

Exercise therapy in juvenile idiopathic arthritis: a Cochrane Review

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Background. Exercise therapy is considered an important component of the treatment of arthritis. The efficacy of exercise therapy has been reviewed in adults with rheumatoid arthritis but not in children with juvenile idiopathic arthritis (JIA).

Objectives. To assess the effects of exercise therapy on functional ability, quality of life and aerobic capacity in children with JIA.

Methods. Several electronic databases were searched up to October 2007 and references were tracked. The selection criteria were randomized controlled trials (RCTs) of exercise treatment in JIA. As for data collection and analysis, potentially relevant references were evaluated and all data were extracted by two review authors working independently.

Results. Three out of 16 identified studies met the inclusion criteria, with a total of 212 participants. All the included studies fulfilled at least seven of 10 methodological criteria. The outcome data of the following measures were homogeneous and were pooled in a meta-analysis: functional ability (N=198; weighted mean difference [WMD] -0.07, 95% CI -0.22 to 0.08), quality of life (CHQ-PhS: N=115; WMD -3.96, 95% CI -8.91 to 1.00) and aerobic capacity (N=124; WMD 0.04, 95% CI -0.11 to 0.19). The results suggest that the outcome measures all favoured the exercise therapy but none were statistically significant. None of the studies reported negative effects of the exercise therapy.

Cochrane review statement for paper publication.—This paper was also published as Takken T, van Brussel M, Engelbert RHH, Van der Net J, Kuis W, Helders PJM. Exercise therapy in juvenile idiopathic arthritis. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005954. DOI: 10.1002/14651858.CD005954.pub2.

Fundings.—Supported in part by a grant from the Dutch Arthritis Association (IMP-04-01).

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Conclusions. Overall, based on “silver-level” evidence there was no clinically important or statistically significant evidence that exercise therapy can improve functional ability, quality of life, aerobic capacity or pain. The included and excluded studies were all consistent about the adverse effects of exercise therapy; no short-term detrimental effects of exercise therapy were found in any study. Both included and excluded studies showed that exercise does not exacerbate arthritis. Although the short-term effects look promising, the long-term effect of exercise therapy remains unclear.

KEY WORDS: Exercise therapy - Arthritis, juvenile rheumatoid - Treatment outcome.

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and is an important cause of short-term and long-term disability. JIA is a disease of unknown etiology that begins before the 16th birthday and persists for at least six weeks. A diagnosis is made when other known conditions are excluded.¹ Studies in developed countries have reported a prevalence that varies between 16 and 150 per 100 000.¹ Data from two cross-sectional studies indicate that children with arthritis are physically less active compared to healthy children.^{2,3} Moreover, it was found that physical activity was related to physical fitness³ indicating that lower physical activity level leads to deconditioning and functional deterioration, which

reinforces an inactive lifestyle.⁴ Exercise therapy (for example, a training program) might prevent the deconditioning due to hypoactivity and break the vicious circle. Exercise therapy is considered as an integral part of the treatment of children with JIA.⁵ Several types of exercise therapy can be distinguished, for example, physical training programs such as strength training for improving muscle strength and endurance exercise for improving cardiorespiratory fitness. Studies in adult rheumatoid arthritis (RA) patients have shown that these exercise modalities, or a combination of both, can improve physical fitness (muscle strength or maximal oxygen uptake) and function.⁶⁻⁹

In both adult RA and JIA, the focus has shifted from inflammation parameters to more patient-centred outcomes. For RA this resulted in the development of the outcome measures in rheumatology (OMERACT) core set for RA¹⁰ and in JIA the Pediatric Rheumatology International Trial Organization (PRINTO) core set.¹¹ The OMERACT core set consists of patient and physician global assessment and measures of pain, disability and an acute-phase reactant. The PRINTO core set consists of physician global assessment of disease activity, parent or patient (as appropriate for age) global assessment of overall wellbeing, functional ability, number of joints with active arthritis, number of joints with limited range of motion, erythrocyte sedimentation rate and health-related quality of life (HRQoL) measurements.

A systematic review on the effects of dynamic exercise therapy for treating adult RA has shown that adults can benefit from exercise in terms of improved exercise capacity, muscle strength and range of motion.¹² There is some evidence that children with JIA can benefit from exercise as well.^{13, 14} Other evidence showed that exercise does not exacerbate arthritis (15, 16). However, not all of these studies are controlled studies. A systematic review of randomized controlled studies can determine whether exercise therapy is effective for children with JIA. Therefore, the authors performed a systematic review on the effects of physical exercise therapy for children with JIA.

Materials and methods

Objectives

The primary objective was to perform a systematic review on the effects of exercise therapy for children

with JIA in terms of functional ability, range of motion, number of joints with swelling (active joint count), number of joints with pain, health-related quality of life, parent or patient global assessment of overall wellbeing, pain, aerobic capacity and muscle strength.

Criteria for considering studies for this review

TYPES OF STUDIES

All full-length randomized controlled trials (RCT) were eligible for inclusion.

TYPES OF PARTICIPANTS

This review concerned children with juvenile idiopathic arthritis (juvenile rheumatoid arthritis [JRA], juvenile chronic arthritis [JCA], JIA) under 18 years of age, including all subgroups ([extended] oligo [paucil] articular JIA, rheumatoid factor [RF] negative and RF positive polyarthritis, systemic onset JIA, psoriatic arthritis, enthesitis related arthritis and other arthritis) as diagnosed by a rheumatologist based on established criteria from national and international organizations (International League of Associations for Rheumatology [ILAR], American College of Rheumatology [ACR], European League Against Rheumatism [EULAR]). Studies of osteoarthritis were excluded as this is not relevant for children with JIA.

TYPES OF INTERVENTION

Physical exercise therapy existing of: endurance training; strength training; a combination of strength and endurance training; physical exercise during summer camps.

Comparators to these interventions were: placebo; therapy Y, where therapy Y is any therapy that can be considered as a placebo exercise therapy as attention is given that is not expected to improve physical function because of a very low exercise intensity, but which may also be beneficial to the participants; standard medical care; because it is very difficult to develop a real placebo for exercise therapy, children receiving assessment only will be considered as receiving placebo.

In order to meet the inclusion criteria for this review all interventions must include an adequate description of the intervention including intensity, frequency, duration of training and mode of administration. Trial duration must be a minimum of two weeks.

TYPES OF OUTCOME MEASURES

The authors included all the outcome measures recommended for use in clinical trials in the PRINTO-core set¹¹ as well as training effects on exercise capacity and muscle strength. When reported, side effects, total number of dropouts and compliance with exercise were also included in the review.

Functional primary outcome measures:

- functional ability (as measured on functional tests and questionnaires (*i.e.* Juvenile Arthritis Functional Assessment Scale [JAFAS], Childhood Health Assessment Questionnaire [CHAQ] and Juvenile Arthritis Functional Status Index [JASI]);
- joint range of motion measures;
- number of joints with swelling (active joint count);
- number of joints with pain;
- health-related quality of life (*i.e.* HR-QoL, Child Health Questionnaire [CHQ]);
- parent or patient global assessment of overall wellbeing;
- pain.

Adverse outcomes (safety of exercise therapy) and other outcomes:

- any reported side effects (*e.g.* disease flares);
- total number of dropouts;
- withdrawals due to inefficacy or negative effects.

Secondary outcomes and measures to evaluate the effects of exercise training on exercise capacity and muscle strength:

- aerobic capacity (VO_{2peak}) determined on maximal ergometer test;
- aerobic capacity (VO_{2peak}) estimated from sub-maximal ergometer test;
- aerobic capacity estimated from field test measuring aerobic fitness;
- muscle strength;
- compliance with exercise.

Search methods for identification of studies: several electronic databases were searched up to October 2007 and references were tracked.

A detailed search strategy can be found elsewhere in the original Cochrane review.

Selection of studies

The search strategy identified a set of potentially relevant references. Two authors (Takken and van Brussel)

screened search results for potentially eligible studies. When titles and abstracts suggested a study was potentially eligible for inclusion, a full paper copy of the report was obtained. Disagreements between the two authors regarding a study's eligibility were resolved by discussion until consensus was reached or, where necessary, a third person (Engelbert) acted as adjudicator.

In addition to extracting data, the review authors independently allocated each included trial to one of three methodology quality categories, based on the Cochrane Handbook for Systematic Reviews of Interventions.¹⁷

Category A: low risk of bias – plausible that bias is unlikely to seriously alter the results, all of the criteria met.

Category B: moderate risk of bias – plausible that bias raises some doubt about the results, one or more criteria partly met.

Category C: high risk of bias – plausible that bias seriously weakens confidence in the results, one or more criteria not met.

Data extraction and management

Two independent observers (Takken and van Brussel) independently extracted data using a standard extraction form. Agreements between observers were assessed using a weighted kappa statistic.

Disagreements were discussed by the two review authors until a consensus was reached. If no consensus was reached, a third review author (Engelbert) acted as adjudicator. Data were extracted at baseline and the end of the intervention period. If data were missing or further information was required, serious attempts were made to contact the first two study authors to request the required information.

Assessment of methodological quality of included studies

Methodological quality was assessed independently by two review authors (Takken and van Brussel) using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale is based on the Delphi list developed by Verhagen *et al.*¹⁸ which is based on “expert consensus” and not, for the most part, on empirical data. To improve the reliability of this scale, any disagreement between the review authors was resolved by discussion with an independent review author (Engelbert) until a consensus was reached.

GRADING OF EVIDENCE

The grading system as described in the 2004 book Evidence-based rheumatology¹⁹ and recommended by the Musculoskeletal Group was used.

Platinum: a published systematic review that has at least two individual controlled trials each satisfying the following criteria:

- sample sizes of at least 50 per group – if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome;
- blinding of patients and assessors for outcomes;
- handling of withdrawals >80% follow up (imputations based on methods such as last observation carried forward (LOCF) are acceptable);
- concealment of treatment allocation.

Gold: at least one RCT meeting all of the following criteria for the major outcome(s) as reported:

- sample sizes of at least 50 per group – if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome;
- blinding of patients and assessors for outcomes;
- handling of withdrawals >80% follow up (imputations based on methods such as LOCF are acceptable);
- concealment of treatment allocation.

Silver: a randomized trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomized cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomized trial with a “head-to-head” comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: the bronze ranking is given to evidence if at least one high quality case series without controls (including simple before and after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

Measures of treatment effect

All the trials to be included in the systematic review were entered into Review Manager 4.2. For continu-

ous outcomes (functional ability, range of motion, number of joints with swelling (active joint count), number of joints with pain, quality of life, parent or patient global assessment of overall wellbeing, pain, aerobic capacity and muscle strength), a weighted mean difference between treatment and control groups was calculated, if possible. Dichotomous outcomes (number of side effects, total number of dropouts from study, compliance with therapy, physician and parent global assessment) were described.

The results from the various studies were tested for heterogeneity using the chi-square statistic, with a significance level of $P=0.05$, and the I^2 statistic where over 50% indicates substantial heterogeneity.¹⁷ Overall effects were only be estimated for groups of trials using the same intervention. As such, several individual meta-analyses were performed. Meta-analyses were conducted according to a fixed-effect model. Where heterogeneity was significant, a random-effects model was used. Potential publication bias was evaluated with the inverted funnel plot technique. A sensitivity analysis was conducted to evaluate the robustness of the meta-analyses. This analysis examined the effects of methodological quality and potential differences in exercise frequency, intensity and duration.

Clinical relevance tables were compiled for pooled outcome measures as additional tables to improve the readability of the review. Weighted absolute change was calculated from the weighted mean difference (WMD) statistic in RevMan when trials using the same scale were pooled. Relative per cent change from baseline was calculated as the absolute benefit divided by the baseline mean of the control group. Since there were no statistically significant outcome measures, the number needed to treat (NNT) was not calculated.

Description of studies

Review authors Takken and van Brussel selected a total of 16 citations of full-length reports and abstracts describing seven controlled exercise therapy trials.²⁰⁻²⁶ In one case, an article in the German language was obtained; this study was considered for inclusion because the review authors were able to read this language as well. Authors of abstracts were asked for a full-length manuscript. Two authors of abstracts responded to the call.^{21, 27} However, they were not able to provide a full-length version. Nor

could they provide any details because the full-length article was not submitted yet. The author of the third abstract did not reply.²² Four studies reported in seven controlled trials were identified by the review authors as RCT.^{20, 21, 24, 28} Three out of these four RCTs were included in this review; one was excluded because it was not a full-length article. Following is a brief description of the three remaining studies. Epps *et al.*²⁰ carried out a RCT in which 78 children (43 girls, 35 boys; aged 4 to 19 years) with JIA were randomly allocated to receive a combined (hydrotherapy and land-based physiotherapy) or a land-based (only land-based physiotherapy) training program. The children in both groups received 16 one-hour treatment sessions over two weeks followed by local physiotherapy attendances for two months. Thirty-nine children were allocated to the combined group. The primary outcome measures included improvement in disease status which was calculated from six core outcome measures: CHAQ, physician's global assessment of disease activity, parent's global assessment of overall well-being, number of joints with limited range of motion (ROM), number of active joints and erythrocyte sedimentation rate; the secondary outcome measures included health-related quality of life (CHQ-PF50), muscle strength (peak power), cardiovascular fitness (time and maximal heart rate), pain (Visual Analog Scale [VAS] scale) and patient satisfaction. These parameters were measured at baseline, two-months follow up and six-months follow up. The authors found that: "Two months after intervention 47% patients in the combined group and 61% patients in the land group had improved disease activity with 11% and 5% worsened, respectively". All secondary outcome measures demonstrated a mean improvement in both groups, with the combined group showing greater improvements compared with the land-based group in physical aspects of HRQoL (improvement of 33% *versus* 28% in the land-based group) and physical fitness.

Singh-Grewal *et al.*²⁴ carried out an RCT in which 80 children (43 girls, 35 boys; aged 4 to 19 years) with JIA were randomly allocated to a high-intensity aerobic training program (experimental group) or low-intensity training program (control group). Both groups participated in a 12-week, three times weekly training program consisting of high-intensity aerobics in the experimental group and Qigong in the control group. Forty-one children were allocated to

the experimental group. The outcome measures included submaximal oxygen uptake at 3 km/hour ($VO_{2submax}$), maximal oxygen uptake (VO_{2peak}), peak power and functional ability (CHAQ). These parameters were measured at baseline and after completing the training program. The authors found that the exercise program was well tolerated in both groups. There was no difference in $VO_{2submax}$ ($P=0.43$) or in any other exercise-testing measure between the groups throughout the study period and no indication of improvement. The functional ability (CHAQ) was similar between groups ($P=0.80$) although the within-group change was statistically significant (mean difference -0.12 ; $P<0.0001$) and clinically meaningful in magnitude. Takken *et al.*²⁵ carried out an RCT in which 54 children (38 girls, 16 boys; aged 5 to 13 years) with JIA were randomly allocated to receive a training program consisting of a one hour per week supervised training program for approximately 20 sessions in a local pool or to a control group that received standard medical care assessment only. Twenty-seven children were allocated to the experimental group. The outcome measures included functional ability (CHAQ and JAFAS), health-related quality of life (CHQ), range of motion, joint status and physical fitness. These parameters were measured at baseline, three months after the start and immediately after the end of the training program. The authors found no significant effects on functional ability ($P=0.35$, $P=0.55$ for CHAQ and JAFAS, respectively), ROM ($P=0.06$), HRQoL ($P=0.19$, $P=0.09$, $P=0.13$ for JAQQ, CHQ-PhS (physical summary score) and CHQ-PsS (psychosocial summary score), respectively) and physical fitness ($P=0.46$).

In summary, of the three studies none compared exercise therapy to a placebo, two studies compared exercise therapy to another therapy and one study compared exercise therapy to receiving standard medical care. The excluded studies are described in the table Characteristics of excluded studies, which provides a summary of why studies were excluded from this review. The number of participating children varied from 54 to 80, with a median number of 78. The age range was between 4 years to 19 years of age. Functional ability, HRQoL and aerobic capacity could be pooled for meta-analysis as the same outcome measures were used in the included studies. Heterogeneity in test protocol, test equipment, outcome or failure to report the measures for range of motion, number of joints with swelling, number of

TABLE I.—*Characteristics of included studies.*

Study	Authors
Methods	<i>Epps et al.</i> ²⁰ RCT comparing the effects of combined hydrotherapy programmes vs physiotherapy land techniques. Blinding: subjects and therapists were not blinded; assessors were blinded. Baseline: no significant differences, only difference the distribution of gender between the two groups. Dropouts: 4 dropouts after randomisation.
Participants	78 children with JIA (43 girls, 35 boys), aged 4-19 years. 7 children had oJIA, 15 children had extended oJIA, 33 children pJIA, 10 children sJIA, 12 children had enthesitis-related arthritis, and 1 child had psoriatic arthritis with psoriasis. Exclusion: severe systemic disease or any other condition that is unstable, suffering from quotidian fevers, inability to give informed consent or complete questionnaires owing to language barriers, musculoskeletal surgery within previous 6 months, neuromuscular condition which increases muscle tone, received intensive physiotherapy, no access to outpatient physiotherapy or hydrotherapy, and met general hydrotherapy exclusion criteria, such as chlorine allergy.
Interventions	Patients in the combined and land groups received 1-hour sessions of treatment over two weeks followed by physiotherapy attendances for 2 months.
Outcomes	Improvement in disease status (CHAQ, physicians). Measures: at baseline, after 2-month follow up, and after 6-month follow up.
Notes	PEDro-score: 8/10. Rank outcome measures: silver.
Allocation concealment	A – Adequate.
Methods	<i>Singh-Grewal et al.</i> ²⁴ RCT comparing the effectiveness of high intensity aerobic training vs low intensity training. Blinding: subjects and therapists were not blinded; assessors were blinded. Baseline: no significant differences, only difference were evident in the distribution of JIA subgroups between the two groups. Dropouts: 10 dropouts after randomisation; 6 from the experimental and 4 from the control group.
Participants	80 children with JIA (29 girls, 35 boys), aged 8 -16 years. 7 children had oJIA, 11 children had extended oJIA, 34 children pJIA, 7 children sJIA, 11 children enthesitis related JIA, 8 children psoriatic JIA, and 2 children with an “other” form of JIA. Exclusion: significant cardiac, pulmonary or metabolic comorbidity; moderate or severe hip pain while walking, and were unable to cooperate with training or testing.
Interventions	Both groups participated in a 12-week, three times weekly training program; high intensity in the experimental group and Qigong in the control group.
Outcomes	Aerobic capacity (submaximal oxygen uptake (VO _{2submax}), maximal oxygen uptake VO _{2max}), and peak power (PP), quality of life (QoL and HRQoL), and physical function (CHAQ). Measures: at enrollment, at baseline and within 2 weeks of completion of the training program.
Notes	PEDro-score: 8/10. Rank outcome measures: silver.
Allocation concealment	A – Adequate.
Methods	<i>Takken et al.</i> ²⁸ RCT comparing an aquatic training program vs controls. Blinding: subject, therapist and assessors were not blinded. Baseline: no significant differences. Dropouts: one dropout; data not excluded from analysis.

(to be continued)

TABLE I.—*Characteristics of included studies (continued).*

Study	Authors
Participants	54 children with JIA (38 girls, 16 boys), aged 5 -13 years. 23 children had oJIA, 29 children pJIA and 2 children sJIA. Exclusion: a systemic disease with fever, low haemoglobin level and a general feeling of malaise; exercise contraindication by a medical specialist; a recipient of a bone marrow transplant; and not feeling confident in water.
Interventions	All patients received their usual care and medical treatment during the study. The patients in the experimental group received an aquatic group (2-4 children/group) exercise program, 1 hr a week, supervised by an instructed community physical therapist, for 6 months.
Outcomes	Included outcomes: function ability (CHAQ and JAFAS), Health-related quality of life (JAQQ and CHQ), joint status (pEPMROM), and aerobic capacity (VO_{2peak} , 6-min walking test). Measures: at baseline, 3 months, and 6 months.
Notes	PEDro-score: 7/10. Rank outcome measures: silver.
Allocation concealment	A – Adequate.

joints with pain, parent or patient global assessment of overall well-being and pain made pooling of these outcome measurements inappropriate. The exercise therapy programs of the included studies showed a great range in duration and exercise frequency (Table I).^{20, 24, 28} Moreover, both land-based and pool-based modalities were used.

Methodological quality

The following PEDro scores were obtained (maximal score =10):^{20, 24, 25} None of the studies described blinding of the participants or therapists who administered the therapy. Based on the characteristics of the therapy, the included studies were categorised into one of three quality categories as described in the Cochrane Handbook for Systematic Reviews of Interventions version 4.2.5.¹⁷

The categories were as follows: Epps *et al.*²⁰ moderate risk of bias due to no blinding of participants or therapists; all other criteria were met.

Singh-Grewal *et al.*:²⁴ moderate risk of bias due to no blinding of participants or therapists; all other criteria were met.

Takken *et al.*:²⁸ moderate risk of bias due to no blinding of participants, therapists and assessors; all other criteria were met.

The evidence on the outcome measures from the studies of Epps *et al.*²⁰ Singh-Grewal *et al.*²⁴ and Takken *et al.*²⁸ were all graded as silver.

Results

Primary outcomes

FUNCTIONAL ABILITY (POOLED)

There was no statistically significant change in functional ability (CHAQ) between exercise and the control (N=198; WMD -0.07, 95% CI -0.22 to 0.08). Moreover, no significant differences were observed for studies which used exercise versus standard medical care assessment²⁸ (P=0.35) or when comparing two different exercise modes.^{20, 24} This is expressed by $I^2=0\%$ in the test for heterogeneity between studies. Takken *et al.*²⁸ measured functional ability using the JAFAS as well. The scores were very low (a mean score of 0.15 at baseline for the experimental group). The JAFAS scores range from 0 to 2 and a score of 0.15 is very close to the lowest possible score on this instrument. This so called “floor effect” makes improvement on this instrument almost impossible. The JAFAS showed no significant differences between the groups (P=0.55).

JOINT RANGE OF MOTION (DESCRIPTIVE)

There was no statistically significant improvement in joint range of motion between the exercise and control groups. Epps *et al.*²⁰ reported a decrease in the number of joints with loss of range of motion after two months follow up in the combined group and in the land group (decrease of five and four joints, respectively); however, this decrease was not statistically

significant. Takken *et al.*²⁸ also reported no significant changes in range of motion from baseline measurement to immediately after the intervention ($P=0.06$). Both groups showed a very small decrease over time (a decrease of 0.02 and 0.07 on the EPROM score in the intervention group and control group, respectively). Singh-Grewal *et al.*²⁴ reported that there was no worsening of range of motion (EPMROM) and also no differences between the groups ($P=0.35$).

NUMBER OF JOINTS WITH SWELLING (DESCRIPTIVE)

None of the included studies reported a statistically significant difference in the number of joints with swelling. Epps *et al.*²⁰ reported a decrease in the number of active joints after two-months follow up, in the combined group as well as the land group (a decrease of four and three active joints, respectively). Takken *et al.*²⁸ reported that the number of swollen and tender joints decreased in the intervention group (-55%) while the number of swollen and tender joints increased in the control group (+21%). These differences were almost statistically significant ($P=0.07$). Singh-Grewal *et al.*²⁴ reported no significant changes in active joint count between the groups ($P=0.41$).

NUMBER OF JOINTS WITH PAIN (DESCRIPTIVE)

None of the included studies measured the number of joints with pain.^{20, 24, 28}

HEALTH-RELATED QUALITY OF LIFE (POOLED)

All outcome measures of health-related quality of life indicated that there was no clinically important or statistically significant change in health-related quality of life between exercise and control groups (CHQ-PhS: $N=115$; WMD -2.85, 95% CI -2.10 to 7.80; CHQ-PsS: $N=112$; WMD 2.57, 95% CI -0.69 to 5.82; JAQQ: $N=54$; SMD 0.33, 95% CI -0.20 to 0.87; QoL: $N=70$; SMD 0.17, 95% CI -0.30 to 0.64). Moreover, no significant differences for both CHQ outcome measures ($P=0.09$, $P=0.13$ for CHQ-PhS and CHQ-PsS, respectively) were observed between studies which used exercise versus standard medical assessment as control²⁸ or when comparing two different exercise modes.²⁰ This is expressed with $I^2=0\%$ in the test for heterogeneity between the studies. Both JAQQ²⁸ and QoL²⁴ did not show any significant effects of the intervention over control or a different exercise mode ($P=0.19$ and $P=0.47$, respectively).

PARENT OR PATIENT GLOBAL ASSESSMENT OF OVERALL WELL-BEING (DESCRIPTIVE)

None of the included studies measuring parent or patient global assessment of overall well-being reported a statistical significant difference. Epps *et al.*²⁰ reported a decrease in scores on the VAS-scale for parent global assessment of overall well-being after two months follow up in the combined group as well as in the land group (decrease of 6 mm and 7 mm, respectively). Singh-Grewal *et al.*²⁴ and Takken *et al.*²⁸ did not measure parent or patient global assessment in their studies.

PAIN (DESCRIPTIVE)

None of the included studies measuring pain reported a significant decrease. Epps *et al.*²⁰ reported no significant decrease in pain, the change in pain was negligible. The pain score was decreased by 0.6 mm (on a 10 cm VAS scale) in the land group and increased by 7.3 mm in the combined exercise group. Singh-Grewal *et al.*²⁴ reported low levels of pain on a 10 cm VAS scale during training sessions. The differences were not different between the two groups (median 0, range 0 to 10 in both groups; $P=0.09$). Takken *et al.*²⁸ did not measure pain in their study.

ADVERSE OUTCOMES

All included studies assessed possible adverse outcomes; however, none of these studies reported negative effects of the exercise therapy.

DROPOUTS

Epps *et al.*²⁴ reported a total of six dropouts after randomisation. Four patients did not complete a two-month assessment, two withdrew and two were lost to follow up. Two children could not be entered into the primary analysis because the preliminary definition of disease improvement was inconclusive. Therefore, 72 of 78 potential data sets were available for primary analysis. Singh-Grewal *et al.*²⁴ reported a total of 10 dropouts after randomization: six children from the experimental group and four from the control group. In the experimental group, four dropped out before and two after baseline testing. In the control group, one dropped out before and three after baseline testing. All reported a lack of time as the reason for dropping out.

Takken *et al.*²⁸ reported one dropout during the training program; one boy stopped the training program after 15 sessions. Since he met the 75% criteria of 20 sessions, his data were not excluded from analysis.

Secondary outcomes

AEROBIC CAPACITY (POOLED)

There was no statistically significant change in aerobic capacity (VO_{2peak}) between the exercise and control groups (N=124; WMD 0.04, 95% CI -0.11 to 0.19). Moreover, no significant differences were observed for studies which used exercise versus standard medical care assessment (P=0.46)²⁸ or when comparing two different exercise modes (P=0.35).²⁴ This is expressed with $I^2=0\%$ in the test for heterogeneity between the studies. Epps *et al.*²⁰ did not measure VO_{2peak} in their study.

MUSCLE STRENGTH (DESCRIPTIVE)

Epps *et al.*²⁰ reported a small increase in the three muscle groups, in both groups, but none of the increases were statistically significant (P values were not provided). Singh-Grewal *et al.*²⁴ and Takken *et al.*²⁸ did not measure muscle strength in their studies.

COMPLIANCE WITH EXERCISE (DESCRIPTIVE)

Epps *et al.*²⁰ reported that four patients did not complete a two-month assessment, two withdrew and two were lost to follow up. Singh-Grewal *et al.*²⁴ reported that completion of training sessions was 78% in the control group and 56% in the experimental group. An average of two sessions per week was completed by the experimental participants and 1.7 sessions by the control participants. The difference was most apparent in the number of home-based sessions. Takken *et al.*²⁸ reported that the children attended a mean number of 19.6 ± 3.9 out of 20 training sessions.

Discussion

This review analyzed the results of three RCTs for the effectiveness of exercise therapy in children with JIA. By applying strict selection criteria for inclusion, only full-length reports of randomised controlled tri-

als were included. All three trials met at least seven criteria on the PEDro scale. Due to the nature of the interventions, the criteria "patient blinded" and "care provider blinded" could not be scored. Therefore, a score of eight might be considered as the best score possible in this kind of intervention study. Evidence on the outcome measures in the included studies were all graded as "silver" according to the grading system described by Tugwell.¹⁹

The trends for the outcome measures functional ability, joint range of motion, number of joints with swelling, health-related quality of life and aerobic capacity were similar. These outcome measures were all in favour of treatment changes but were not statistically significant. Functional ability, health-related quality of life and aerobic capacity were the only outcome measures which could be pooled into a meta-analysis and, therefore, could be used to provide stronger evidence compared to the other outcome measures. Importantly, all outcome measures reported no worsening with exercise therapy in the short term. The study of Takken *et al.*²⁸ showed a decrease in the number of joints with swelling after aquatic fitness training; this was the only study where improvements almost reached statistical significance. The randomized design also allowed controlling for maturation and developmental effect on the outcome measures such as functional ability, health-related quality of life, aerobic capacity and muscle strength. The size of the improvement on functional ability (CHAQ) in the pooled data (N.=231) is still clinically irrelevant when compared with the results of the study of Dempster *et al.*,²⁹ who state that the minimal clinical important improvement on the CHAQ is a reduction in score of 0.13. This meta-analysis showed an average reduction of 0.07 and can not be considered clinically relevant. The CHAQ has been demonstrated to suffer from a floor effect whereby scores are clustered at the normal end of the scale, or near 0.³⁰⁻³² This floor effect is also observed in this review and, therefore, might explain the missing significant improvement with exercise therapy.

Results for pain were contradictory. In the study by Epps *et al.*,²⁰ the pain score was marginally decreased in the land-based group but increased in the combined group. Because these differences were small (7.9 mm on a VAS scale from 0 to 100 mm) it is hard to determine if these changes could be explained by the different types of training or by measurement errors of the outcome measure. The study by Singh-

Grewal *et al.*²⁴ showed low levels of pain in both therapies. It is important to note that none of the participants of the included studies withdrew because of pain during exercise therapy. Parent or patient global assessment of overall well-being and muscle strength was only described in the study by Epps *et al.*²⁰ The evidence on this outcome measure is, therefore, inconclusive. The evidence in support of the effectiveness of exercise therapy on the number of joints with pain is also inconclusive as none of the included studies described this outcome measure in detail.

The excluded studies found comparable results for functional ability,^{33, 34} health-related quality of life,^{33, 34} and aerobic capacity.^{27, 33} However, none of the studies reported improvements. Pain scores reported in the excluded studies^{16, 27, 33} did not show increases in pain. Furthermore, none of the excluded studies described the parent/ or patient global assessment of overall well-being or the number of joints with pain.

The following findings in the excluded non-RCT studies were in contrast with the findings in the included RCT studies: the number of joints with swelling,^{14, 16, 22} muscle strength^{23, 27} and joint ROM.^{13, 35} The study by Baldwin,¹⁴ despite the lack of data, reported that the changes in the number of joints with swelling were not statistically significant. The studies by Moncur *et al.*²² and Klepper¹⁶ both reported a significant decrease in the joint count after intervention. The studies of Fisher *et al.*²⁷ and Oberg *et al.*²³ reported muscle strength before and after intervention. Both studies reported significant increases in quadriceps strength; Fisher *et al.*²⁷ also reported a significant increase in hamstring strength. Both studies only studied two muscle groups. The studies of Bacon *et al.*¹³ and Latzka *et al.*³⁵ both reported significant improvements in joint ROM but only described a few joints. The strength of this review lies in its rigorous methods, which include thorough grading of evidence, systematic appraisal of study quality and, where possible, the use of meta-analysis. However, its main limitation is the low number of available RCTs. There were only seven controlled trials of exercise therapy for JIA found, of which three with a total number of 212 participants could be included. Because there are few RCTs, indirect methods of identifying publication bias such as funnel plots are of limited value and were not conducted. The limited number of studies, participants, and the heterogeneity of interventions and outcome measures limits the precision of the

results of this review. Consequently, it also means that a single unidentified trial, or further trials, could have a substantial effect on the results and conclusions.

Conclusions

Overall, exercise therapy did not result in significant effects on functional ability, health-related quality of life, aerobic capacity or pain. However, the low number of available RCTs limits the generalisability. The included and excluded studies are all consistent about adverse effects of exercise therapy; no short-term detrimental effects of exercise therapy were found in any of the studies. Both the included and excluded studies showed that exercise does not exacerbate the arthritis. The large heterogeneity in outcome measures, as seen in this review, emphasises the need for a standardised assessment or a core set of functional and physical outcome measurements suited for health research to generate evidence about the possible effects of physical exercise for children with JIA. Despite the short-term results of the intervention studies, the long-term effect of exercise therapy remains unclear and warrants further research.

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