Systematic Review and Meta-Analysis

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Effectiveness of resistance exercises in the treatment of rheumatoid arthritis

A meta-analysis

Zhigang Wen, MD, Yi Chai, MD*

Abstract

Background: We aimed to assess the efficacy of resistance exercise in rheumatoid arthritis (RA) in randomized controlled trials (RCTs).

Method: PubMed, the Cochrane Library, and Embase were searched according to the index words to identify eligible RCTs, and relevant literature sources were also searched. The latest search was done in August 2019. Odds ratios (OR), mean difference (MD), and 95% confidence interval (95% CI) were used to analyze the main outcomes.

Result: Seventeen RCTs were included in the meta-analysis with 512 patients in the resistance exercise group and 498 patients in the control group. The results showed that compared with the control group, resistance exercise significantly decreased disease activity score in 28 joints (DAS-28) scores (standard mean difference [SMD]: –0.69, 95% CI: –1.26 to –0.11), reduced erythrocyte sedimentation rate (ESR) (SMD: –0.86, 95% CI: –1.65 to –0.07), and shortened the time of 50 ft. walking (SMD: –0.64, 95% CI: –0.99 to –0.28). No significant difference was observed in visual analog scale (VAS) scores (SMD: –0.61, 95% CI: –1.49–0.27) and health assessment questionnaire (HAQ) scores (weighted mean difference: –0.10, 95% CI: –0.26–0.06).

Conclusion: Resistance exercise showed reducing DAS-28 score, ESR score, and the time of 50 ft. walking in RA patients compared with the control group. However, high quality multicenter RCTs with larger sample sizes to confirm the conclusion.

Abbreviations: 95% CI = 95% confidence interval, MD = mean difference, OR = odds ratios, RA = rheumatoid arthritis, RCTs = randomized controlled trials.

Keywords: meta-analysis, randomized controlled trial, resistance exercise, rheumatoid arthritis

1. Introduction

Despite the remarkable impact of pharmaceutical interventions, physical therapy and exercise training remain an important part of rheumatoid arthritis (RA) management.[1,2] Moreover, given that cardiovascular events are an important issue in RA outcomes, improving cardiovascular risk[3] through aerobic exercise seems to be the most relevant ancillary therapy in RA management.[4] Indeed, aerobic exercises have been shown to improve cardiovascular fitness and the quality of life of patients, while reducing RA-associated disability and pain.[5] However, the use of resistance exercise therapy for RA patients is still controversial because its effects on cardiovascular risk are still a concern.[6] Although some studies have shown a statistically significant effect on RA disability,[7–9] other studies have suggested that this improvement is not statistically significant[10] or clinically relevant.[11] Similarly, discrepancies were observed between studies reporting a positive effect of exercise on functional capacity[11] versus others that did not find such a positive effect.[8,10] These disparities are likely due to sample size variations and the fact that most of the studies on resistance exercises only addressed changes in muscle strength. In fact, few studies have addressed the efficacy of resistance exercise-based therapy for RA patients with respect to pain, disease activity, functional capacity, quality of life, and structural damage; thus, the effects of this therapy remain unclear. Therefore, we conducted a systematic review of the literature to determine whether resistance exercise effectively improved the above-mentioned parameters of RA. Finally, we assessed whether this treatment addition is clinically relevant, and evaluated its dependence on exercise modalities and/or patient characteristics.

Based on these considerations, the aim of this study was to perform a meta-analysis of all available literature to obtain updated evidence on the efficacy of resistance exercise for women with RA.

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Department of Orthopedics, Hebei Provincial Hospital of Traditional Chinese Medicine, Shijiazhuang, China.

* Correspondence: Yi Chai, Department of Orthopedics, Hebei Provincial Hospital of Traditional Chinese Medicine, No.389 East Zhongshan Road, Shijiazhuang, Hebei, 050000, China (e-mail: 290507602@qq.com).

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2. Methods

2.1. Search strategy

The Cochrane Library, PubMed, and Embase were searched for all randomized control trials (RCTs) on the efficacy of resistance exercise in the treatment of RA. Other related articles and reference materials were also searched. The latest research was performed on August 2019. Two investigators carried out the literature search independently; a third investigator was involved when disagreement occurred.

2.2. Inclusion and exclusion criteria

A study was included if it was: a RCT; the research subjects were patients with RA and did not have other serious diseases; the intervention of the treatment group was resistance exercise, repetition training aimed to improve muscle strength, and rehabilitation exercise was initiated at the discretion of the rehabilitation specialist; the interventions of the control group were general nursing, non-aerobic exercise, or range of motion exercise; only articles published in English were included.

A study was excluded if it was: duplicate publication, or the content and result were the same; data had obvious mistake; case report, theoretical research, conference report, systematic review, meta-analysis, expert comment, or economic analysis; the outcomes were not what we need; postoperative rehabilitation training.

All the studies were screened by 2 reviewers independently to determine whether an article satisfied the inclusion and exclusion criteria, and discrepancies were resolved by a third reviewer.

2.3. Data extraction and quality assessment

The data were extracted from all the included studies and consisted of 2 parts: baseline information and primary outcomes. The first part was baseline information: author name, publication year, the interventions of the treatment group and the control group, sample size, treatment, main age, sex, and Jadad score. The second part was clinical outcomes: disease activity score in 28 joints (DAS-28), the erythrocyte sedimentation rate (ESR), visual analog scale (VAS) score, the health assessment questionnaire (HAQ), and 50 ft. walking test. The Jadad scoring checklist was used to appraise the quality of involved studies. We evaluated all the RCTs from the 5 items: statement of randomization; appropriateness of generating randomized sequence; use of double blind; description of double blinding method; detail of withdrawals and dropouts. Studies with a score of <3 represented a low-quality and high bias risks, studies gota score exceed 3 were indicated as high-quality trial. All the above process was done by 2 reviewers independently, and disagreements between the 2 reviewers were resolved by discussion until a consensus was reached.

2.4. Statistical analysis

All statistical analyses were performed using STATA 10.0 (StataCorp LLC, College Station, Texas). Chi-squared and I^2 tests were used to test the heterogeneity of clinical trial results and decided the analysis model (the fixed-effects model or the random-effects model). When the Chi-squared test P-value was $\leq .05$ and I^2 tests-value was $>50\%$, it was defined as high heterogeneity and assessed by the random-effects model. When the Chi-squared test P-value was $>.05$ and I^2 tests-value was $\leq 50\%$, it was defined as acceptable heterogeneity data and assessed by the fixed-effects model. Continuous variables were expressed as mean ± standard deviation and analyzed by mean difference (MD). Categorical data were presented as percentages and analyzed by relative risk (RR) or odds ratio (OR). MD along with 95% CI was used to analyze all the outcomes.

3. Results

3.1. Characteristics of the included studies

Totally 1157 articles were searched by the indexes, and 1095 articles were excluded by screening the title or abstract, leaving

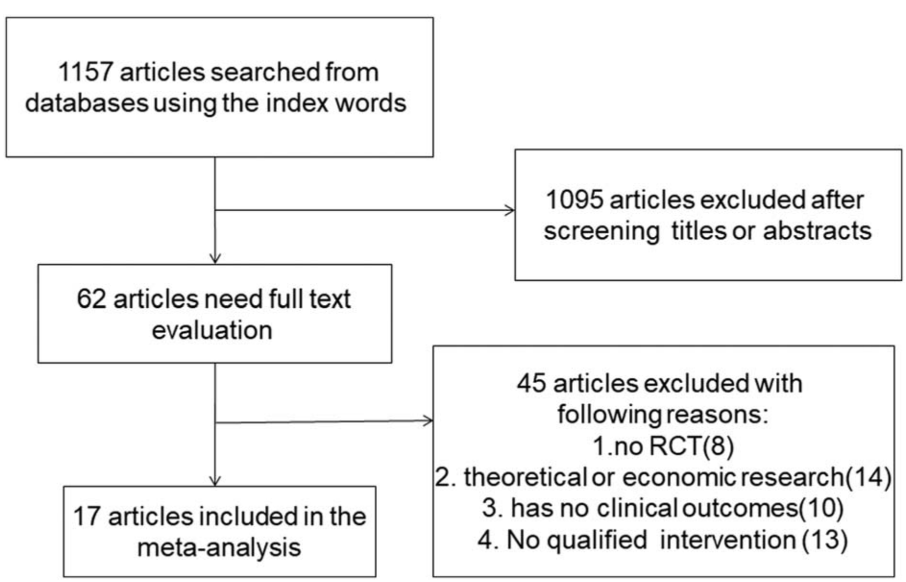

Figure 1. The flow diagram of the literature search and selection process.

Table 1

The basic characteristics description of included studies.

Study	Country	Duration of RA, y		Therapy		No. of patients		Age		Gender		Jadad score
		T	C	T	C	T	C	T	C	T	C	
Joan Mcmeeken 1999	USA	–	–	Quadriceps strength training, maximum load 70%, 4 times/wk, 40–80 min, 24 weeks	Routine nursing	17	18	51.4	49.7	15F	14F	3
C.H.M. van denEnde 2000	Netherlands	8	7	Quadriceps strength training and shoulder strength training, maximum load 60%, 3 times/wk, 15 min, 4 weeks	ROM exercise	34	30	62	58	20F	20F	5
Hilary G. Flint-Wagner 2009	USA	11.2 ± 8.9	15.4 ± 10.8	Leg and arm strength training, maximum load 90%, 3 times/wk, 75 min, 16 weeks	Routine nursing	16	8	52.2	49	–	–	4
L.M.Bearne 2002	UK	-	-	Quadriceps strength training, maximum load 100%, 2 times/wk, 30–45 min, 5 weeks	Routine nursing	47	46	–	–	–	–	5
Amir I. Buljina 2001	Bosnia and Herzegovina	5.04 ± 4.80	5.23 ± 4.89	Grip strength training, maximum load 85%, 7 times/wk, 20–30 min, 3 weeks	Routine nursing	50	50	47.94	48.46	38F	37F	3
A. Haè Kkinen 1997	Fineland	-	-	Quadriceps strength training, maximum load 40–80%, 2–3 times/wk, 24 weeks	Routine nursing	21	18	41.4	45.6	–	–	3
Arja Hakkinen 2001	Fineland	10	8	Lumbar, leg and arm strength training, maximum load 50–70%, 2 times/wk, 30–45 min, 104 weeks	ROM exercise	31	31	49	49	18F	20F	4
Andrew B. Lemmey 2009	USA	6.17 ± 6.33	10.42 ± 8.42	Leg and arm strength training, maximum load 80%, 2 times/wk, 24 weeks	ROM exercise	13	15	55.6	60.6	11F	12F	4
C. BostrÎm 1998	Sweden	10.5 (0.3–27)	7 (3–43)	Shoulder strength training, maximum load 30%, 3 times/wk, 40–60 min, 10 weeks	Anaerobic exercise	20	17	56	59	–	–	3
Usmary S. Siqueira 2017 a	USA	7.7 ± 2.9	8.5 ± 4	Land-based aerobic group, knee, hip and lower limbr strength training, maximum load 90%, 5–30 min, 3 times/wk, 16 weeks	Routine nursing	33	34	54	53.2	-	-	5
Usmary S. Siqueira 2017 b	USA	9.2 ± 3.1	8.5 ± 4	Water-based aerobic group, knee, hip and lower limbr strength training, maximum load 90%, 5–30 min, 3 times/wk, 16 weeks	Routine nursing	33	34	55	53.2	-	-	5
Jeong-Hun Shin 2015	Korea	10.3 ± 9.4	15.4 ± 8.0	Arm and leg strength training (Tai Chi exercise), 1 times/wk, 60 min, 3 months	Routine nursing	29	14	64	62.7	–	–	5
Susan V.Baxter 2015	New Zealand	16 ± 10.9	11 ± 11.2	Walking programme	Routine nursing	11	22	66.6	59.4	–	–	3
Laura Durcan 2014	Ireland	-	-	Walking programme, 30–60 min/d	Routine nursing	40	38	61	59	30F	20F	5
Keegan Knittle 2013	Netherlands	-	-	-	-	38	40	60.7	64.7	30F	22F	3
Victoria L. Manning 2014	UK	1.67 ± 1.50	1.67 ± 1.58	-	-	52	56	53	57	44F	38F	3
Antonios Stavropoulos-Kalinoglou 2012	UK	5.5 (3.0–9.7)	7.0 (5.0–10.0)	Strength training, 3 times/wk, 60 min, 3–6 months	Routine nursing	18	18	55	52.8	14F	14F	3
Andrew B. Lemme 2012	UK	6.85 ± 7.34	7.89 ± 7.59	-	-	9	9	55.7	59.4	8F	6F	3

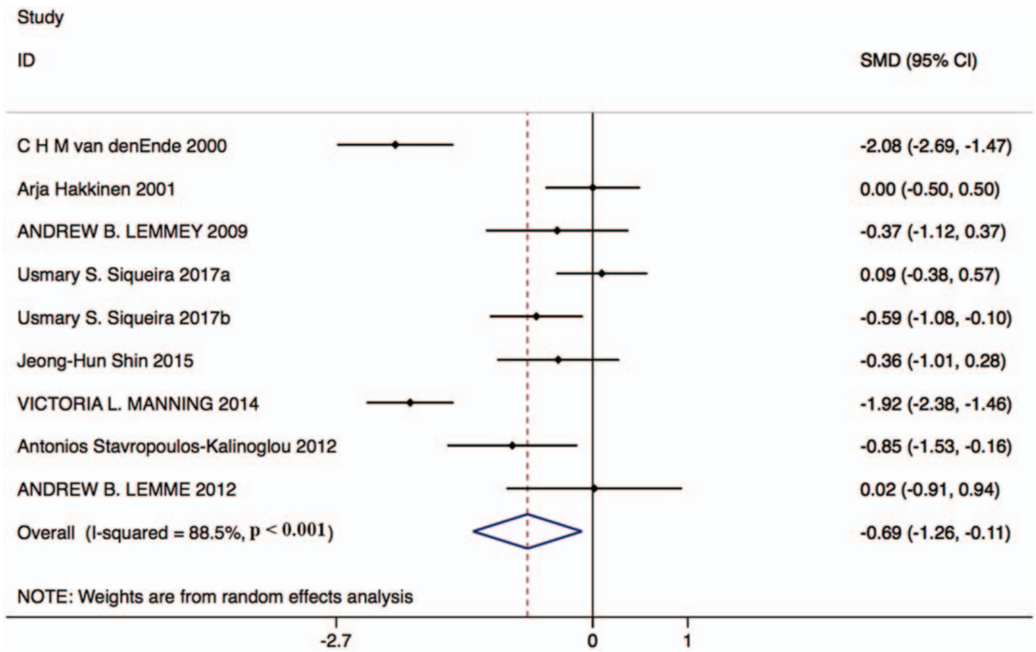

Figure 2. Forest plot of changes in DAS-28 in the resistance exercise group and the control group. DAS-28 = disease activity score in 28 joints.

62 articles for further evaluation. After obtaining and thoroughly reviewing the complete manuscripts, 45 articles did not meet the inclusion criteria because they were non-RCTs (8), they were theoretical or economic studies (14), they had no clinical outcomes (10), and the intervention was not qualified (13). At last, 17 RCTs[11–28] were involved in the meta-analysis with 512 patients in the resistance exercise group and 498 patients in the control group. The selection process is presented in Fig. 1.

The main characteristics of the included studies are summarized in Table 1. The basic information included treatment, country, age, and sex. The main Jadad score of the included studies was 3.83, and the main score was higher than 3, indicating high-quality of the 17 included RCTs.

3.2. DAS-28

Eight studies with 252 patients in the resistance exercise group and 241 patients in the control group reported DAS-28 changes. Based on the Chi-squared test P-value of $= .000 < .05$ and I^2 test-value $= 88.5\% > 50\%$, we chose the random effects model to analyze changes in DAS-28. The pooled results showed that compared with the control group, resistance exercise significantly

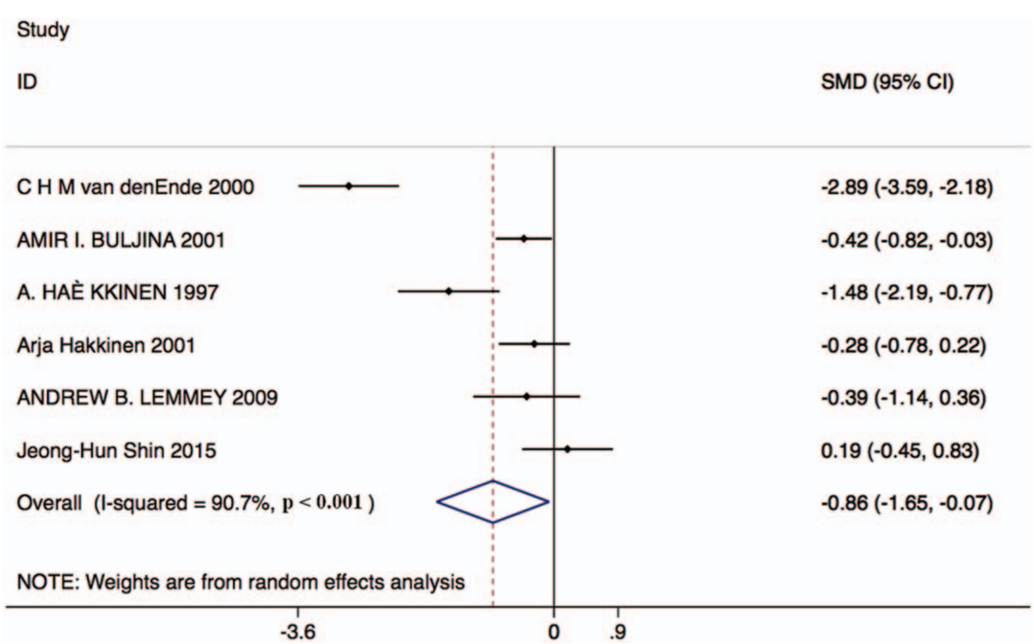

Figure 3. Forest plot of ESR in the resistance exercise group and the control group. ESR = erythrocyte sedimentation rate.

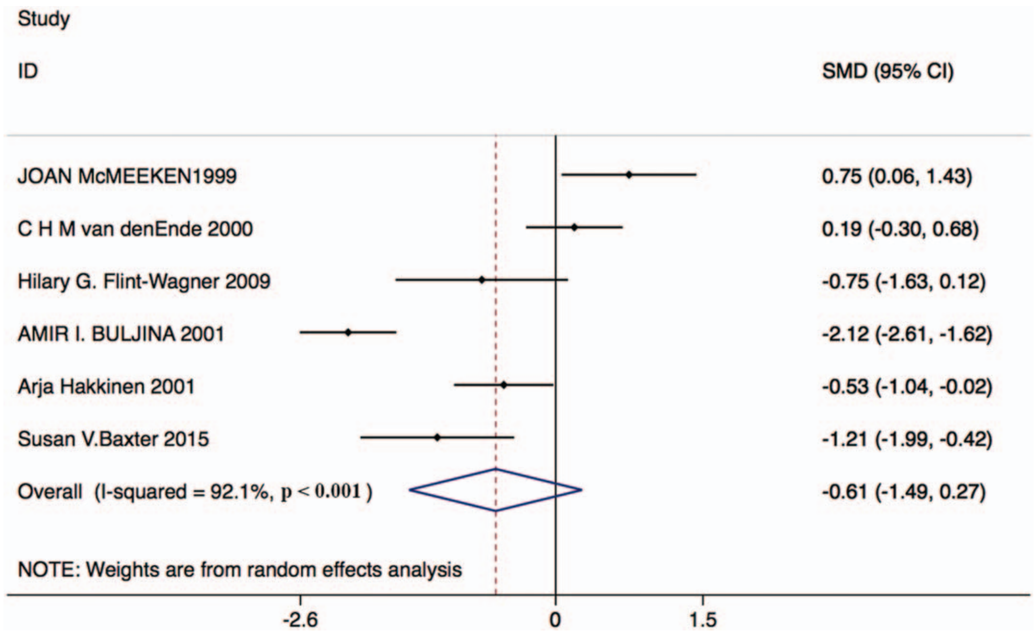

Figure 4. Forest plot of VAS score in the resistance exercise group and the control group. VAS=visual analog scale.

decreased DAS-28 score (standard mean difference [SMD]: –0.69, 95% CI: –1.26 to –0.11, Fig. 2).

3.3. ESR

Six studies with 178 patients in the resistance exercise group and 158 patients in the control group reported ESR changes. Based on the Chi-squared test P-value of $=.000<.05$ and I^2 tests-value $=90.7\%>50\%$, we chose the random effects model to analyze changes in ESR. The pooled results showed that the ESR score was significantly decreased by resistance exercise versus the control group (SMD: –0.86, 95% CI: –1.65 to –0.07, Fig. 3).

3.4. VAS score

Six studies with 159 patients in the resistance exercise group and 159 patients in the control group reported changes in VAS scores. Based on the Chi-squared test P-value of $=.000<.05$ and I^2 tests-

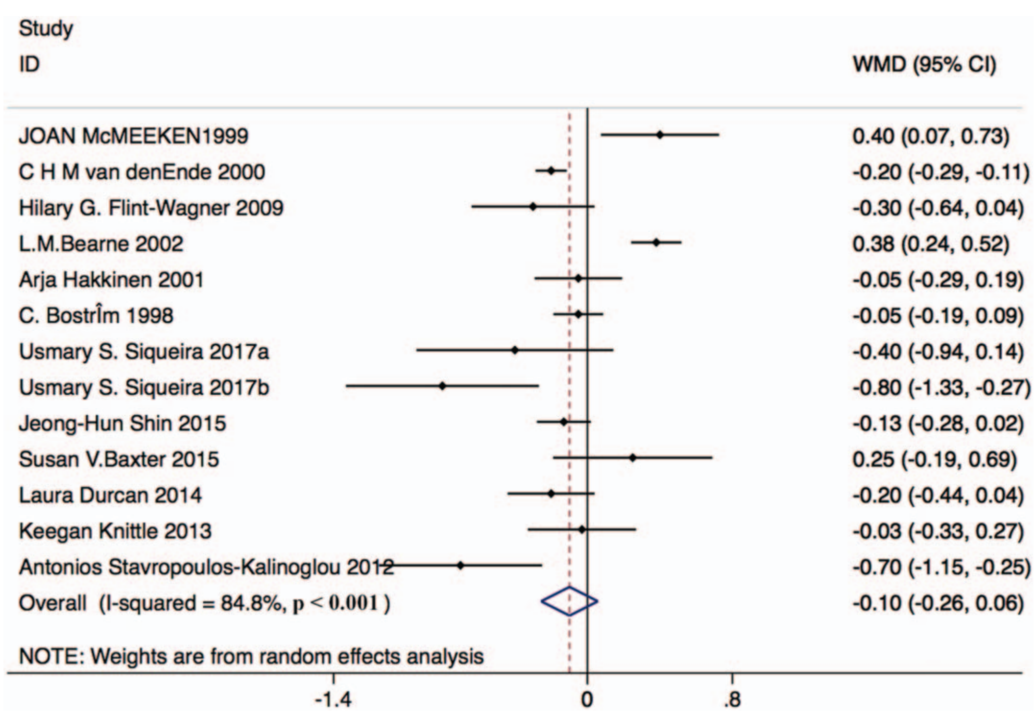

Figure 5. Forest plot of HAQ in the resistance exercise group and the control group. HAQ=health assessment questionnaire.

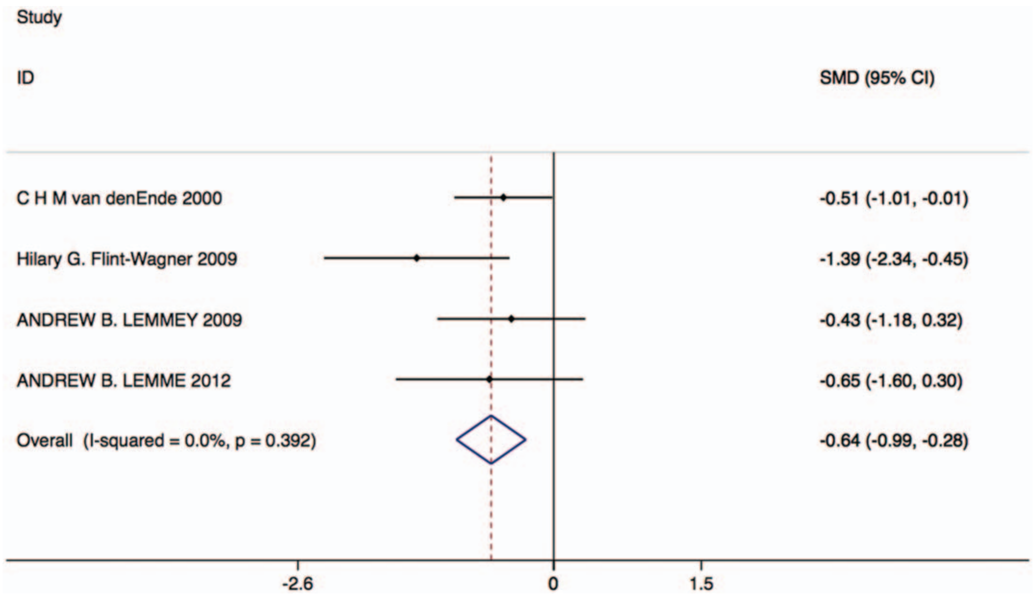

Figure 6. Forest plot of 50 ft. walking test in the resistance exercise group and the control group.

value = 92.1% > 50%, we chose the random effects model to analyze changes in VAS scores. The pooled results showed no significant difference in VAS scores after the intervention between the 2 groups (SMD: –0.61, 95% CI: –1.49–0.27, Fig. 4).

3.5. HAQ

Thirteen studies with 380 patients in the resistance exercise group and 365 patients in the control group reported HAQ changes. Based on the Chi-squared test *P*-value of = 0.000 < 0.05 and I^2 tests-value = 84.8% > 50%, we chose the random effects model to analyze changes in HAQ. The pooled results showed no significant difference in HAQ score after the intervention between the 2 groups (weighted mean difference [WMD]: –0.10, 95% CI: –0.26–0.06, Fig. 5).

3.6. 50 ft. walking test

Four studies with 72 patients in the resistance exercise group and 62 patients in the control group reported changes in the 50 ft. walking test. Based on the Chi-square test *P*-value of = .392 > .05 and I^2 tests-value = 0.0% < 50%, we chose the fixed effects model to analyze the 50 ft. walking test. The pooled results showed that compared with the control group, resistance exercise significantly decreased the time of 50 ft. walking (SMD: –0.64, 95% CI: –0.99 to –0.28, Fig. 6).

3.7. Quality assessment and potential bias

Based on the inclusion and exclusion criteria, 17 articles were included in the meta-analysis. Quality assessment and potential bias were assessed by funnel plot, Begg and Mazumdar rank test, and Egger test. The funnel plot for log WMD in HAQ of the included studies was notably symmetrical, suggesting no significant publication bias (Fig. 7). In addition, significant symmetry was detected by Begg and Mazumdar rank test (*Z* = 0.67, *P* = .502). However, the Egger test result showed no significant publication bias (*P* = .784).

4. Discussion

In previous similar studies, Baillet et al[29] found that resistance exercises significantly improved isokinetic strength, isometric strength, grip strength, and HAQ. Exercise also had a positive effect on the 50-foot walking test and ESR. Withdrawals (RR = 0.95, 95% CI 0.61, 1.48) and adverse events (RR = 1.08, 95% CI 0.72, 1.63) were well balanced in both groups. Patient and exercise characteristics did not influence the results. Wang et al[30] include 13 studies, found that functional exercises could delay the development of the disease activity of RA patients (MD = –0.76; 95% CI: –1.13, –0.38), improve the joint function (MD = 0.36; 95% CI: –0.47, –0.24), alleviate the pain of joints (MD = –1.75; 95% CI: –1.98, –1.53), and reduce the duration of morning stiffness (MD = –17.65; 95% CI: –22.09, –13.21). Sieczkowska et al[31] included 29 studies, indicated that resistance training improves the general health-related quality of life (HR-

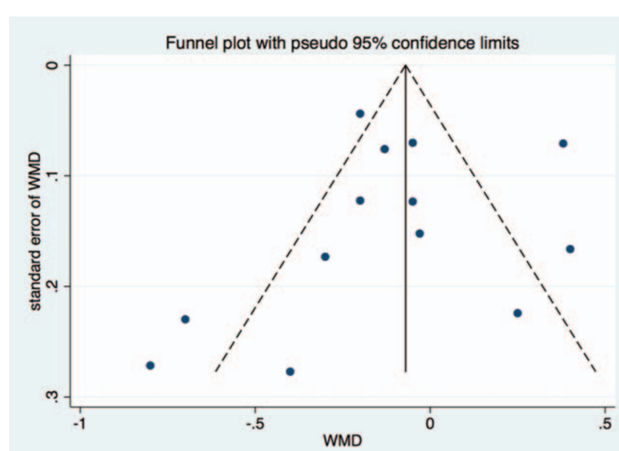

Figure 7. Funnel plot of studies included in the meta-analysis.

QoL), the physical role functioning, physical functioning, social aspects, and body pain compared with control group.

In our study, we included 17 RCTs with the main Jadad score of 3.83. Compared with the general nursing or non-aerobic exercise, resistance exercise significantly decreased DAS-28 scores (SMD: –0.69, 95% CI: –1.26 to –0.11), reduced ESR (SMD: –0.86, 95% CI: –1.65 to –0.07), and shortened the time of 50 ft. walking (SMD: –0.64, 95% CI: –0.99 to –0.28). No significant difference was observed in VAS scores (SMD: –0.61, 95% CI: –1.49–0.27) and HAQ scores (WMD: –0.10, 95% CI: –0.26–0.06). The conclusion about ESR and the time of 50 ft. walking was consistented with the previous meta-analysis.

Some advantages of the present meta-analysis are as follows: this systemic review findings might be more convincing than any individual study among all included RCTs because the effect of resistance exercise in patients with RA was quantitatively determined using pooled large sample size; this meta-analysis provided evidence for the effects of resistance exercise; the strict inclusion and exclusion criterion were used to select eligible studies; all the data were analyzed by standard statistical analysis to make sure the results were accuracy.

However, there are some limitations should be attention in this analysis. The limitations are as follows: only randomized controlled trials were included; differences in the inclusion criteria and exclusion criteria for patients; different patients with previous disease and treatments were unavailable; most trials with low quality and low Jadad score were included in our study; the frequency, maximum load, and duration of resistance exercise were various; pooled date were used for analysis, and individual patients' data were unavailable, so it limited us to make more comprehensive analysis.

Based on the available evidence, our meta-analysis demonstrated that compared with the control group, resistance exercise could significantly reduce DAS-28 scores, ESR scores, and the time of 50 ft. walking in patients with RA. Thus, further high-quality studies with lager sample sizes and longer follow-up duration are needed to confirm the results of our meta-analysis. In future study, researchers can explore the relationship between intensity and frequency of resistance exercise and outcomes of RA.

Author contributions

Conceptualization: Zhigang Wen, Yi Chai.
Data curation: Zhigang Wen, Yi Chai.
Formal analysis: Zhigang Wen, Yi Chai.
Methodology: Yi Chai.
Writing – original draft: Zhigang Wen.
Writing – review & editing: Yi Chai.

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