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SCIENTIFIC RESEARCH ARTICLE

Evidence of Improvement in Various Impairments by Exercise Interventions in Patients with Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Clinical Trials

Ryo TANAKA, PhD[1], Junya OZAWA, PhD[1], Nobuhiro KITO, PhD[1], Takahiro YAMASAKI, PhD[1], Hideki MORIYAMA, PhD[2]

[1)] *Department of Integrated Rehabilitation, Hiroshima International University, Japan*

[2)] *Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Japan*

ABSTRACT. Purpose: To investigate improvement in various impairments by exercise interventions in patients with knee osteoarthritis (OA). Methods: We collected data on randomized controlled trials (RCTs) comparing the effects of exercise intervention with those of either nonintervention or psychoeducational intervention in patients with knee OA. Data on pain, stiffness, muscle strength, range of motion, flexibility, maximal oxygen uptake, and position sense were synthesized. The Grading of Recommendations Assessment, Development, and Evaluation system was used to determine the quality of the evidence. Results: Thirty-three RCTs involving 3,192 participants were identified. Meta-analysis provided high-quality evidence that exercise intervention improves maximal oxygen uptake, and moderate-quality evidence that exercise intervention also improves pain, stiffness, knee extensor and flexor muscle strength, and position sense. The evidence that exercise intervention improves knee extension and flexion range of motion was deemed as undetermined-quality. Conclusion: In patients with knee OA, improvement in pain, stiffness, muscle strength, maximal oxygen uptake, and position sense with the use of exercise intervention can be expected. Although the quality of evidence of the effect of exercise intervention on range of motion was inconclusive, exercise intervention should be recommended for patients with knee OA to improve various impairments.

Key words: knee osteoarthritis, exercise, evidence

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Knee osteoarthritis (OA) is the most common type of OA[1)], and its prevalence is rising in parallel with the increasing age of the population[2)]. The condition is associated with pain and inflammation of the joint capsule[3)], impaired muscular stabilization[4)], reduced range of motion[5)], and disability. Treatment of knee OA is focused on reducing joint pain and stiffness, and improving muscular stabilization and joint mobility[6)].

According to Osteoarthritis Research Society International (OARSI) recommendations on the management of hip and knee OA[6)], patients with symptomatic knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. In OARSI guideline[7)], patients with knee OA should be encouraged to undertake and continue regular aerobic, muscle strengthening, and range-of-motion exercises. This recommendation is also supported by a systematic review and meta-analysis[8–11)]. Therefore, there is consensus that exercise therapy, including strengthening and aerobics, is an effective intervention method for treating knee OA.

Cochrane review reported by Fransen and McConnell[12)], which examined the effect of exercise interventions in the patients with knee OA, showed that land-based therapeutic exercise has at least short term benefit in terms of reduced knee pain and improved physical function for people with knee OA. However, the effects on impairments except for pain, such as stiffness, muscle weakness, limited range of motion and sensory disturbance remain un-

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Correspondence to: Ryo Tanaka, Department of Integrated Rehabilitation, Hiroshima International University, Japan.
e-mail: r-tanaka@hs.hirokoku-u.ac.jp

Table 1. Search strategy

(1) PubMed	#1 osteoarthritis, knee[MeSH Terms]
	#2 exercise[MeSH Terms]
	#3 exercise therapy[MeSH Terms]
	#4 (#1 AND (#2 OR #3))
	Limits: Randomized Controlled Trial
(2) CENTRAL	#1 osteoarthritis, knee[MeSH Terms]
	#2 exercise[MeSH Terms]
	#3 exercise therapy[MeSH Terms]
	#4 (#1 AND (#2 OR #3))
(3) PEDro	•Advance search
	Title or Abstract: osteoarthritis, knee, exercise
	Method: clinical trial
(4) CINAHL	#1 osteoarthritis, knee[MeSH Terms]
	#2 exercise[MeSH Terms]
	#3 exercise therapy[MeSH Terms]
	#4 (#1 AND (#2 OR #3))
	Limits: Randomized Controlled Trial

clear. In fact, although several previous systematic reviews and meta-analyses[8,9,11] have reported the effect of exercise interventions on pain and impairment, the effect sizes for synthesized data of stiffness, muscle strength, or joint mobility have not been reported in their reviews. Devos-Comby *et al*.[10] synthesized these data together with swelling of the knee, joint effusion, peak oxygen uptake, body weight, and quadriceps muscle strength; however, the effect on each outcome has never been examined with meta-analysis. Therefore, regardless of the OARSI recommendations mentioned above[6], high-quality evidence that exercise interventions improve impairments in patients with knee OA has yet to be confirmed.

The purpose of this systematic review and meta-analysis was to search for evidence of improvement in various impairments by exercise interventions in patients with knee OA.

Methods

Search Strategy

The study design was a systematic review and meta-analysis. The electronic databases PubMed, Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Database (PEDro), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were used. All studies until February 2012 included in our search. The 2 concepts of “population” and “intervention” were combined with the “AND” operator. Population was defined as participants with OA of the knee. Intervention was defined as an exercise intervention for the treatment of OA. The design was a randomized controlled trial (RCT) to achieve the most valid information on the effectiveness of the interventions. For each concept, synonyms and Medical Subject Headings (MeSH) terms were combined with the “OR” operator (Table 1).

Two reviewers independently screened the articles by title and abstract, utilizing predetermined eligibility criteria. Any disagreements were resolved by discussion. Full-text copies of articles that were not definitely excluded based on title or abstract were retrieved, and the criteria were reapplied. Uncertain cases were discussed by the reviewers to achieve consensus. Database searching was supplemented by hand searching the reference lists of past systematic reviews.

Eligibility Criteria

The studies were included if (1) participants had knee OA, (2) the intervention was exercise, (3) the control was no intervention or psychoeducational intervention, (4) the researchers assessed pain or impairments, (5) an RCT design was used, and (6) the paper was written in English. In the outcome measures for pain, since we knew that the visual analog scale (VAS) or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were frequently used to evaluate pain[12], we included the studies using these outcome measures only.

The studies were excluded if (1) participants had hip OA or rheumatic disease, (2) patients had undergone total knee arthroplasty, (3) the intervention included intra-articular injections (e.g., sodium hyaluronate), (4) sufficient data for the synthesis of results were not reported, or (5) key outcome measure was already different significantly at baseline between groups. After screening for paper title and abstract, the studies using a minor outcome measurement that was not used in other extracted studies were excluded.

Data Collection Process

Predesigned spreadsheets were used to extract data on participants, interventions, outcome measurements, and results.

Risk of Bias in Individual Studies

Two researchers independently applied a validated scale (PEDro) to rate the methodological quality of all the trials[13]. The 11 items are based upon the Delphi list[14]. Each item is scored "yes" or "no," with a maximum score of 10, as criterion 1 is not scored. The PEDro score has demonstrated moderate interrater reliability (intraclass correlation coefficient = 0.68 [95% CI, 0.57-0.76]) for clinical trials[15]. A trial with a score of 6 or more was considered to be high quality, which is consistent with previous reviews[16].

Synthesis of Results

Standardized mean differences (SMDs) (effect sizes) and 95% confidence intervals (CIs) were calculated from postintervention means and SDs. When the standard error or 95% CI was provided, this was converted to SDs. Secondly, the *P* value was used for estimating the SD.

The data were coded so that a positive effect size indicated improvement and a negative effect size indicated worsening of impairment. Values of 0.2–0.5 indicated a small effect size, 0.5–0.8 a moderate effect size, and >0.8 a large effect size[17].

Meta-analysis was performed using an inverse variance method and random effects analysis. The Review Manager Version 5.1 (The Cochrane Collaboration, Freiburg, Germany) was used for the meta-analysis. Combining data in a meta-analysis was planned, in which a minimum of 2 trials were clinically homogenous. A trial was considered clinically homogenous if a common population and outcome measurement were used. In the intervention, there were no restrictions with respect to type, frequency, duration, or intensity of exercise.

Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[18] was applied to each meta-analysis performed to determine the quality of the evidence. This approach entailed downgrading the evidence from high quality to moderate quality to low quality and to very-low quality based on certain criteria. Downgrading the evidence one place (e.g., from high to moderate quality) would occur if (1) the PEDro score was ≤5 for the majority of trials (more than 50%) in the meta-analysis, (2) there was greater than low levels of statistical heterogeneity between the trials (I^2 >25%)[19], or (3) there were large CIs, indicating a small number of participants. If there were serious issues with the methodological quality, such as all trials in the meta-analysis had a PEDro score <6 without allocation concealment and blinded assessors, then a double downgrade would occur (e.g., from high to low quality). A footnote was used to explain the reasons for the grade applied to each meta-analysis. If the number of selected trials measuring a certain outcome was only 1 and that trial included multiple intervention groups, we synthesized the data but did not determine the quality of evidence for that outcome.

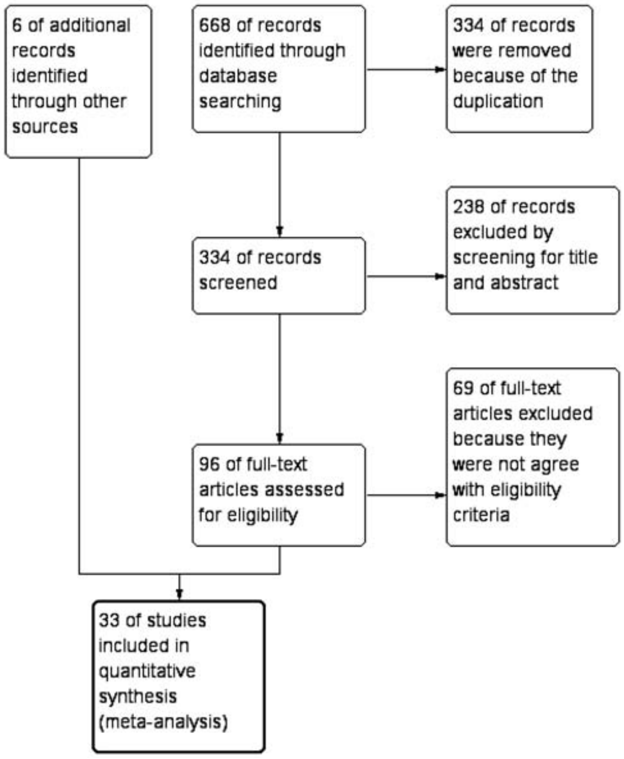

Fig. 1. Study flow diagram

Results

Study Selection

The combined database search yielded 668 trials (inclusive of duplicates). A total of 33 trials fulfilled the inclusion criteria (Fig. 1).

Study Characteristics

1. Participants

The included studies involved 3,192 participants (1,878 interventions and 1,314 comparisons). From available data in the interventions, the participants were aged from 55 to 74 years, and the female ratio was from 48.9% to 100%. A summary of included trials is shown in Table 2.

2. Interventions

Trials included in our study used muscle strengthening exercise with or without weight bearing, balance exercise,

Table 2. Summary of included trials

Study	Participants (Exercise group)	Participants (Control group)	Exercise intervention	Frequency (per a week)	Duration (weeks)
Aglamis *et al*. 2009	n = 16 Age (yrs) = 56.8 (4) Female (%) = 100	n = 9 Age (yrs) = 54.4 (12) Female (%) = 100	Aerobic, functional strengthening, and flexibility exercises	3	12
An *et al*. 2008	n = 14 Age (yrs) = 65.4 (8.2) Female (%) = 100	n = 14 Age (yrs) = 64.6 (6.7) Female (%) = 100	Baduanjin	5	8
Baker *et al*. 2001	n = 23 Age = 69 (6) Female (%) = 73.9	n = 23 Age = 68 (6) Female (%) = 82.6	Two functional exercises (squats and step-ups)	3	16
Bautch *et al*. 1997	n = 17 Age (yrs) = 69	n = 17 Age (yrs) = 69	Range of motion exercises and an individualized low intensity walking	3	12
Bennell *et al*. 2010	n = 45 Age (yrs) = 64.5 (9.1) Female (%) = 48.9	n = 44 Age (yrs) = 64.6 (7.6) Female (%) = 54.5	Six exercises to strengthen hip abductor and adductor muscles	5	12
Brismee *et al*. 2007	n = 22 Age (yrs) = 70.8 (9.8) Female (%) = 86.4	n = 19 Age (yrs) = 68.8 (8.9) Female (%) = 78.9	Tai Chi exercise	3	6
Doi *et al*. 2008	n = 71 Age (yrs) = 66.8 (12.8) Female (%) = 77.5	n = 70 Age (yrs) = 68.9 (21.1) Female (%) = 74.6	Quadriceps strengthening exercises	7	8
Ettinger *et al*. 1997	Group 1 n = 144 Age (yrs) = 69 (6) Female (%) = 69 Group 2 n = 146 Age (yrs) = 68 (6) Female (%) = 73	n = 149 Age (yrs) = 69 (6) Female (%) = 69	Group 1: Facility-based walking Group 2: Resistive exercise (9 exercises)	3	72
Fransen *et al*. 2001	Group 1 n = 43 Age (yrs) = 68.5 (8.7) Female (%) = 74 Group 2 n = 40 Age (yrs) = 65.3 (7.1) Female (%) = 78	n = 43 Age (yrs) = 66.1 (10.3) Female (%) = 67	Group 1: The choice, frequency, and duration of individual treatments at the discretion of the treating physical therapist Group 2: Quadriceps muscle strengthening exercise, stretching, aerobic exercise, and patella taping	2	8
Hale *et al*. 2012	n = 23 Age (yrs) = 73.6 (1.5) Female (%) = 74	n = 16 Age (yrs) = 75.7 (1.1) Female (%) = 75	In water-based class, warm-up/ warm-down exercises (stretching, walking forward, backward, sideways, calf and toe raises), balance exercises	2	12
Huang *et al*. 2003	Group 1: n = 33 Group 2: n = 33 Group 3: n = 33 Age (yrs) = 62 (4.5) Female (%) = 70	n = 33	Group 1: Isokinetic muscle-strengthening exercise Group 2: Isotonic muscle-strengthening exercise Group 3: Isometric muscle-strengthening exercise	3	8
Hay *et al*. 2006	n = 109 Age (yrs) = 67.9 (8.5) Female (%) = 65	n = 108 Age (yrs) = 68.2 (8.0) Female (%) = 65	Aerobic exercise, muscle strengthening exercises and stretching exercises	3-6 sessions / 10 weeks	10
Jan *et al*. 2008	Group 1 n = 34 Age (yrs) = 63.3 (6.6) Female (%) = 79.4 Group 2 n = 34 Age (yrs) = 61.8 (7.1) Female (%) = 79.4	n = 34 Age (yrs) = 62.8 (6.3) Female (%) = 83.3	Group 1: The high-resistance exercise (60% of 1 RM) Group 2: The low-resistance exercise (10% of 1 RM)	3	8

Table 2. Summary of included trials (continued)

Study	Participants (Exercise group)	Participants (Control group)	Exercise intervention	Frequency (per a week)	Duration (weeks)
Jan *et al*. 2009	Group 1 n = 36 Age (yrs) = 62.0 (6.7) Female (%) = 66.7 Group 2 n = 36 Age (yrs) = 63.2 (6.8) Female (%) = 71.4	n = 36 Age (yrs) = 62.2 (6.7) Female (%) = 68.6	Group 1: The weight-bearing exercise in a sitting position with 1 foot fixed on the center of the pedal of an EN-Dynamic resistance device Group 2: The nonweight-bearing exercise	3	8
Lee *et al*. 2009	n = 29 Age (yrs) = 70.2 (4.8) Female (%) = 93	n = 15 Age (yrs) = 66.9 (6.0) Female (%) = 93	Tai Chi exercise	2	8
Lim *et al*. 2008	n = 26 Age (yrs) = 67.2 (6.7) Female (%) = 50	n = 26 Age (yrs) = 64.1 (9.3) Female (%) = 63	Quadriceps strengthening exercises (5 exercises)	5	12
Lin *et al*. 2007	Group 1 n = 29 Age (yrs) = 61.6 (8.1) Female (%) = 69 Group 2 n = 26 Age (yrs) = 61.0 (7.7) Female (%) = 77	n = 26 Age (yrs) = 62.8 (6.3) Female (%) = 77	Group 1: Computerized proprioception facilitation exercise Group 2: Closed kinetic chain exercise with resistance device	3	8
Lin *et al*. 2009	Group 1 n = 36 Age (yrs) = 63.7 (8.2) Female (%) = 69.4 Group 2 n = 35 Age (yrs) = 61.6 (7.2) Female (%) = 66.7	n = 36 Age (yrs) = 62.2 (6.7) Female (%) = 72.2	Group 1: Computer game foot-stepping exercise Group 2: The strength training in non–weight-bearing position	3	8
Lund *et al*. 2008	Group 1 n = 25 Age (yrs) = 68 (9.5) Female (%) = 88 Group 2 n = 27 Age (yrs) = 65 (12.6) Female (%) = 83	n = 27 Age (yrs) = 70 (9.9) Female (%) = 66%	Group 1: Strengthening/endurance exercise, balance exercise and stretching exercise (land-based) Group 2: Strengthening/endurance exercise, balance exercise and stretching exercise (aquatic based)	2	8
Messier *et al*. 2004	Group 1 n = 80 Age (yrs) = 69 (0.8)† Female (%) = 74 Group 2 n = 76 Age (yrs) = 69 (0.8)† Female (%) = 74	n = 78 Age (yrs) = 69 (0.1)† Female (%) = 68	Group 1: Aerobic training and resistance training Group 2: Diet, aerobic training and resistance training	3	72
Miller *et al*. 2006	n = 44 Age (yrs) = 69.7 (0.9)† Female (%) = 63.6	n = 43 Age (yrs) = 69.3 (0.9)† Female (%) = 60.5	Aerobic exercise and strengthening exercise	3	24
O'Reilly *et al*. 1999	n = 78 Age (yrs) = 61.9 (10.0)	n = 113 Age (yrs) = 62.2 (9.7)	Isometric quadriceps contraction, Isotonic quadriceps contraction, Isotonic hamstring contraction, and Dynamic stepping exercise	7	24
Peloquin *et al*. 1999	n = 59 Age (yrs) = 65.6 (7.4) Female (%) = 71.2	n = 65 Age (yrs) = 66.4 (8.3) Female (%) = 69.2	Aerobic exercises, muscle-strengthening exercises, stretching exercises	3	12

†:Standard error

Table 2. Summary of included trials (continued)

Study	Participants (Exercise group)	Participants (Control group)	Exercise intervention	Frequency (per a week)	Duration (weeks)
Quilty *et al.* 2003	n = 43 Age (yrs) = 66.8 (9.5)	n = 44 Age (yrs) = 66.7 (11.2)	Patellar taping, 7 exercises, posture correction, and footwear advice	1	10
Salli *et al.* 2010	Group 1 n = 25 Age (yrs) = 55.7 (8.2) Female (%) = 82.6 Group 2 n = 25 Age (yrs) = 57.1 (6.8) Female (%) = 83.3	n = 25 Age (yrs) = 58.3 (6.7) Female (%) = 79.2	Group 1: Combined concentric-eccentric exercise Group 2: Isometric exercise (progressive)	3	8
Schilke *et al.* 1996	n = 10 Age (yrs) = 64.5 (59-74)‡	n = 10 Age (yrs) = 68.4 (53-85)‡	Isotonic muscle-strengthening exercise	3	8
	Female (%) = 85				
Song *et al.* 2003	n = 38 Age (yrs) = 64.8 (6.0) Female (%) = 100	n = 34 Age (yrs) = 62.5 (5.6) Female (%) = 100	Tai Chi exercise	3	12
Song *et al.* 2010	n = 30 Age (yrs) = 63 (7.3) Female (%) = 100	n = 35 Age (yrs) = 61 (8.0) Female (%) = 100	Tai Chi exercise	7	24
Thorstensson *et al.* 2005	n = 26 Age (yrs) = 54.8 (7.1) Female (%) = 50	n = 23 Age (yrs) = 57.3 (4.7) Female (%) = 50	Ergometer cycling, trampoline, step-board, floor exercises, and pulley	2	6
Topp *et al.* 2002	Group 1 n = 32 Age (yrs) = 65.6 (1.8)† Female (%) = 80 Group 2 n = 35 Age (yrs) = 63.5 (1.9)† Female (%) = 71	n = 35 Age (yrs) = 60.9 (1.8)† Female (%) = 66	Group 1: Resistance-training exercises across a functional range of motion Group 2: Resistance-training exercises at discrete joint angles	3	16
Topp *et al.* 2009	n = 26 Age (yrs) = 64.1 (7.1)	n = 28 Age (yrs) = 63.5 (6.6)	Resistance training	3	5
	Female (%) = 68				
Wang *et al.* 2007	n = 40 Age (yrs) = 69.9 (5.7) Female (%) = 62.5	n = 33 Age (yrs) = 68.8 (5.7) Female (%) = 63.6	Diet, aerobic training and strength training	3	24
Wang *et al.* 2011	Group 1 n = 26 Age (yrs) = 67.7 (5.6) Female (%) = 84.6 Group 2 n = 26 Age (yrs) = 68.3 (6.4) Female (%) = 88.5	n = 26 Age (yrs) = 67.9 (5.9) Female (%) = 84.6	Group 1: Flexibility training, aerobic training, lower body training, upper body training (aquatic based) Group 2: Flexibility training, aerobic training, lower body training, upper body training (land-based)	3	12

†: Standard error, ‡: Range

muscle stretching exercise, walking, Tai chi exercise, Baduanjin, functional exercise, computerized proprioception facilitation exercise, or range of motion exercise. Some trials added diet[20,21] or patellar taping[21,22] with exercise, or performed water-based exercise[23–25].

3. Outcome

Trials included in our study measured pain, stiffness, muscle strength, range of motion, flexibility, maximal oxygen uptake, or position sense as the outcome of body function and structure. Stiffness was evaluated with the WOMAC. Muscle strength was measured for knee extensors or flexors, and the majority of trials used peak torque at concentric isokinetic contraction as muscle strength. Range of motion was measured at maximum knee extension or flexion. Flexibility was measured by asking the patient to bend at the waist and stretch both hands toward the feet without bending the knees, and the distance between the hands and feet was measured. Maximal oxygen uptake was measured as the volume of oxygen taken up in 1 minute per kilogram of body weight at peak exercise. Position sense was evaluated by the reposition error test.

Risk of Bias within Studies

There were 23 higher-quality trials (PEDro score > 5/10), and the average score across all trials was 6.2/10. The most adhered to items on the PEDro scale were random allocation, measurements of variability for at least one key outcome, and between group comparisons, which were evident in almost all of the trials. None of the trials blinded participants or therapists, which was expected given these items are the most difficult to adhere to in trials of interventions, such as exercise. Seventeen trials used allocation concealment and 18 had blinded outcome assessors. Sixteen trials reported intention-to-treat analysis, and 27 trials had measurements of at least one key outcome from >85% of participants (Table 3).

Synthesis of Results

Synthesis of the results of exercise intervention are shown in Figs. 2–11, and Tables 4.

1. Pain

Meta-analysis of 9 trials[23,26–33] with 1,095 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at reducing pain, as measured by the VAS. Meta-analysis of 16 trials[20,22,24,27,28,31,34–43] with 1,667 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at reducing pain, as measured by the WOMAC.

2. Stiffness

Meta-analysis of 8 trials[24,28,34,38,41–44] with 424 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at reducing stiffness, as measured by the WOMAC.

3. Muscle strength

Meta-analysis of 13 trials[21,22,33,34,37,42,45–51] with 1,692 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at improving knee extensor muscle strength. Meta-analysis of 9 trials[22,37,45–51] with 1,503 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at improving knee flexor muscle strength.

4. Range of motion

Meta-analysis of 1 trial[25] with 104 participants (2 intervention groups) provided undetermined-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at improving knee extension and flexion range of motion.

5. Flexibility

Meta-analysis of 2 trials[42,47] with 167 participants provided low-quality evidence showing that compared with no exercise intervention, exercise intervention was not effective at improving flexibility.

6. Maximal oxygen uptake

Meta-analysis of 3 trials[42,51,52] with 680 participants provided high-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at improving maximal oxygen uptake.

7. Position sense

Meta-analysis of 2 trials[40,45] with 285 participants provided moderate-quality evidence showing that compared with no exercise intervention, exercise intervention was effective at improving position sense.

Discussion

Summary of Evidence

To the best of our knowledge, this is the first report to investigate the effectiveness of exercise intervention to individual impairments on OA patients by meta-analysis. The results of this systematic review provide moderate- to high-quality evidence that exercise intervention can have a small to large effect on knee OA by reducing pain and stiffness, and improving muscle strength, maximal oxygen uptake, and position sense. However, sufficient evidence of the effects on range of motion and flexibility were not shown in exercise intervention.

1. Pain

In several systematic reviews, the effect of exercise intervention has been supported with a high level of evidence[12,53]. In our reviews, that is confirmed with a moderate level of evidence. Additionally, in high-quality RCTs only (PEDro score > 5), of 9 exercise groups measured by VAS and 13 exercise groups measured by WOMAC, 9 exercise groups (100%) and 11 exercise groups (84.6%) showed more pain relief than control groups respectively. Therefore, we believe firmly in the effect of exercise intervention on pain. Although a variance in effect size was observed in our study, this may be explained by the lack of similarity in exercise interventions among trials, which also was shown in past meta-analysis studies[8,54,55], including the Cochrane reports[12]. At present, the factors that influence the variance in effect size remain unclear.

Table 3. Methodological quality of the trials (PEDro)

Study	1	2	3	4	5	6	7	8	9	10	Total (/10)
Aglamis *et al*. 2009	Yes	No	No	No	No	No	No	No	Yes	Yes	3
An *et al*. 2008	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Baker *et al*. 2001	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Bautch *et al*. 1997	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	5
Bennell *et al*. 2010	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Brismee *et al*. 2007	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Doi *et al*. 2008	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Ettinger *et al*. 1997	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Fransen *et al*. 2001	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Hale *et al*. 2012	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Huang *et al*. 2003	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Hay *et al*. 2006	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Jan *et al*. 2008	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Jan *et al*. 2009	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Lee *et al*. 2009	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Lim *et al*. 2008	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Lin *et al*. 2007	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Lin *et al*. 2009	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Lund *et al*. 2008	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Messier *et al*. 2004	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Miller *et al*. 2006	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
O'Reilly *et al*. 1999	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Peloquin *et al*. 1999	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Quilty *et al*. 2003	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Salli *et al*. 2010	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	6
Schilke *et al*. 1996	Yes	No	No	No	No	No	Yes	No	Yes	Yes	4
Song *et al*. 2003	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	6
Song *et al*. 2010	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	6
Thorstensson *et al*. 2005	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Topp *et al*. 2002	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Topp *et al*. 2009	Yes	No	Yes	No	No	No	Yes	No	No	Yes	4
Wang *et al*. 2007	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Wang *et al*. 2011	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7

PEDro Criteria: (1) Random allocation. (2) Allocation concealed. (3) Groups similar at baseline. (4) Participant blinding. (5) Therapist blinding. (6) Assessor blinding. (7) Measures of at least one key outcome were obtained from >85% of subjects. (8) Data were analyzed by intention to treat. (9) Results reported for at least one key outcome. (10) Point measures and measures of variability provided.

2. Stiffness

In the systematic review by Lange *et al*.[11)], 5 studies measured stiffness; of which, 2 demonstrated significant improvement in the strength training group, compared with the control group. However, they did not perform a meta-analysis, and could not confirm the effect of exercise intervention on stiffness. We synthesized the data from 8 studies that examined the effect of exercise intervention on stiffness, as measured by the WOMAC, and confirmed a small effect size, which tends to be less than the effect on pain. To our knowledge, this evidence has not been reported previously. Our findings might indicate a difficulty in improving stiffness with exercise intervention in contrast to pain relief.

3. Muscle strength

With regard to muscle strength (not as is the case of pain), there are few systematic reviews that confirmed

	Exercise			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bautch 1997	-2.19	1.6654	15	-2.08	2.0914	15	7.6%	-0.06 [-0.77, 0.66]
Bennell 2010	-2.6	2.1	45	-3.9	2.6	44	8.5%	0.55 [0.12, 0.97]
Brismee 2007	-3.2	2.2	22	-3.66	1.96	19	7.9%	0.22 [-0.40, 0.83]
Doi 2008	-22.55	20.68	61	-29.59	23.94	56	8.7%	0.31 [-0.05, 0.68]
Huang 2003	-3.6	0.6	62	-4.4	0.4	66	8.6%	1.57 [1.17, 1.97]
Huang 2003	-3.1	1.2	58	-4.4	0.4	66	8.6%	1.48 [1.08, 1.88]
Huang 2003	-2.6	0.7	62	-4.4	0.4	66	8.2%	3.16 [2.64, 3.69]
Lund 2008	-55.8	20.7846	27	-58.1	20.7846	27	8.2%	0.11 [-0.42, 0.64]
Lund 2008	-51.5	20.5	25	-58.1	20.7846	27	8.2%	0.31 [-0.23, 0.86]
O'Reilly 1999	6.64	19.2047	78	0.43	23.1233	113	8.8%	0.29 [-0.00, 0.58]
Quilty 2003	-42.8	25.1	44	-50.5	25.6	43	8.5%	0.30 [-0.12, 0.72]
Topp 2009	-4.77	2.2946	26	-6.8	2.2753	28	8.1%	0.88 [0.31, 1.44]
Total (95% CI)			**525**			**570**	**100.0%**	**0.77 [0.29, 1.24]**

Heterogeneity: Tau² = 0.64; Chi² = 147.07, df = 11 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.15 (P = 0.002)

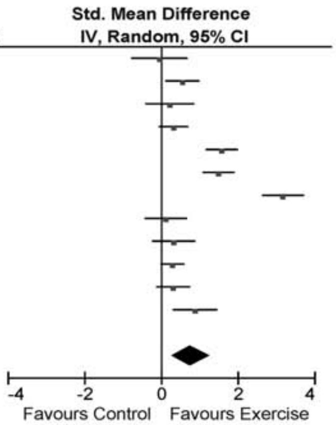

Fig. 2. SMD (95% CI) of effect of exercise intervention on pain (VAS)

	Exercise			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
An 2008	-71.1	110.1	11	-138.2	112.6	10	2.1%	0.58 [-0.30, 1.46]
Baker 2001	-128	94.7279	22	-189	108.2605	22	3.7%	0.59 [-0.02, 1.19]
Bennell 2010	-4.9	3.3	45	-6.5	3.3	44	5.7%	0.48 [0.06, 0.90]
Brismee 2007	-15.39	5.7	22	-16.64	4.57	19	3.6%	0.24 [-0.38, 0.85]
Fransen 2001	10.6	19.6926	83	-1.5	12.9974	43	6.3%	0.68 [0.30, 1.06]
Hale 2012	-7.8	3.9544	23	-7.1	1.6515	16	3.4%	-0.21 [-0.85, 0.43]
Hay 2006	-7.36	4.3	93	-8.99	3.7	89	7.6%	0.40 [0.11, 0.70]
Jan 2008	-4.8	2.7	34	-7.1	3.4	30	4.6%	0.75 [0.24, 1.25]
Jan 2008	-4.8	3.5	34	-7.1	3.4	30	4.7%	0.66 [0.15, 1.16]
Lee 2009	-4.6	4	29	-5.9	3.7	15	3.5%	0.33 [-0.30, 0.95]
Lim 2008	-28.5	16.9	26	-36.2	16.2	26	4.2%	0.46 [-0.09, 1.01]
Lin 2009	-4.3	2.3	36	-7.3	3.4	36	4.8%	1.02 [0.53, 1.52]
Lin 2009	-4.2	3	36	-7.3	3.4	36	4.8%	0.96 [0.47, 1.45]
Messier 2004	-5.07	4.0974	76	-6.02	3.9743	78	7.2%	0.23 [-0.08, 0.55]
Messier 2004	-6.24	4.2038	80	-6.02	3.9743	78	7.3%	-0.05 [-0.37, 0.26]
Miller 2006	-4.1	2.498	39	-6.1	2.958	35	5.0%	0.73 [0.25, 1.20]
O'Reilly 1999	1.45	2.6168	78	0.42	3.5946	113	7.7%	0.32 [0.03, 0.61]
Song 2003	2.45	3.9	22	-0.61	5.1	21	3.6%	0.66 [0.05, 1.28]
Topp 2002	-10.71	3.1355	35	-10.77	3.1947	35	5.1%	0.02 [-0.45, 0.49]
Topp 2002	-10.38	3.1678	32	-10.77	3.1947	35	4.9%	0.12 [-0.36, 0.60]
Total (95% CI)			**856**			**811**	**100.0%**	**0.43 [0.29, 0.57]**

Heterogeneity: Tau² = 0.05; Chi² = 36.39, df = 19 (P = 0.009); I² = 48%
Test for overall effect: Z = 5.94 (P < 0.00001)

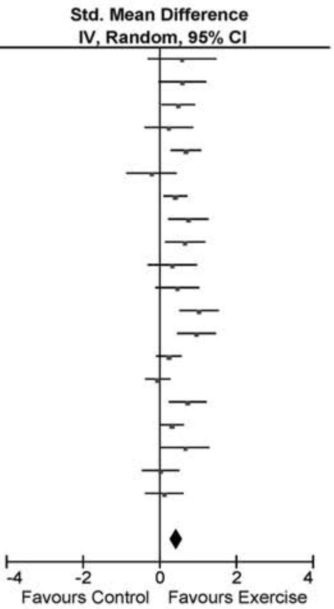

Fig. 3. SMD (95% CI) of effect of exercise intervention on pain (WOMAC)

	Exercise			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Aglamis 2009	-4.9	1.4	16	-6.1	1.9	9	5.3%	0.73 [-0.12, 1.57]
An 2008	-30.8	43.8	11	-62.3	49.3	10	4.8%	0.65 [-0.23, 1.53]
Brismee 2007	-4.73	1.42	22	-4.71	1.96	19	10.0%	-0.01 [-0.63, 0.60]
Hale 2012	-3.7	1.5725	23	-3.4	1.3137	16	9.2%	-0.20 [-0.84, 0.44]
Lee 2009	-1.5	1.7	29	-1.8	1.7	15	9.6%	0.17 [-0.45, 0.80]
Miller 2006	-3	1.249	39	-3.1	1.7748	35	18.1%	0.07 [-0.39, 0.52]
Song 2003	0.91	1.6	22	-0.23	1.8	21	9.9%	0.66 [0.04, 1.27]
Topp 2002	-5.03	1.5839	32	-5.5	1.5382	35	16.2%	0.30 [-0.18, 0.78]
Topp 2002	-5.04	1.5973	35	-5.5	1.5382	35	16.9%	0.29 [-0.18, 0.76]
Total (95% CI)			**229**			**195**	**100.0%**	**0.24 [0.05, 0.44]**

Heterogeneity: Chi² = 7.05, df = 8 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

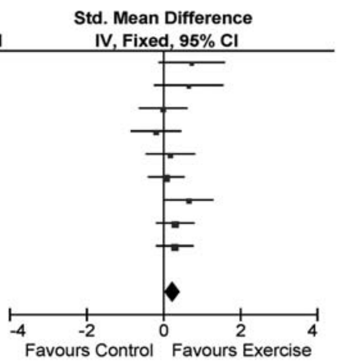

Fig. 4. SMD (95% CI) of effect of exercise intervention on stiffness (WOMAC)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
An 2008	39.2	11.4	11	36.2	15.8	10	2.1%	0.21 [-0.65, 1.07]
Ettinger 1997	90.2	24.1661	146	87	23.1925	149	10.9%	0.13 [-0.09, 0.36]
Ettinger 1997	89	26.4	144	87	22.9578	149	10.9%	0.08 [-0.15, 0.31]
Fransen 2001	10.8	29.7679	83	-2.4	22.0955	43	7.1%	0.48 [0.11, 0.85]
Jan 2008	86.7	24.2	34	72.7	22.3	30	4.8%	0.59 [0.09, 1.10]
Jan 2008	88.1	21.6	34	72.7	22.3	30	4.8%	0.69 [0.19, 1.20]
Jan 2009	83.2	24.8	36	73.6	24	35	5.3%	0.39 [-0.08, 0.86]
Jan 2009	89.1	27.1	35	73.6	24	35	5.2%	0.60 [0.12, 1.08]
Lin 2007	84.3	23.7	58	71.7	29	52	6.9%	0.48 [0.10, 0.85]
Lin 2007	85.5	24.8	52	71.7	29	52	6.7%	0.51 [0.12, 0.90]
Peloquin 1999	85.08	37.36	59	82.15	33.64	65	7.5%	0.08 [-0.27, 0.43]
Salli 2010	61.89	13.76	23	47.13	11.75	24	3.5%	1.14 [0.52, 1.76]
Salli 2010	57.43	16.72	24	47.13	11.75	24	3.9%	0.70 [0.12, 1.29]
Schilke 1996	55.6	31.54	10	49.6	17.51	10	2.0%	0.23 [-0.65, 1.11]
Song 2003	6.75	8.9	22	4.25	6.6	21	3.7%	0.31 [-0.29, 0.91]
Song 2010	232.5	67	30	229.3	57.2	35	5.0%	0.05 [-0.44, 0.54]
Topp 2009	56.51	31.41	26	54.02	31.4315	28	4.4%	0.08 [-0.46, 0.61]
Wang 2007	3.2	1.1	40	2.45	1.21	33	5.3%	0.64 [0.17, 1.12]
Total (95% CI)			**867**			**825**	**100.0%**	**0.37 [0.24, 0.50]**

Heterogeneity: Tau² = 0.03; Chi² = 27.45, df = 17 (P = 0.05); I² = 38%
Test for overall effect: Z = 5.51 (P < 0.00001)

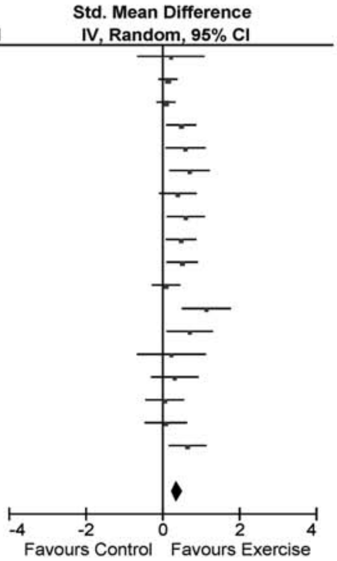

Fig. 5. SMD (95% CI) of effect of exercise intervention on knee extensors muscle strength

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ettinger 1997	50.1	13.2914	146	45.8	12.2066	149	11.0%	0.34 [0.11, 0.57]
Ettinger 1997	49.5	13.2914	146	45.8	12.2066	149	11.0%	0.29 [0.06, 0.52]
Fransen 2001	8.4	20.1506	83	-0.6	15.9218	43	8.4%	0.48 [0.10, 0.85]
Jan 2008	57.4	18.9	34	42.5	20.8	30	6.3%	0.74 [0.23, 1.25]
Jan 2008	61.7	20.1	34	42.5	20.8	30	6.2%	0.93 [0.41, 1.45]
Jan 2009	51.2	19.8	35	41.6	18.1	35	6.7%	0.50 [0.02, 0.98]
Jan 2009	55.2	20.2	36	41.6	18.1	35	6.7%	0.70 [0.22, 1.18]
Lin 2007	60.9	20.4	52	40.8	23.1	52	7.8%	0.92 [0.51, 1.32]
Lin 2007	53	17.6	58	40.8	23.1	52	8.2%	0.59 [0.21, 0.98]
Peloquin 1999	66.02	34.32	59	56.29	28.28	65	8.7%	0.31 [-0.05, 0.66]
Salli 2010	31.43	7.98	23	20.98	5.21	24	4.6%	1.53 [0.87, 2.19]
Salli 2010	29.15	7.86	24	20.98	5.21	24	5.0%	1.21 [0.59, 1.82]
Schilke 1996	43.5	15.5	10	37.5	16.33	10	3.0%	0.36 [-0.52, 1.25]
Song 2010	129.5	40.1	30	123.9	29.2	35	6.6%	0.16 [-0.33, 0.65]
Total (95% CI)			**770**			**733**	**100.0%**	**0.59 [0.42, 0.77]**

Heterogeneity: Tau² = 0.06; Chi² = 31.18, df = 13 (P = 0.003); I² = 58%
Test for overall effect: Z = 6.67 (P < 0.00001)

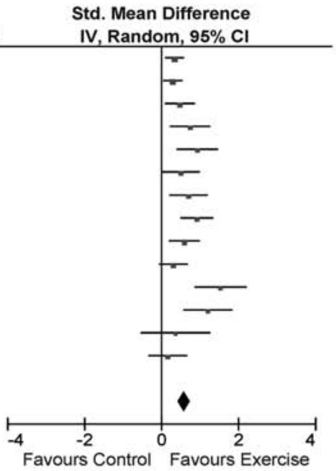

Fig. 6. SMD (95% CI) of effect of exercise intervention on knee flexors muscle strength

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Wang 2011	-2.4	1.2	26	-3.3	1.1	26	51.3%	0.77 [0.21, 1.34]
Wang 2011	-2	1.4	26	-3.3	1.1	26	48.7%	1.02 [0.44, 1.60]
Total (95% CI)			**52**			**52**	**100.0%**	**0.89 [0.49, 1.30]**

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 4.31 (P < 0.0001)

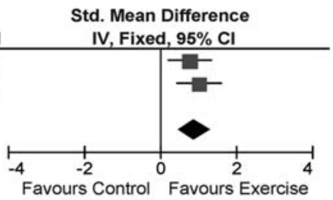

Fig. 7. SMD (95% CI) of effect of exercise intervention on knee extension range of motion

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Wang 2011	125	6.1	26	122.3	5.3	26	50.3%	0.47 [-0.09, 1.02]
Wang 2011	125	4.2	26	122.3	5.3	26	49.7%	0.56 [0.00, 1.11]
Total (95% CI)			**52**			**52**	**100.0%**	**0.51 [0.12, 0.90]**

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)

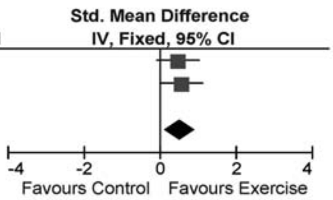

Fig. 8. SMD (95% CI) of effect of exercise intervention on knee flexion range of motion

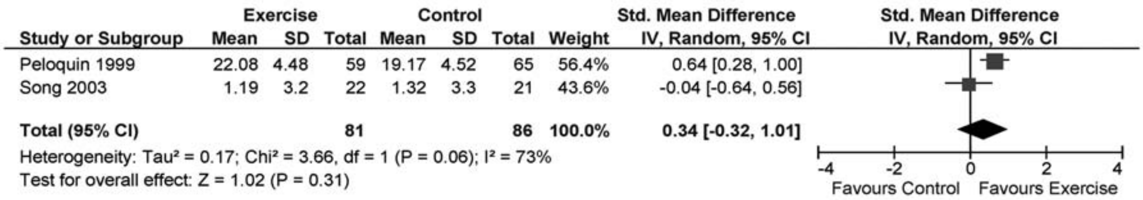

Fig. 9. SMD (95% CI) of effect of exercise intervention on flexibility

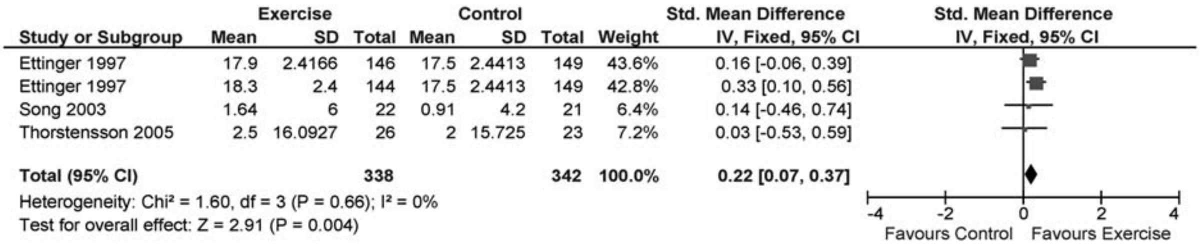

Fig. 10. SMD (95% CI) of effect of exercise intervention on maximal oxygen uptake

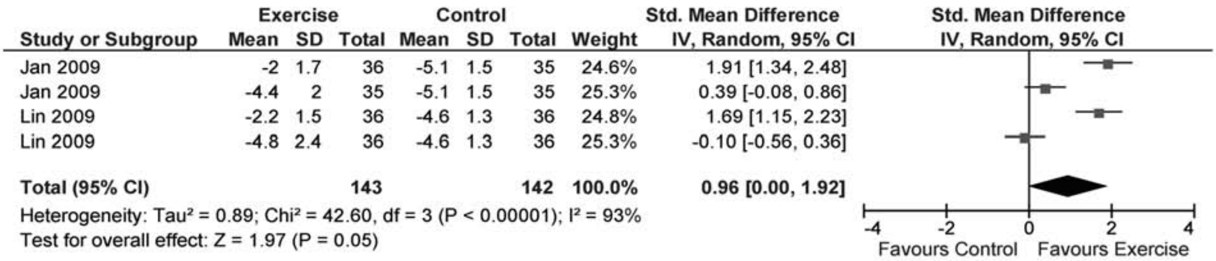

Fig. 11. SMD (95% CI) of effect of exercise intervention on position sense

Table 4. Meta-analyses for the effect of exercise intervention

	No. of trials (No. of groups)	Ratio of trials (PEDro <6)	No. of participants	SMD [95% CI]	I^2	Quality of the evidence (GRADE)
Pain (VAS)	9(12)	33%	1,095	0.77 [0.29, 1.24]	93%	Moderate §
Pain (WOMAC)	16(20)	25%	1,667	0.43 [0.29, 0.57]	48%	Moderate §
Stiffness (WOMAC)	8(9)	63%	424	0.24 [0.05, 0.44]	0%	Moderate //
Muscle strength (knee extension)	13(18)	38%	1,692	0.37 [0.24, 0.50]	38%	Moderate §
Muscle strength (knee flexion)	9(14)	22%	1,503	0.59 [0.42, 0.77]	58%	Moderate §
ROM (knee extension)	1(2)	0%	104	0.89 [0.49, 1.30]	0%	–
ROM (knee flexion)	1(2)	0%	104	0.51 [0.12, 0.90]	0%	–
Flexibility	2(2)	0%	167	0.34 [-0.32, 1.01]	73%	Low ¶
Maximal oxygen uptake	3(4)	0%	680	0.22 [0.07, 0.37]	0%	High
Position sense	2(4)	0%	285	0.96 [0.00, 1.92]	93%	Moderate §

GRADE = GRADE working group grades of evidence.

VAS: Visual Analogue Scale, WOMAC: Western Ontario and McMaster Universities Arthritis Index, ROM: Range of Motion.

§ Reason for downgrade: Statistical heterogeneity (I^2 > 25%)

// Reason for downgrade: Less than 6 PEDro score for the majority of trials (more than 50%)

¶ Reason for downgrade: Large confidence intervals, statistical heterogeneity (I^2 > 25%)

strong evidence of the effectiveness of exercise intervention. According to Lange *et al*.[11], there were 14 RCTs that examined the effect of strength training on muscle strength; of which, 9 (64%) showed significant improvement in the strength training group, compared with the control group. They concluded that resistance training improved muscle strength. Our results also demonstrated that exercise intervention, including strength training, was effective at improving the muscle strength of either knee extensors or knee flexors. Additionally, this positive effect was supported by a moderate-quality evidence. This finding is additional evidence to recommend exercise in patients with weak muscle strength caused by knee OA.

4. Range of motion

Except for the report by Lange *et al*.[11], there were no systematic reviews or meta-analysis studies that examined the effect of exercise intervention on range of motion. According to Lange *et al*.[11], the number of studies measuring the effect on range of motion was 6; of these studies, only 1 showed significant improvement in the strength training group, compared with the control group. According to our synthesized data, the effect on extension or flexion range of motion was positive; however, the data were extracted from only 2 exercise groups in 1 study[25]. Therefore, we could not judge the effect of exercise intervention on range of motion with a strong evidence level.

5. Flexibility

The effect of exercise intervention on flexibility has been investigated in past systematic review[56]. In the present review, the number of studies examining the effect on flexibility was only 2. Although we could synthesize the data from the 2 studies, the results did not show a positive effect in exercise groups, and this evidence level was low. Thus, we could not support the effect on flexibility positively.

6. Maximal oxygen uptake

Brosseau *et al*.[57] reviewed and judged the efficacy of aerobic exercise for respiratory capacity for the reason of the positive results by only one RCT of Minor[58]. We believe attention should be given to this judgment. The reason is that the RCT by Minor[58] included data from patients with rheumatoid arthritis and OA, and lacked concealed allocation, blind assessors, adequate follow-up, and intention-to-treat analysis, which corresponded to a PEDro score of 4. In contrast, 3 studies selected in our meta-analysis included patients with OA only and had a PEDro score >6. The synthesized data for 3 studies that examined the effect of exercise intervention on maximal oxygen uptake were positive, and the quality of this evidence was high. However, 2 RCTs[42,52] showed no positive effect of exercise intervention, synthesized data might be reflected strongly from 1 RCT[51] because of its large sample size compared with those in the other 2 RCTs[42,52]. Additionally, exercise intervention duration in this RCT[51] was longer (72 weeks) than in the other 2 RCTs[42,52] (6 weeks and 12 weeks, respectively). This information suggests that improvement in maximal oxygen uptake might require long-term exercise intervention. Accordingly, at present, the effect of exercise intervention on maximal oxygen uptake should be recognized with caution.

7. Position sense

The effect of exercise intervention on position sense has not been confirmed with strong evidence; therefore, there is no consensus on its efficacy. A positive effect was revealed in 2 previous high-quality RCTs, and the synthesized data in our meta-analysis was of a significantly large effect size. However, a statistical heterogeneity was detected between the 2 studies[40,45] (4 exercise groups). In these studies, the effect size was significantly large in the exercise groups that performed weight-bearing exercise, whereas no significant effect was detected in the exercise groups that performed non-weight-bearing exercise. Therefore, the effect on position sense might depend on weight-bearing condition during exercise.

Strong Points and Limitations of the Study

Our study has 2 strong points. First, we synthesized the objective outcome data from multiple studies. Previously, high-quality evidence of the effect of exercise intervention was obtained from self-reported outcomes (e.g., VAS, WOMAC) in some meta-analysis studies (e.g., Roddy *et al*.[8], Fransen and McConnell[12]). We obtained moderate- to high-quality evidence from objective outcomes (e.g., muscle strength, maximal oxygen uptake, and position sense), which are difficult to be influenced by psychological bias. Second, we revealed the evidence level of various types of outcomes. Previously, the evidence level was judged for each type of exercise (e.g., muscle strengthening exercise and aerobic exercise). In our studies, we judged the evidence level of each outcome according to the GRADE approach, which is recognized as a general system for practice guidelines.

We can identify 2 research limitations. First, subject characteristics were not identical among the studies included in our study. The inclusion criteria on OA grade and severity of impairment were not established in detail. For example, exercise intervention might not be effective in patients with severe OA grade, pain, or impairments. Clarification of the effective exercise intervention corresponding to subject characteristics could be a research objective in future studies. Second, statistical heterogeneity between studies (groups) was observed in pain, muscle strength, flexibility, and position sense. The effect of exercise intervention might be influenced by factors such as exercise type or intention; previous studies could not identify the influencing factors. If these factors could be clarified, clinicians could achieve a more effective exercise intervention program.

Conclusion

There is high-quality evidence that exercise intervention is effective at improving maximal oxygen uptake. There is moderate-quality evidence that exercise intervention is effective at improving pain, stiffness, knee extensor and flexor muscle strength, and position sense. There is low-quality evidence that exercise intervention is not effective at improving flexibility. There is no strong evidence that exercise intervention is effective at improving knee extension and flexion range of motion.

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