up.
Methods: We performed a multi-center parallel pragmatic randomized controlled trial in 120 general practices in the Netherlands. 203 patients, aged ≥45 years, with a new episode of hip complaints, complying with the ACR criteria for hip OA were randomized to the intervention group ($n = 101$; GP care with additional exercise therapy) or the control group ($n = 102$; GP care only). GP care was given by patient's own GP. The intervention group received, in addition, a maximum of 12 exercise therapy sessions in the first 3 months and hereafter three booster sessions. Blinding was not possible. Primary outcomes were hip pain and hip-related function measured with the HOOS questionnaire (score 0–100).
Results: The overall estimates on hip pain and function during the 12-month follow-up showed no between-group difference (intention-to-treat). At 3-months follow-up there was a statistically significant between-group difference for HOOS pain −3.7 (95% CI: −7.3; −0.2), effect size −0.23 and HOOS function −5.3 (95% CI: −8.9; −1.6), effect size −0.31. No adverse events were reported.
Conclusions: No differences were found during 12-months follow-up on pain and function. At 3-months follow-up, pain and function scores differed in favor of patients allocated to the additional exercise therapy compared with GP care alone.
Trial registration: The Netherlands Trial Registry NTR1462.

Introduction

In the Netherlands most patients with hip osteoarthritis (OA) are treated in a primary care setting. Patients are diagnosed clinically with or without confirmation of radiography. Most research however is focused on radiographic confirmed OA and/or patients treated in hospitals. But the population of patients with hip OA in primary care is of particular interest, since severity of hip pain and disability showed a weak association with severity of radiological OA[1]. Conservative treatment is the cornerstone of the treatment of hip OA since no definitive cure exists; moreover, surgery is only considered in individuals with significant pain and limitations, and when other treatment options have failed[2].

Although guidelines recommend exercise therapy[3], the evidence to support this recommendation is mostly based on studies with knee OA[4]. Also, multiple systematic reviews conclude that there is a lack of high-quality research to confirm the effectiveness of exercise therapy in patients with hip OA[5–7]. A Cochrane review, last updated in 2014, combined nine trials and found a reduction in pain and physical function immediately after exercise therapy with a small to moderate effect size (ES −0.38)[8]. Five of the included trials provided data for long-term follow-up and showed a

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sustained effect until three to six months. Only five of all trials recruited only hip OA patients. The other trials included more mixed populations with knee OA and hip OA. Therefore more research is needed to assess the long-term effectiveness of exercise therapy targeting patients with hip OA specifically.

The study of Bennell *et al.* compared a multimodal exercise treatment with sham treatment[9]. They found no difference in effect on hip pain and hip function score directly after treatment between both groups. The authors suggested that their multimodal intervention (education, advice, manual therapy, home exercises and possible a walking stick) may have compromised the effect of each individual intervention (especially strengthening and flexibility) because of a fixed clinic time. This raises the question if an exercise program which is not combined with manual therapy does improve pain and functioning since there may exist an adverse interaction between these two modalities as seen in one trial[10].

Therefore, the aim of this study was to evaluate the effectiveness of exercise therapy added to GP care compared with GP care alone, on hip pain and function in patients with hip OA, during 12-month follow-up.

Methods

Design

We performed a multi-center pragmatic randomized controlled trial with two parallel groups in a primary care setting. The study was approved by the Medical Ethical committee of the Erasmus MC. Detailed information on the study design is available in the protocol published by van Es *et al.*[11]. Alongside the trial a cost-utility analysis was performed; results are presented in a separate paper.

Setting and participants

GPs in the area of Rotterdam (the Netherlands) searched their patient registries for patients who visited them during the past year for a new episode of hip complaints. Patients received an invitation and, after a positive response, were screened for eligibility, provided written informed consent, and were enrolled by our research team.

Patients were eligible if they were aged $\geq$45 years, and suffered from a new episode of non-traumatic hip complaints fulfilling the clinical criteria for hip OA of the American College of Rheumatology (ACR)[12].

Exclusion criteria:

- exercise therapy in the past 3 months;
- hip pain score <2 on an 11-point numeric rating scale (NRS: 0 = no pain);
- high level of physical function (score of <2 on the Algofunctional Index)[13],
- hip surgery or on waiting list;
- disabling co-morbidity (e.g., severe heart failure);
- insufficient comprehension of the Dutch language;
- mentally incapable of participation.

Sample size

A sample size of 210 patients was required to detect a 25% clinical difference in the WOMAC pain score (mean 4.83, SD 2.25) after 12 months with two-tailed testing, a power of 80% and an alpha 5%. In this calculation we took into account a 25% referral to a physiotherapist in the control group (cross-over) and a 10% loss to follow-up. Mean and standard deviation (SD) were derived from the study of Veenhof *et al.*[14] This study included patients with knee OA and/or hip OA. For our sample size calculation we only used the data of the patients with hip OA, by contacting the authors. At the time of writing the study protocol, no published data on HOOS scores were available to help calculate the sample size.

Randomization and interventions

For the random allocation sequence (allocation ratio 1:1) a computer-generated random table was used, provided by an independent person. Block randomization was used with random blocks of 4, 6 and 8 patients. Based on the randomization list, opaque, sealed, sequentially numbered envelopes were prepared by an independent person. In this way the member of the research team was blinded for treatment allocation. After informed consent and baseline measurement the envelop was opened in presence of the patient by the researcher. Blinding for subsequent treatment of patient, of care provider and researcher during follow-up was not possible due to the intervention of interest.

Patients were randomized into two groups. The intervention group received usual GP care with additional exercise therapy (GP + ET). The control group received usual GP care only (GP). The exercise therapy consisted of maximally 12 treatment sessions during the first 3 months of follow-up and was administered by physiotherapists. Physiotherapists were allowed to end the treatment earlier if treatment goals were reached before the twelfth session. After completion of the initial treatment sessions three booster sessions should follow in the fifth, seventh and ninth month.

The participating physiotherapists were instructed during a consensus meeting. The exercise protocol was based on the Dutch Guideline for Physiotherapy[13]. Physiotherapist advised patients about lifestyle adaptations, possible walking aids, appropriate postural loading of joints, (in)appropriate pain behavior and more. Exercises consisted of strengthening and improving flexibility of muscles around the hip joint (especially extensors and abductors), leg and abdominal muscles. Aerobic exercises to improve endurance were also included. Passive treatment forms were not allowed. Patients were expected to perform home exercises and were provided a booklet describing the exercises. More detailed information is available as supplementary file. Each treatment session lasted 30 min and the physiotherapist was allowed to follow their own approach according to the patient's need. During booster sessions advices and exercises were repeated and possible problems and obstacles to perform the home exercises were discussed.

All patients in both groups received usual care given by the patient's own GP and an identical brochure with information about hip OA[15]. GP care could include education, counselling, prescription of pain medication, additional diagnostic tests or referral to an orthopedic surgeon. In the control group, referral to a physical therapist was discouraged, but was not restricted.

Primary and secondary outcomes

Patients received questionnaires at baseline, at 6 weeks, and at 3, 6, 9 and 12 months. At baseline and at 12 months, a physical examination of the knee and hip joints was performed. A pelvic X-ray (anterior–posterior) was obtained at baseline.

Primary outcomes were hip pain and hip-related limitations in activity as measured with the Hip disability Osteoarthritis Outcome Score (HOOS)[16] overall during the 12 months of follow-up. The HOOS questionnaire is an extension of the Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index[17] and consists of five subscales (pain, symptoms, function in daily living, function in sport and recreation, and hip-related quality of life)

with a score ranging from 0 indicating no problems and 100 indicating extreme problems.

Secondary outcomes were hip pain and hip-related limitations in activity as measured with the HOOS at 6 weeks, and at 3, 6, 9 and 12 months, hip pain measured with a NRS score (0 indicates no pain and 10 indicates the worst pain imaginable)[18], recovery, measured on a 7-point Likert scale (from 'total recovery' to 'worse than ever')[19] and quality of life, measured with the EuroQol, (EQ-5D3L). Utility values of the Dutch public for EuroQol health states were applied on the EuroQol scores, in which −0.329 indicates a bad health status and 1.0 is a maximum quality of life[20].

Other demographic and clinical data collected were Timed 'Up and Go' test[21], limitations in range of motion, age, gender, height, weight, education, duration of complaints, previous hip pain, co-morbidity, compliance to assigned treatment and co-interventions (e.g., visits to healthcare providers (including the GP, physiotherapist, medical specialist, company physician, psychotherapist and rehabilitation specialist), inpatient days at the hospital, rehabilitation center, nursing home and residential home, medical imaging (X-rays and magnetic resonance imaging), laboratory services, medications, appliances (including cold and hot compresses, orthopedic insoles and wheelchairs) and home care).

Changes to trial outcomes after the trial commenced

Because the 5-m walking test at most test sites could not be performed, we removed this test from our protocol. Furthermore, after protocol registration, the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire[22,23], was introduced by the OARSI/OMERACT initiative and was added to our protocol. The ICOAP questionnaire consists of 11 items measured on a 5-point Likert scale. The items are divided into a subscale for constant pain (score 0–20), intermittent pain (score 0–24) and total pain (sum of both scales, transformed into a score of 0–100; for which 0 indicates no pain). Finally, the outcome recovery was dichotomized in recovered ('total recovery' or 'substantial recovery') and no recovery ('some recovery', 'no change', 'some worsening', 'substantial worsening' or 'worse than ever').

Statistical analysis

Success of randomization and the distribution of outcome measures were assessed before the analyses were performed. Data were analyzed according to the intention-to-treat principle. A linear mixed model analysis with repeated measurements was used to assess differences between the intervention and control group. Covariance structure was assumed to be unstructured after comparing Akaike's information criterion between the different covariance structures. The analysis was adjusted for age, gender and body mass index (BMI), and clinically relevant differences ($\geq$10%) between the groups at baseline. Data from patients who underwent total hip replacement were included until surgery; after surgery the collected data were set as missing. Effect sizes were calculated for outcomes using the estimates derived from the mixed model analyses. We divided the estimate by the pooled SD of the intervention and control group at baseline. Effect sizes were considered to be small (0.2–0.29), moderate (0.3–0.79) or large ($\geq$0.8)[24]. An overall estimate during the 12-month follow-up was estimated by expressing the mean of the estimates on the five different follow-up measurements.

In addition, analyses were repeated as per protocol, defined as patients receiving >80% (12 sessions or more) of the maximum number of exercise therapy sessions (booster sessions included). In the control group, cross-overs were excluded from the analysis. For explorative purpose we performed subgroup analyses for six different *a priori* defined subgroups: age (45–65 years; >65 years), NRS score at baseline (NRS score 2; NRS score $\geq$ 3), education (lower than higher vocational education; higher vocational education or university), gender (female; male), knee OA (no self-reported knee OA; self-reported knee OA) and radiographic OA (Kellgren & Lawrence[25] K&L score 0–1; K&L score $\geq$2). These subgroups were suspected of having a possible altered effect of exercise therapy because of differences in co-morbidities, general health, disability, severity of OA or attitude towards exercise therapy.

Although specified in the Netherlands Trial Register (NTR1462), we had to discontinue the analysis of the subgroup of patients with low back pain as co-morbidity, because this information was not acquired.

All analyses were conducted with SPSS 21 (SPSS Inc., USA).

Results

Participants

Fig. 1 shows the flow of patients through the trial. From September 2009 to October 2011, 203 patients were included and randomized to the GP + ET (n = 101) or GP care only group (n = 102). At the 12-month follow-up, five patients (5%) in the GP + ET group and six patients (6%) in the GP group were lost to follow-up.

The baseline characteristics of the patients are presented in Table I. Mean age was 64 (SD 8.5) years in the GP + ET group and 67 (SD 9.6) years in the GP group. In the GP + ET group 62% (n = 63) was female, compared with 55% (n = 56) in the GP group. The mean HOOS pain score was 37.6 (SD 16.1) and 38.9 (SD 15.7) in the GP + ET group and GP group, respectively. The mean HOOS function score was 35.4 (SD 18.0) in the GP + ET group and 38.0 (SD 16.6) in the GP group. The two groups had no clinically relevant differences at baseline, except for self-exercise and use of daily pain medication. Therefore besides age, gender and BMI, the analysis was also adjusted for self-exercises and daily use of pain medication.

Interventions

In the GP + ET group, patients received a median of 8 treatments (IQR 7.0) in the first 3 months. In the following 9 months 48 (48%), 46 (46%) and 36 (36%) patients received booster sessions in the fifth, seventh and ninth month, respectively. A total of 91 patients (90%) in the GP + ET group and 19 patients (19% cross-over) in the GP group visited a physiotherapist during the 12-month follow-up. Median number of visits was 11 (IQR 8.0) in the GP + ET group and 9 (IQR 17.0) in the GP group. During the follow-up more patients in the GP + ET group reported performing self-exercises at home then in the GP group. This proportion in the GP + ET group was the highest at 6 weeks follow-up, 86 (85%) patients of the GP + ET group and 27 (27%) patients of the GP group. At 3 months and 12 months, 79 (78%) and 61 (60%) patients of the GP + ET group respectively, reported to perform self-exercises. In the GP group 33 (32%) at 3 months follow-up and 22 (22%) patients at 12 months follow-up reported self-exercises. At 6 weeks and 3 months follow-up the GP + ET group self-exercisers reported a median of 105 min per week of self-exercise, while a median of 70 min per week was spent on self-exercise by patients in the GP group. At 6, 9 and 12 months follow-up the median of time spent per week decreased in the GP + ET group to 70 min per week, while the GP group reported 70 min per week at 6 and 9 months and 60 min per week at 12 months follow-up.

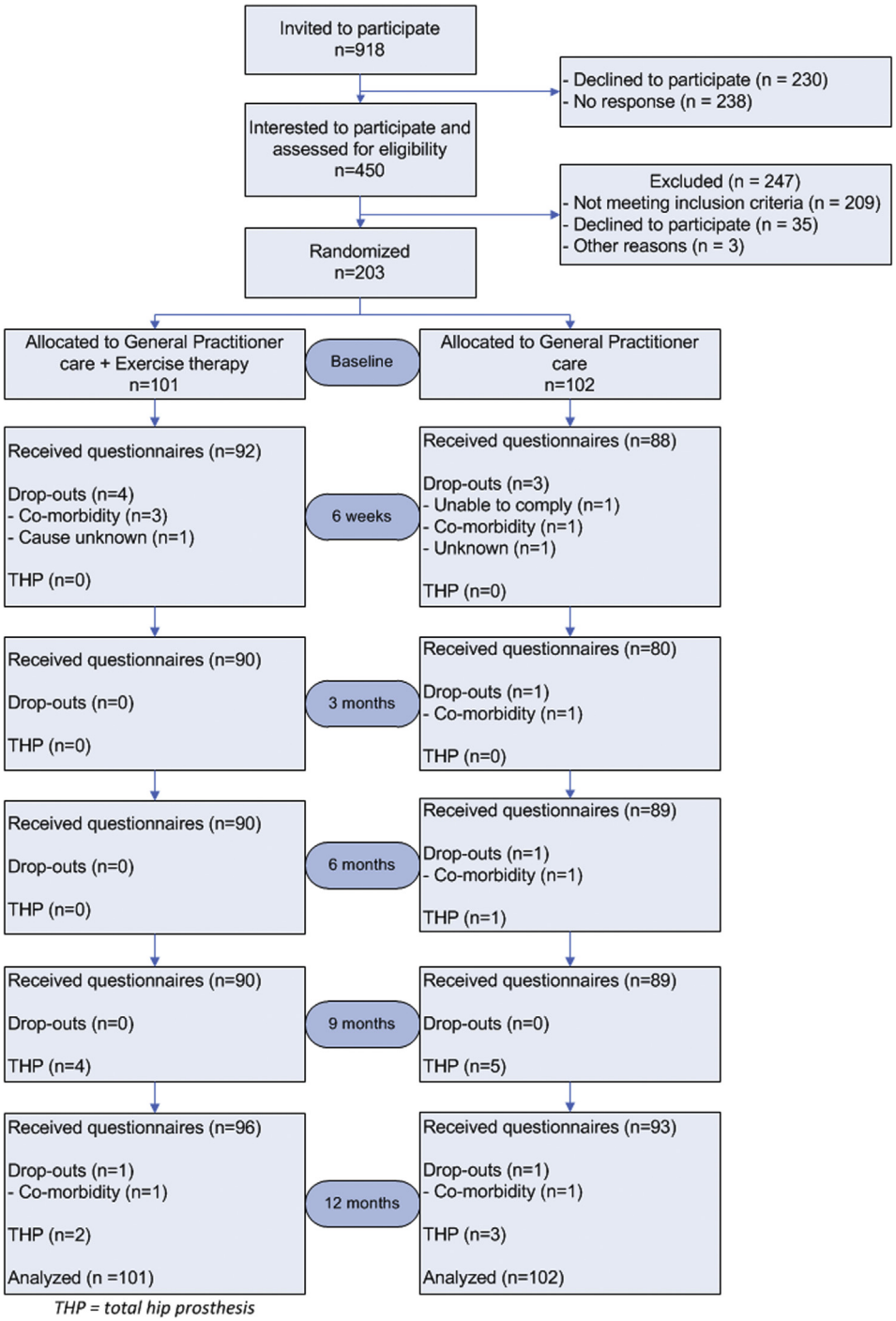


Fig. 1. Flow of the participants during the 12-month study period.

Primary and secondary outcomes

Fig. 2 presents the course of the primary outcome HOOS pain and HOOS function. Table II presents the adjusted and unadjusted results of the linear mixed model analysis with repeated measurements. The adjusted overall estimates during the 12-month follow-up were −1.7 (95% CI −4.8; 1.4, ES −0.11) for HOOS pain and −3.3 (95% CI −6.7; 0.2, ES −0.19) for HOOS function; these differences were not statistically significant. Statistically significant differences were found in the adjusted analysis for HOOS pain and HOOS function at 3-months follow-up, estimate −3.7(95% CI −7.3; −0.2, ES −0.23) and −5.3 (95% CI −8.9; −1.6, ES −0.31), respectively.

At 3-months follow-up, 16% of the patients in the GP + ET group reported recovery compared with 4% in the GP group (Chi-square; $P = 0.011$). At 12-months follow-up 25% (GP + ET group) and 8% (GP group) of the patients perceived recovery (Chi-square; $P = 0.002$). The patients who reported perceived recovery at 12 months follow-up in the GP + ET group did not visit the physiotherapist more often or followed more booster-sessions, compared to the patients reporting no recovery. Also no statistical difference was found between patients who reported no or perceived recovery in number

Table I
Baseline characteristics of the total study population ($n = 203$)

	GP + ET ($n = 101$)	GP ($n = 102$)
Age in years; mean (SD)	64 (8.5)	67 (9.6)
Females; *n* (%)	63 (62)	56 (55)
BMI; mean (SD)	27 (3.9)	28 (4.1)
Education, higher vocational education/university; *n* (%)	14 (14)	16 (16)
Comorbidity; *n* (%)		
High blood pressure	37 (37)	45 (44)
Heart disease	17 (17)	16 (16)
Lung disease	8 (8)	9 (9)
Diabetes	10 (10)	16 (16)
Knee OA	29 (29)	32 (31)
Hand OA	29 (29)	32 (31)
Rheumatoid arthritis	1 (1)	5 (5)
Visited specialist in past 3 months; *n* (%)	12 (12)	14 (14)
Kellgren and Lawrence score *n* (%)		
0	16 (16)	17 (17)
1	31 (31)	29 (28)
2	28 (28)	32 (31)
3	16 (16)	14 (14)
4	2 (2)	3 (3)
Duration of current hip complaints, days; median (IQR)	365 (810)	365 (819)
Self-exercised in past 3 months*; *n* (%)	23 (23)	39 (38)
Used pain medication daily in past 3 months; *n* (%)	21 (21)	32 (31)
Hip pain severity; mean (SD)	4.6 (2.1)	4.8 (1.8)
Timed 'Up and Go' test in seconds; mean (SD)	10.0 (2.22)	10.5 (2.92)
HOOS 0–100; mean (SD)		
Pain	37.6 (16.1)	38.9 (15.7)
Function	35.4 (18.0)	38.0 (16.6)
ICOAP; mean (SD)		
Intermittent	8.0 (3.9)	8.4 (4.3)
Constant	5.4 (3.5)	5.8 (3.8)
Total	30.4 (15.8)	32.2 (17.5)
EuroQol 5D-3L; mean (SD)		
Health status (−0.329-1.0)	0.778 (0.122)	0.748 (0.161)
Preference of treatment; *n* (%)		
GP + ET	64 (63)	52 (51)
GP	6 (6)	6 (6)
No preference	30 (30)	44 (43)

GP + ET = general practitioner care added with exercise therapy (intervention group); GP = general practitioner care (control group); IQR = interquartile range (25th–75th percentile); HOOS = Hip Osteoarthritis Outcome Score: 0 indicates no problems; Hip pain severity averaged over last week: 0 indicates no pain; ICOAP = intermittent and constant osteoarthritis pain: 0 indicates no pain. EuroQol: −0.329 indicates a bad health status and 1.0 is a maximum quality of life.

* Patients were asked whether they performed unsupervised exercises to reduce their hip complaints.

of patients who performed self-exercises. There were no statistically significant differences between the groups for hip pain NRS score and quality of life. Differences between the groups were significant at 3-months follow-up for all ICOAP scores.

Co-interventions

In total, 6 (6%) patients in the GP + ET group and 9 (9%) in the GP group underwent total hip replacement (Fig. 1). More patients in the GP group made use of co-interventions than in the GP + ET group (Table III). At 3 months follow-up 10 (10%) patients of the GP + ET group and 21 (21%) patients of the GP group reported daily use of pain medications (chi square test $P = 0.034$). At 12 months follow-up this was reported by 14 (14%) patients of the GP + ET group and 23 (23%) patients of the GP group (chi square test $P = 0.085$).

Ancillary analyses

In the per-protocol analysis, 38 patients in the GP + ET group and 80 in the GP group could be included. The primary outcomes showed no significant differences and estimates showed less difference between the treatment groups in comparison to the main analysis.

Subgroup analysis

Age

In patients aged ≥65 years the adjusted estimate was −5.9 (95% CI −11.3; −0.6, ES −0.37) for HOOS pain and −7.2 (95% CI −12.6; −1.7, ES −0.43) for HOOS function at 3-months follow-up. Estimates of patients aged 45–65 years old were not statistical significant.

Gender

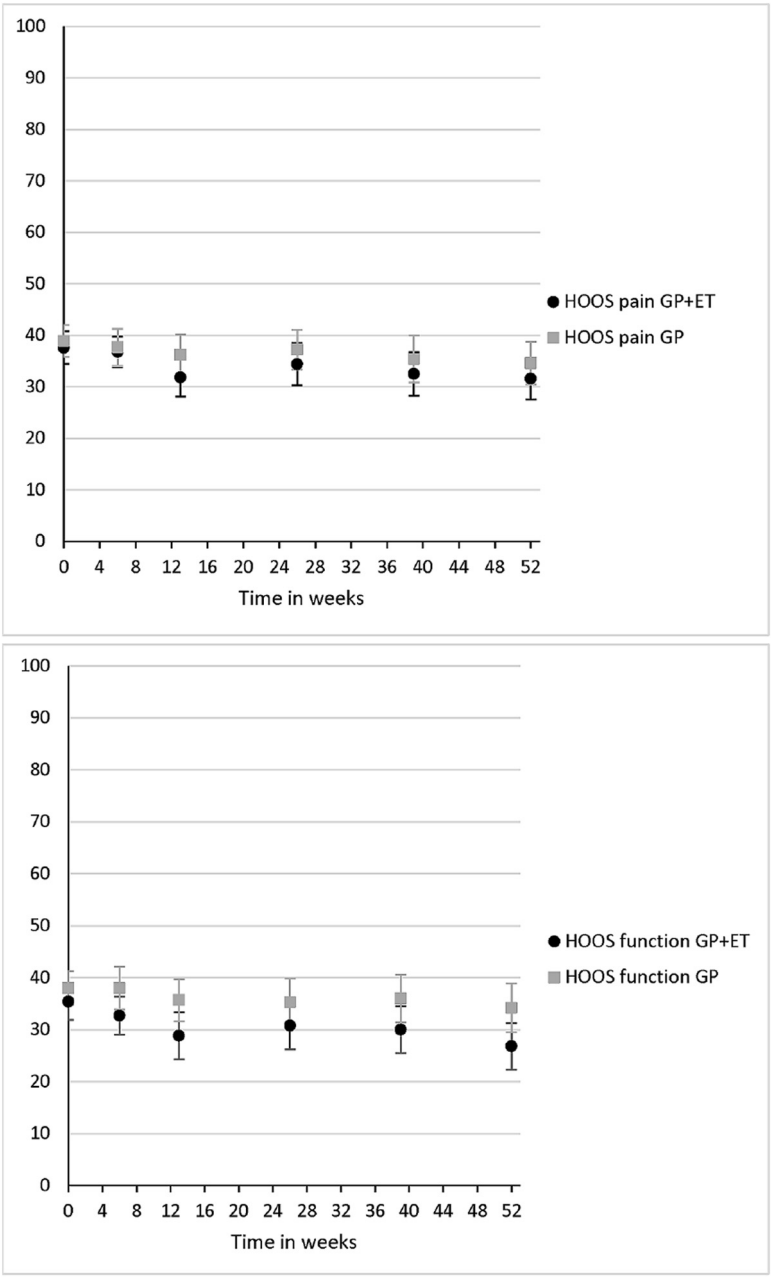
Female patients showed an adjusted estimate of −8.5 (95% CI −13.4; −3.6, ES −0.49) at 3 months for HOOS function, while male patients showed no significant differences.

NRS score at baseline

Between the groups, patients with a NRS score ≤3 showed a larger difference in HOOS function scores at 3-months follow-up (−8.2, 95% CI −14.6; −1.8, ES −0.62) than patients with a NRS ≥ 3 (−4.6, 95% CI −8.9; −0.4, ES −0.28).

Radiographic OA

In patients with a K&L score <2 the adjusted estimate for HOOS function was −5.6 (95% CI −10.9; −0.4, ES −0.36) at 3 months follow-up, while HOOS pain was not statistical significant. In patients with a K&L ≥2 and higher the adjusted estimate for HOOS pain was −5.5 (95% CI −10.8; −0.2, ES −0.34) and for HOOS



GP+ET=general practitioner care with additional exercise therapy (intervention group); GP=general practitioner care only (control group); HOOS=hip osteoarthritis outcome score (0=no problems). Bars indicate the 95% confidence interval of the mean.

Fig. 2. Course of the HOOS pain and HOOS function subscale.

function −6.1 (95% CI −11.5; −0.8, ES −0.34) at 3 months follow-up. The overall adjusted estimate for HOOS function was −5.5 (95% CI −10.6; −0.3, ES −0.31). No additional relevant information was retrieved from the analysis of the other subgroups.

Harm

No serious adverse events were reported.

Discussion

During the 12 months follow-up, no significant differences were found between the two groups. At 3-months follow-up, significant differences were found between the groups on the primary outcomes HOOS pain −3.7 (ES −0.23) and HOOS function −5.2 (ES −0.30), on a scale of 0–100, in favor of the GP + ET group. This effect was no longer present at 12-months follow-up. No significant effect was found on quality of life; however, at 12-months follow-up 25% of the patients in the exercise therapy group reported total or substantial recovery compared with 8% in the GP care only group ($P = 0.002$).

The clinical relevance of the differences at 3 months follow-up (−3.7 for HOOS pain and −5.2 for HOOS function on a scale of 0–100) is debatable, especially since this effect did not last. In the systematic review of Pisters *et al.*, additional booster sessions positively influenced the sustaining effect of exercise therapy

Table II
Results of the multivariable linear mixed models analysis with repeated measurements for primary and secondary outcomes between the intervention and control group

		Mean (SD)		Unadjusted mixed model			Adjusted* mixed model		
		GP + ET	GP	Coefficient (95% CI)	*P*-value	Effect size	Coefficient (95% CI)	*P*-value	Effect size
Primary outcomes									
HOOS pain (0–100)	6 w	36.8 (14.6)	37.7 (17.0)	0.07 (−3.5; 3.6)	0.97	0.00	0.5 (−2.9; 4.0)	0.76	0.03
	3 m	31.8 (17.7)	36.2 (18.9)	−3.9 (−7.5; −0.4)	**0.030**	−0.25	−3.7 (−7.3; −0.2)	**0.039**	−0.23
	6 m	34.4 (19.7)	37.2 (18.0)	−2.5 (−6.5; 1.5)	0.22	−0.16	−2.2 (−6.2; 1.7)	0.27	−0.14
	9 m	32.5 (19.9)	35.4 (21.1)	−1.8 (−6.5; 2.9)	0.46	−0.11	−1.5 (−6.2; 3.2)	0.53	−0.09
	12 m	31.6 (19.5)	34.6 (19.3)	−1.9 (−6.5; 2.7)	0.42	−0.12	−1.6 (−6.2; 3.0)	0.49	−0.10
	Overall			−2.0 (−5.1; 1.1)	0.21	−0.13	−1.7 (−4.8; 1.4)	0.28	−0.11
HOOS function (0–100)	6 w	32.7 (17.6)	38.0 (19.0)	−2.8 (−6.5; 0.9)	0.14	−0.16	−2.4 (−6.1; 1.3)	0.20	−0.14
	3 m	28.8 (21.3)	35.7 (19.0)	−5.5 (−9.1; −1.8)	**0.004**	−0.32	−5.3 (−8.9; −1.6)	**0.005**	−0.31
	6 m	30.8 (21.9)	35.3 (20.7)	−2.7 (−7.0; 1.6)	0.22	−0.16	−2.4 (−6.7; 1.9)	0.27	−0.14
	9 m	30.0 (21.4)	36.0 (20.7)	−3.6 (−8.2; 1.1)	0.13	−0.21	−3.2 (−7.9; 1.4)	0.17	−0.18
	12 m	26.8 (21.2)	34.2 (21.4)	−3.2 (−8.3; 1.8)	0.21	−0.18	−3.0 (−8.0; 2.1)	0.25	−0.17
	Overall			−3.6 (−7.0; −0.1)	**0.042**	−0.21	−3.3 (−6.7; 0.2)	0.06	−0.19
Secondary outcomes									
Hip pain past week (NRS 0–10)	6 w	3.9 (2.2)	3.9 (2.2)	0.3 (−0.3; 0.8)	0.38	0.15	0.3 (−0.2; 0.9)	0.26	0.15
	3 m	3.4 (2.3)	3.8 (2.3)	−0.2 (−0.7; 0.4)	0.50	−0.10	−0.1 (−0.7; 0.4)	0.61	−0.05
	6 m	3.7 (2.5)	4.1 (2.3)	−0.2 (−0.8; 0.5)	0.59	−0.10	−0.1 (−0.7; 0.5)	0.73	−0.05
	9 m	3.5 (2.5)	3.9 (2.4)	−0.2 (−0.9; 0.4)	0.46	−0.10	−0.2 (−0.8; 0.5)	0.58	−0.10
	12 m	3.4 (2.3)	3.8 (2.4)	−0.2 (−0.9; 0.4)	0.44	−0.10	−0.2 (−0.8; 0.4)	0.57	−0.10
	Overall			−0.1 (−0.6; 0.4)	0.62	−0.05	−0.1 (−0.5; 0.4)	0.81	−0.05
ICOAP intermittent (0–24)	6 w	7.3 (3.9)	8.4 (4.5)	−0.7 (−1.8; 0.4)	0.20	−0.17	−0.6 (−1.7; 0.5)	0.31	−0.15
	3 m	6.4 (4.1)	7.9 (4.5)	−1.3 (−2.4; −0.3)	**0.015**	−0.31	−1.2 (−2.3; −0.1)	**0.027**	−0.29
	6 m	7.0 (4.6)	7.9 (4.6)	−0.7 (−1.9; 0.5)	0.24	−0.17	−0.6 (−1.7; 0.6)	0.33	−0.15
	9 m	6.4 (4.7)	7.5 (4.9)	−0.8 (−2.1; 0.4)	0.18	−0.19	−0.7 (−2.0; 0.5)	0.26	−0.17
	12 m	6.1 (4.1)	7.2 (4.9)	−0.7 (−2.0; 0.5)	0.24	−0.17	−0.6 (−1.8; 0.6)	0.35	−0.15
	Overall			−0.9 (−1.7; −0.01)	0.047	−0.22	−0.7 (−1.6; 0.1)	0.09	−0.17
ICOAP constant (0–20)	6 w	4.9 (3.5)	5.5 (3.9)	−0.3 (−1.2; 0.6)	0.49	−0.08	−0.2 (−1.1; 0.7)	0.70	−0.05
	3 m	3.9 (3.7)	5.4 (4.2)	−1.3 (−2.2; −0.4)	**0.004**	−0.36	−1.2 (−2.1; −0.3)	**0.008**	−0.33
	6 m	4.0 (4.2)	5.3 (4.3)	−1.0 (−2.0; 0.03)	0.06	−0.27	−0.9 (−1.9; 0.1)	0.09	−0.25
	9 m	4.1 (4.3)	5.1 (4.1)	−0.8 (−1.9; 0.3)	0.13	−0.22	−0.7 (−1.7; 0.4)	0.20	−0.19
	12 m	3.6 (3.8)	4.7 (4.3)	−0.8 (−1.9; 0.3)	0.14	−0.22	−0.7 (−1.7; 0.4)	0.23	−0.19
	Overall			−0.8 (−1.6; −0.1)	**0.026**	−0.22	−0.7 (−1.5; 0.02)	0.055	−0.19
ICOAP total (0–100)	6 w	27.8 (15.7)	31.6 (18.7)	−2.3 (−6.6; 2.0)	0.29	−0.14	−1.7 (−6.0; 2.6)	0.44	−0.10
	3 m	23.5 (16.3)	30.2 (19.3)	−6.0 (−10.1; −1.9)	**0.005**	−0.36	−5.5 (−9.6; −1.4)	**0.008**	−0.33
	6 m	24.9 (19.1)	29.8 (19.3)	−3.8 (−8.5; 0.9)	0.11	−0.23	−3.3 (−8.0; 1.4)	0.16	−0.20
	9 m	23.9 (19.7)	28.7 (20.1)	−3.6 (−8.7; 1.5)	0.16	−0.22	−3.1 (−8.2; 2.0)	0.23	−0.19
	12 m	22.2 (17.1)	27.0 (19.8)	−3.4 (−8.2; 1.4)	0.17	−0.20	−2.8 (−7.6; 2.0)	0.25	−0.17
	Overall			−3.8 (−7.3; −0.4)	**0.031**	−0.23	−3.3 (−6.7; 0.2)	0.06	−0.19
Quality of life (EQ-5D −0.329–1.0)	6 w	0.788 (0.126)	0.756 (0.177)	0.020 (−0.021; 0.060)	0.34	0.14	0.015 (−0.025; 0.055)	0.45	0.10
	3 m	0.780 (0.162)	0.777 (0.147)	−0.014 (−0.055; 0.027)	0.51	−0.10	−0.018 (−0.060; 0.023)	0.39	−0.14
	6 m	0.771 (0.187)	0.759 (0.174)	−0.004 (−0.054; 0.045)	0.87	−0.03	−0.008 (−0.059; 0.041)	0.73	−0.06
	9 m	0.781 (0.176)	0.763 (0.197)	0.006 (−0.049; 0.061)	0.84	0.04	0.002 (−0.053; 0.056)	0.95	0.01
	12 m	0.784 (0.198)	0.784 (0.151)	−0.005 (−0.055; 0.044)	0.83	−0.03	−0.010 (−0.060; 0.040)	0.69	−0.07
	Overall			0.0003 (−0.032; 0.033)	0.99	0.00	−0.004 (−0.037; 0.029)	0.81	−0.03
TUG test (sec)	12 m	9.7 (2.7)	10.7 (3.9)	−0.4 (−1.1; 0.2)	0.20	−0.15	−0.4 (−1.1; 0.3)	0.22	−0.15

P-values in bold are statistical significant ($P < 0.05$). GP + ET = general practitioner care added with exercise therapy (intervention group); GP = general practitioner care (control group), w = week; m = month; HOOS = hip osteoarthritis outcome score (0 = no problems); NRS = numerical rating scale (0 = no hip pain); ICOAP = intermittent and constant osteoarthritis pain (0 = no pain); EQ = EuroQol (1.0 = maximum quality of life); TUG test = Timed 'Up and Go' test.
* Analyses adjusted for age, gender, BMI, self-exercise in the past three months, and taking daily pain medication at baseline.

during long-term follow-up[26]. Although booster sessions with this aim were also included in our protocol, the decreasing effectiveness of exercise therapy after 3 months might be attributable to poor compliance with the booster sessions after cessation of treatment and, possibly, to not continuing the exercises at home. More patients reported to perform self-exercises at home in the GP + ET group compared to the GP group during the total follow-up. But time per week spent on these exercises was highest at 6 weeks and 3 months in the GP + ET group and decreased during the follow-up. This may suggest that a certain intensity of (self) exercises is needed to maintain the effect of exercise therapy. In patients with knee and hip OA, adherence to exercise programs is reported to correlate with effectiveness[27]. Improving adherence could augment the clinical relevance of the difference we found between our groups. Also determining optimal intensity, duration and number of exercise therapy could improve the effectiveness of exercise therapy.

In a meta-analysis by Hernandez-Molina *et al.*, an effect size of −0.46 was found for exercise therapy on hip pain[5]. The period of follow-up differed between the included trials and evaluation was at the end of the treatment sessions for each trial. More treatment sessions, or treatment sessions being spread out over a longer time period, are potential explanations for this relatively large effect compared with our results. Fernandes *et al.* reported effect sizes comparable with our study at 4-months follow-up on WOMAC pain (ES −0.26 95% CI −0.64; 0.11) and WOMAC function (ES −0.29 95% CI −0.67; 0.09)[28]. Fransen *et al.* combined nine trials with a total of 549 patients and reported an effect size of −0.38 (95% CI −0.55; −0.20) on hip pain and −0.38 (95%CI −0.54; −0.05) on hip function immediately after treatment sessions[8]. No effect was found on quality of life; this was consistent with our results. Five of the trials provided data (391 patients) on sustainability of effect with a follow-up up to 3–6 months. The effect size was −0.38 (95% CI −0.58; −0.18). Our trial did not show the same sustainability of

Table III
Co-interventions during the 12-month follow-up period

Co-intervention	GP + ET	GP
Visit GP	25	36
Visit specialist	16	26
Visit company physician	0	2
Visit psychologist	1	1
Visit rehabilitation physician	0	2
Use of acetaminophen	46	46
Use of NSAID	23	28
Use of opioid	8	12
Hip injection with anti-inflammatory drug	7	7
Other medication	2	12
Use of cold compresses	3	4
Use of warm compresses	7	8
Use of crutches	3	4
Use of cane	6	12
Use of insoles	25	29
Use of wheeled walker	0	12
Use of walking frame	0	1
Use of wheel chair	0	2
Use of mobility scooter	1	1
Use of bicycle with electrical assistance	8	14
Domestic help	10	17
Personal care assistance	1	1

Data are numbers of patients. GP + ET = general practitioner care with additional exercise therapy (intervention group $n = 101$); GP = general practitioner care only (control group $n = 102$).

effect. As mentioned above this could be explained by differences in intensity of exercises and compliance of patients since the patients in these five trials were a mix of community volunteers and clinical patients. In addition our follow-up lasted 12 months.

Strength of our study is the randomized and pragmatic design. Because of the pragmatic design we had some cross-over in the control group and relatively high compliance to study procedure (84%). Therefore, the results of the trial reflect 'real life' and the value of exercise therapy in addition to usual GP care for patients with hip OA. Furthermore, we believe that our study population is comparable to the general population of hip OA patients in primary care, because we included patients from general practitioner (GP) practices who complied with the clinical ACR criteria without radiographic proof of OA. In our study population 54% had a Kellgren & Lawrence score of 2 or higher on X-ray, which may differ from the population of patients with hip OA treated in secondary care. Therefore, our results are especially generalizable to patients in primary care.

In addition, few patients were lost to follow-up ($n = 11$; 5%). The treatment allocation was carefully blinded for the researcher concerned with inclusion of patients to prevent a possible selection bias.

A limitation was the relatively low compliance to the exercise protocol in the intervention group. Most patients did not follow the booster sessions and some physiotherapists only contacted patients by telephone and scored that as a booster session. This could have diminished the effectiveness of exercise therapy on long term follow-up.

The per-protocol analysis showed no significant differences between both groups. One explanation for this could be that only 38% of the patients in the intervention group could be indicated as per protocol, because of low compliance. Another reason is that patients with a fast and good result of exercise therapy possibly finished the sessions earlier because of reaching their therapy goals before treatment session 12, as was approved in our study design. In this way the 'good responders' were not included in the per-protocol analysis since their number of therapy session was low. We tested this hypothesis by repeating the per protocol analysis with less strict criteria for the intervention group and found a larger effect, although still not significant.

For clinicians not only the effect of exercise therapy in general is of interest but also which patients are more likely to benefit from exercise therapy. Therefore several baseline features were explored in our subgroup analysis. Patients aged ≥65 years, women, patients with a low score on the pain NRS at baseline and patients with radiographic OA, showed somewhat larger effects of exercise therapy. However, sample sizes in the subgroup analysis were low and these initial subgroup effects need to be confirmed in future trials.

Conclusion

Overall, during 12-months follow-up there were no significant differences between the groups GP care alone and GP care with additional exercise therapy. At 3-months follow-up (immediately after the treatment sessions) there was a significant and clinically small difference between the groups in favor of patients with additional exercise therapy, on the primary outcomes HOOS pain and HOOS function and on the secondary outcome ICOAP.

Contributors

CT: analysis, data interpretation and manuscript writing. PL: conception, design, analysis, data interpretation and extensive editorial review of manuscript writing. JD: design, data interpretation and editorial review of manuscript. AB: design, data interpretation, editorial review of manuscript. JV: design, data interpretation, editorial review of manuscript. MK: design, data interpretation, editorial review of manuscript. PE: design, data collection, editorial review of manuscript. BK: design, data interpretation and editorial review of manuscript. SBZ: conception, design, data interpretation and extensive editorial review of manuscript. SBZ is guarantor. All authors had full access to all of the data and can take responsibility for the integrity. All authors approved the final version.

Ethical approval

The study was conducted according to the declaration of Helsinki and the study protocol was approved by the Medical Ethical Committee of the Erasmus MC. All the patients gave informed written consent. The study has been registered at The Netherlands Trial Registry (www.trialregister.nl, registration code: NTR1462).

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr Bierma-Zeinstra reports grants from Netherlands Organization for Health Research and Development (Health Care Efficiency Research Program), during the conduct of the study; grants from Dutch Arthritis Foundation, the Netherlands Organization for Health Research and Development (120520001, 17099.2402), Fonds Nuts Ohra (1003-064), and the European Union (HEALTH-F2-2012-305815), grants from Dutch Arthritis Foundation (NR10-1-305, NR12-1-304, IMP12-1-161), personal fees from Biomedis International LTD (Japan), outside the submitted work. All other authors declare no competing interests.

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Supplementary data

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References

1. Dekker J, Boot B, van der Woude LH, Bijlsma JW. Pain and disability in osteoarthritis: a review of biobehavioral mechanisms. J Behav Med 1992;15(2):189–214.
2. Lohmander LS, Roos EM. Clinical update: treating osteoarthritis. Lancet 2007;370(9605):2082–4.
3. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007;15(9):981–1000.
4. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, *et al*. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72(7):1125–35.
5. Hernandez-Molina G, Reichenbach S, Bin Z, Lavalley M, Felson DT. Effect of therapeutic exercise for hip osteoarthritis pain: results of a meta-analysis. Arthritis Care Res 2008;59(9):1221–8.
6. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Does land-based exercise reduce pain and disability associated with hip osteoarthritis? A meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2010;18(5):613–20.
7. McNair PJ, Simmonds MA, Boocock MG, Larmer PJ. Exercise therapy for the management of osteoarthritis of the hip joint: a systematic review. Arthritis Res Ther 2009;11(3).
8. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;4. CD007912.
9. Bennell KL, Egerton T, Martin J, Abbott JH, Metcalf B, McManus F, *et al*. Effect of physical therapy on pain and function in patients with hip osteoarthritis: a randomized clinical trial. JAMA 2014;311(19):1987–97.
10. Abbott JH, Robertson MC, Chapple C, Pinto D, Wright AA, Leon de la Barra S, *et al*. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. Osteoarthritis Cartilage 2013;21(4):525–34.
11. van Es PP, Luijsterburg PAJ, Dekker J, Koopmanschap MA, Bohnen AM, Verhaar JAN, *et al*. Cost-effectiveness of exercise therapy versus general practitioner care for osteoarthritis of the hip: design of a randomised clinical trial. BMC Musculoskelet Disord 2011;12:232.
12. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, *et al*. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34(5):505–14.
13. Peter WFH, Jansen MJ, Bloo H, Dekker-Bakker LMMCJ, Dilling RG, Hilberdink WKHA, *et al*. Revision of the KNGF guideline osteoarthritis of the hip and knee [Dutch]. Nederlands Tijdschrift Fysiotherapie 2010;120(1):2–15.
14. Veenhof C, Koke AJA, Dekker J, Oostendorp RA, Bijlsma JWJ, Van Tulder MW, *et al*. Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: a randomized clinical trial. Arthritis Care Res 2006;55(6):925–34.
15. Dutch College of General Practitioners. I have hip osteoarthritis [Dutch] www.thuisarts.nl.
16. de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra SM, Favejee M, Roos EM, *et al*. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. Osteoarthritis Cartilage 2007;15(1):104–9.
17. Bellamy N. WOMAC Osteoarthritis Index. A User's Guide. University of Western Ontario; 1995.
18. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976;2(2):175–84.
19. Bombardier C, Tugwell P, Sinclair A, Dok C, Anderson G, Buchanan WW. Preference for endpoint measures in clinical trials: results of structured workshops. J Rheumatol 1982;9(5):798–801.
20. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199–208.
21. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39(2):142–8.
22. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, *et al*. Development and preliminary psychometric testing of a new OA pain measure—an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16(4):409–14.
23. Maillefert JF, Kloppenburg M, Fernandes L, Punzi L, Gunther KP, Martin Mola E, *et al*. Multi-language translation and cross-cultural adaptation of the OARSI/OMERACT measure of intermittent and constant osteoarthritis pain (ICOAP). Osteoarthritis Cartilage 2009;17(10):1293–6.
24. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New Jersey: Lawrence Erlbaum Associates; 1988.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16(4):494–502.
26. Pisters MF, Veenhof C, Van Meeteren NLU, Ostelo RW, De Barker DH, Schellevis FG, *et al*. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. Arthritis Care Res 2007;57(7):1245–53.
27. Mazieres B, Thevenon A, Coudeyre E, Chevalier X, Revel M, Rannou F. Adherence to, and results of, physical therapy programs in patients with hip or knee osteoarthritis. Development of French clinical practice guidelines. Joint Bone Spine 2008;75(5):589–96.
28. Fernandes L, Storheim K, Sandvik L, Nordsletten L, Risberg MA. Efficacy of patient education and supervised exercise vs patient education alone in patients with hip osteoarthritis: a single blind randomized clinical trial. Osteoarthritis Cartilage 2010;18(10):1237–43.