

## Original Research Article

# Effects of routine drug therapy in combination with health exercise training on pain and joint function in patients with rheumatoid arthritis: A meta-analysis

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## Abstract

**Purpose:** To logically review the effect of conventional drug therapy in combination with healthy exercise training on pain and joint function in patients with rheumatoid arthritis (RA).

**Methods:** A search on case-control trials was conducted in PubMed, EMBASE, ScienceDirect, Cochrane Library, China National Knowledge Infrastructure (CNKI), China VIP database, Wanfang database and China Biomedical Literature Database (CBM) online database from January 2005 to May 2022. A separate extraction of the data was conducted by two researchers. A meta-analysis of the data was undertaken using RevMan5.3 statistical software as a tool for assessing the bias risk of each contained article.

**Results:** A total of 7 clinical controlled studies with 483 samples were obtained. Based on the meta-analysis, the study group was significantly lower ( $p < 0.05$ ) on the Visual Analogue Scale (VAS) score, Joint Tenderness Count (JTC), Joint Swelling Number (JSN), Morning Stiffness Time (MST) and DAS28 score. However, it was significantly higher ( $p < 0.05$ ) on the average grip strength of both hands, Health Assessment Questionnaire (HAQ) and patients' general assessment (PGA).

**Conclusion:** Routine drug therapy, in combination with healthy exercise training significantly reduces the degree of pain, relieves joint symptoms, and improves quality of life in patients with RA.

**Keywords:** Drug therapy, Healthy exercise training, Rheumatoid arthritis, Pain, Joint function

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## INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory and destructive condition of the joints that affect millions of people worldwide, and manifest as chronic synovitis and joint destruction [1]. The joints of the hands and wrists are often violated

and are symmetrical, with joint swelling and pain as the main symptoms, which can bring about severe deformation of the patient's limbs. In addition to joint damage, it can also involve the heart, lungs, kidneys, nervous system and other organs or tissues. At present, the pathogenesis of RA is still in the research stage in the medical

field, and it is speculated that it may be related to immune cells, inflammatory factors, matrix metalloproteinases, abnormal oxidative stress, genetics and living environment [2]. The commonly drugs used to treat RA in modern medicine are non-steroidal anti-inflammatory drugs, glucocorticoids, chronic anti-rheumatic drugs, early biological agents and Chinese herbal medicine [3,4]. Western drugs are effective in delaying the progression of RA and controlling most of its symptoms. However, they often fail to cure RA, and are often accompanied by certain toxic side effects and limitations, which limit their clinical application to some extent.

The long-term treatment of RA patients not only refers to drug treatment, but also to non-drug rehabilitation therapy [5]. When treating RA, non-drug therapy shows a more economical, save and more lasting effect, which is accepted by more and more people. The impacts of systemic performance can be effectively reduced and clinical symptoms can be improved by increasing physical activity and exercise in patients with RA [6,7]. Any exercise that involves the use of skeletal muscles and consumes energy is considered physical activity. In physical activity, exercise involves planned, organized and repetitive activities with the aim of improving or maintaining health. Exercise methods have been shown to have remarkable benefits during treatment of RA [8]. Therapeutic exercise can inhibit joint destruction by inhibiting the expression of inflammatory cytokines, increasing the biomolecular inhibition of arthritis [8]. In 2010, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) jointly revised the new RA classification criteria and the RA treatment guidelines and principles published by EULAR and the International Steering Committee in 2010, emphasizing that in addition to the use of drugs. In addition to treatment, non-drug intervention (rehabilitation intervention) should also be paid attention to [9,10].

The ultimate goal of up-to-standard treatment of RA is to restore normal joint function and make patients return to daily work and social activities. Today, most RA patients are told to use at least one type of rehabilitation intervention, such as exercise therapy, physiotherapy, orthosis/assistive use, or self-management intervention. In general, these measures should involve the participation of medical professionals, patients, and their families. Through an integrated rehabilitation model within and outside the hospital on an ongoing basis, patient care is systematically coordinated and the quality of medical services is improved.

Exercise therapy which includes aerobic exercise, endurance training and a joint range of motion training, is one of the common methods of rehabilitation therapy for RA patients [11]. It is also the most recommended because of its safety, simplicity, convenience, economy, and closeness to life. It has been widely used in orthopedic rehabilitation and neurorehabilitation. Through planned, organized and repetitive physical activities aimed at improving or maintaining physical health, it is utilized and is suitable for the restoration or maintenance of joint function in patients with early and mid-stage RA, and postoperative rehabilitation in patients with mid- and late-stage RA.

As a stressor, exercise makes the body produce complex stress effects, which affects the composition and metabolism of the human body through a series of complex processes. Appropriate motor function exercise can inhibit the level of inflammatory factors in the body, reduce disease activity, relieve pain, improve joint function, and achieve the purpose of relieving RA [12].

Several case-control studies have confirmed that routine drug therapy in combination with healthy exercise training can significantly promote the recovery of joint function in patients with RA. However, the findings varied among different studies because there were also remarkable differences between the different designs and various evaluation indicators. The clinical application value of routine drug therapy in combination with health exercise training in the clinical treatment of RA patients is explained simply by the effectiveness of a literature or the enhancement of an assessment index. In the absence of high-quality research evidence, the results of routine drug therapy in combination with healthy exercise training are unconvincing. In this context, further relevant studies are necessary, and more authoritative scientific studies are needed to demonstrate the feasibility and safety of conventional drug therapy in combination with healthy exercise training to treat RA patients, in order to offer a theoretical basis for the promotion and application of this treatment method.

This study utilized meta-analysis to conduct a systematic, quantitative, and comprehensive review of the results of similar independent studies to assess the effect of routine drug therapy in combination with healthy exercise training on pain and joint function relief in patients with RA, and to offer objective basis for its clinical application and further research.

## METHODS

### The sources and retrieval methods of documents

A computer search of PubMed, EMBASE, ScienceDirect, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP full-text Database, Wanfang Database and Chinese Biomedical Literature data (CBM), as well as relevant Chinese and foreign periodicals, conference papers, degree papers, and supplemented by literature tracing, was conducted in order to collect relevant data of the case-control trial of routine drug therapy, and in combination with the health exercise training in patients with RA. Literature search was performed when forming free words and subject words, with the keywords being, drug therapy, health exercise training, RA, pain, joint function, meta-analysis, drug treatment, healthy exercise training, RA, joint function, from January 2005 to May 2022.

### Literature inclusion and exclusion

#### *Inclusion criteria*

*The type of study:* All the case-control trials at home and abroad using routine drug therapy in combination with health exercise training to intervene patients with RA. *Subjects:* all patients met the diagnostic criteria of RA put forward by the American Rheumatic Society in 1987 [13]. *Intervention:* The control group was only treated with routine drugs (such as Tripterygium wilfordii polyglycosides, methotrexate, leflunomide, and diclofenac sodium). The experimental group was in combination with exercise training (including aerobic, resistance exercise or comprehensive exercise methods) based on the control group, and the specific medication plan and health exercise training program was determined according to the patient's condition.

*More than one of the following outcome indicators was reported:* Tender Joint Count (TJC), swollen joint count (SJC) and stiffness in the morning; comprehensive assessment of disease activity score of 28 joints (DAS28); average grip strength of both hands; health status (HAQ score), patient global assessment (PGA), etc.

#### *Exclusion criteria*

Literatures were excluded if no case-control or a cohort study was conducted; there was an incomplete data report, so the data could not be adopted; the research content was repeated; or

they were reviews, animal experiments, personal clinical experience summaries and other non-clinical efficacy studies.

### Quality evaluation and data extraction

Using the Cochrane System Review Manual 5.3 bias risk assessment tool, this study evaluated bias risk. The screening of literature and data extraction were conducted independently by two researchers. The data was extracted and its quality was evaluated and then cross-checked. The management and extraction of the research data was done using Note Express document management software and Excel office software. The data extracted contained, basic information (writer, publication time, number of cases); intervention (plan, course of treatment); outcome indicators, joint symptoms: (TJC, SJC and morning stiffness time); comprehensive assessment of disease range of motion (28 joint disease range of motion score (DAS28)); and average grip strength of both hands. Health status contained HAQ, PGA and other indicators.

### Statistical analysis

RevMan5.3 software was used for Meta analysis. In counting the data, the relative risk (RR) was adopted, and in measuring the data, the mean difference (MD) was adopted. Each effect was indicated with its point estimate and 95 % confidence interval (CI). An  $I^2$  test was used to measure heterogeneity, and the  $\chi^2$  test was used to determine whether heterogeneity existed. It is appropriate to use fixed effect models if there is no heterogeneity. There can be heterogeneity in the data, which can be analyzed through subgroup analysis, sensitivity analysis, or descriptive analysis, and a random effect model can be used if there is heterogeneity. A  $p < 0.05$  was considered statistically significant. To test the funnel chart's asymmetry, the Eggers's test was applied to the inverted funnel chart in order to determine the publication bias in the literature. A TrimandFill method can be used when the test  $p$ -value is less than 0.1, so that the funnel chart can be corrected and the effect of a possible release deviation can be adjusted.

## RESULTS

### Literature retrieval and inclusion

A total of 1342 articles were harvested through computer database retrieval, and 664 articles after excluding duplicates were sorted. Through a preliminary reading of article titles and abstracts, 357 articles were selected, disregarding irrelevant studies, reviews, case

reports, and uncontrolled articles. After carefully reading the full text of the literature, 134 articles were excluded due to incomplete data and lack of primary outcome indicators. There were 7 clinical controlled studies finally contained, with 483 samples for meta-analysis. Figure 1 shows the diagram used for literature screening, and Table 1 shows the basic characteristics of the literature found.

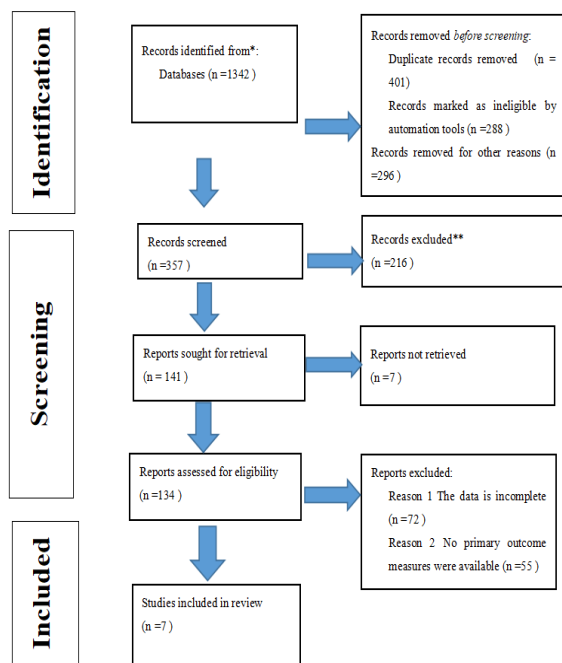


Figure 1: Illustration of literature screening

### An evaluation of the quality of the methodology adopted

There were seven case-control studies contained in this meta-analysis, all of which reported the baseline health conditions of the patients. All of these documents specified detailed interventions, but did not specify randomization methods. It is not clear from the seven publications whether blinding was done, or how many and why participants were lost to follow-up or withdrew. In accordance with the analysis of the Jadad scale, high-quality literature scored  $\geq 3$ , and low-quality literature scored  $\leq 2$ . Risk bias analysis is shown in Figure 2.

### Meta-analysis result

#### Visual analogue pain score (VAS)

The 7 clinical controlled studies had 483 samples. Based on the VAS scores, a meta-analysis was conducted. Heterogeneity test results indicated that  $\text{Chi}^2 = 12.15$ ,  $\text{df} = 2$ ,  $P = 0.002$ ,  $I^2 = 84\%$ , it shows that among the

contained research data, heterogeneity was evident. The random effect model analysis shows that the VAS score of the research group was significantly lower ( $p < 0.05$ ) (Figure 3).

### Joint symptoms

Meta-analysis of TJC, SJC and morning stiffness times indicated that TJC:  $\text{Chi}^2 = 20.82$ ,  $\text{df} = 3$ ,  $P = 0.0001$ ,  $I^2 = 86\%$ ; SCJ:  $\text{Chi}^2 = 10.34$ ,  $\text{df} = 2$ ,  $P = 0.006$ ,  $I^2 = 81\%$ ; and Morning stiffness time:  $\text{Chi}^2 = 14.87$ ,  $\text{df} = 3$ ,  $P = 0.002$ ,  $I^2 = 80\%$ , indicating that among the contained research data, heterogeneity was evident, which can be seen by random effect model analysis (Figure 4), the TJC score, SJC score and morning stiffness time in the study group, which were significantly lower ( $p < 0.05$ ).

### DAS28 motion score

Meta-analysis of DAS28 scores showed that  $\text{Chi}^2 = 0.10$ ,  $\text{df} = 2$ ,  $P = 0.95$ ,  $I^2 = 0\%$ , which indicated that among the contained research data, heterogeneity was evident. It can be seen from the fixed effect model analysis (Figure 5) that DAS28 scores of the study group were lower ( $p < 0.05$ ).

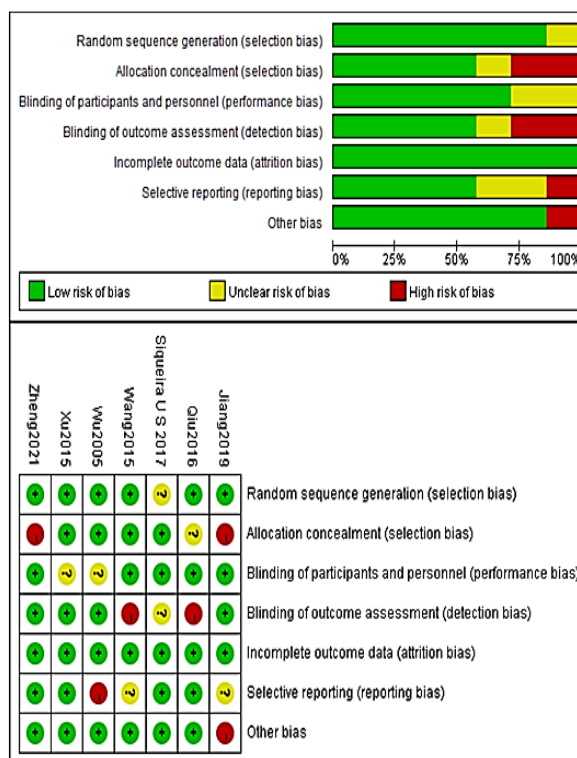


Figure 2: Risk bias chart of included studies

**Table 1:** Basic characteristics of literature

Reference	Year of publication	Sample size		Intervention measures		Research Type	Grouping method	Outcome index
		Control group	Research group	Control group	Research group			
[14]	2016	41	41	Routine treatment	Routine treatment + staged exercise training	Prospective study	Random grouping	①②
[15]	2021	40	40	Routine treatment + routine measures	Routine treatment + routine measures + staged exercise training	Prospective study	Alternating grouping method	①
[16]	2005	20	20	Routine drug therapy	Routine drug therapy + joint function rehabilitation exercise	Prospective study	Order of admission	①④
[17]	2019	30	40	Routine intervention	Routine intervention + exercise rehabilitation exercise	Prospective study	Random grouping	②③④⑤
[18]	2017	34	33	Routine drug therapy	Routine drug therapy + lower limb special exercise	Prospective study	Not specified	⑤⑥⑦
[19]	2015	42	42	Drug therapy + self-functional activity	Joint range of motion + muscle strength enhancement training	Prospective study	Random grouping	②③④⑥
[20]	2015	30	30	medication	Range of motion + muscle strength training	Prospective study	Random grouping	②③④⑤⑥⑦

Note: ① VAS score; ② Joint tenderness count; ③ Joint swelling number; ④ Morning stiffness time; ⑤ Range of motion of joint disease; ⑥ Average grip strength of both hands; ⑦ Life quality

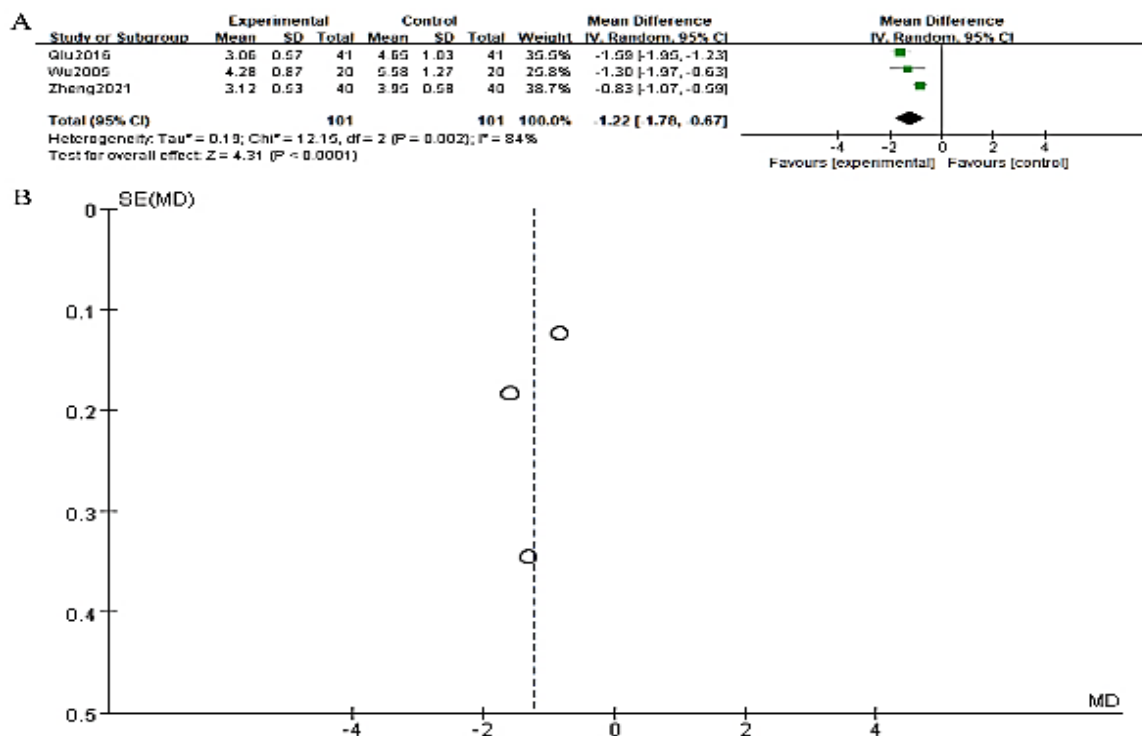


Figure 3: Forest analysis map of comparison of VAS scores A. Forest Plot. B. Funnel Plot

**Average grip strength of both hands**

A meta-analysis was performed on the average grip strength of both hands. Heterogeneity test results showed that Chi<sup>2</sup> = 1.72, df = 2, P = 0.42, I<sup>2</sup> = 0 %, indicating that among the contained research data, heterogeneity was evident. Based on the fixed-effect model analysis shown in Figure 6, both hands in the study group exhibited stronger grip strength (p < 0.05).

**Quality of life**

In this study, there were 7 clinical controlled studies with 483 samples contained. Meta-analysis was made on HAQ scores and PGA scores of patients. The results of heterogeneity test indicated that HAQ scores: Chi<sup>2</sup> = 0.00, df = 1, P = 0.95, I<sup>2</sup> = 0 %; PGA score: Chi<sup>2</sup> = 0.00, df = 1, P = 0.95, I<sup>2</sup> = 0 %. Among the contained research data, heterogeneity was evident. According to the analysis of fixed effect model (Figure 7), the HAQ score and PGA score of the research group are obviously better (p < 0.05).

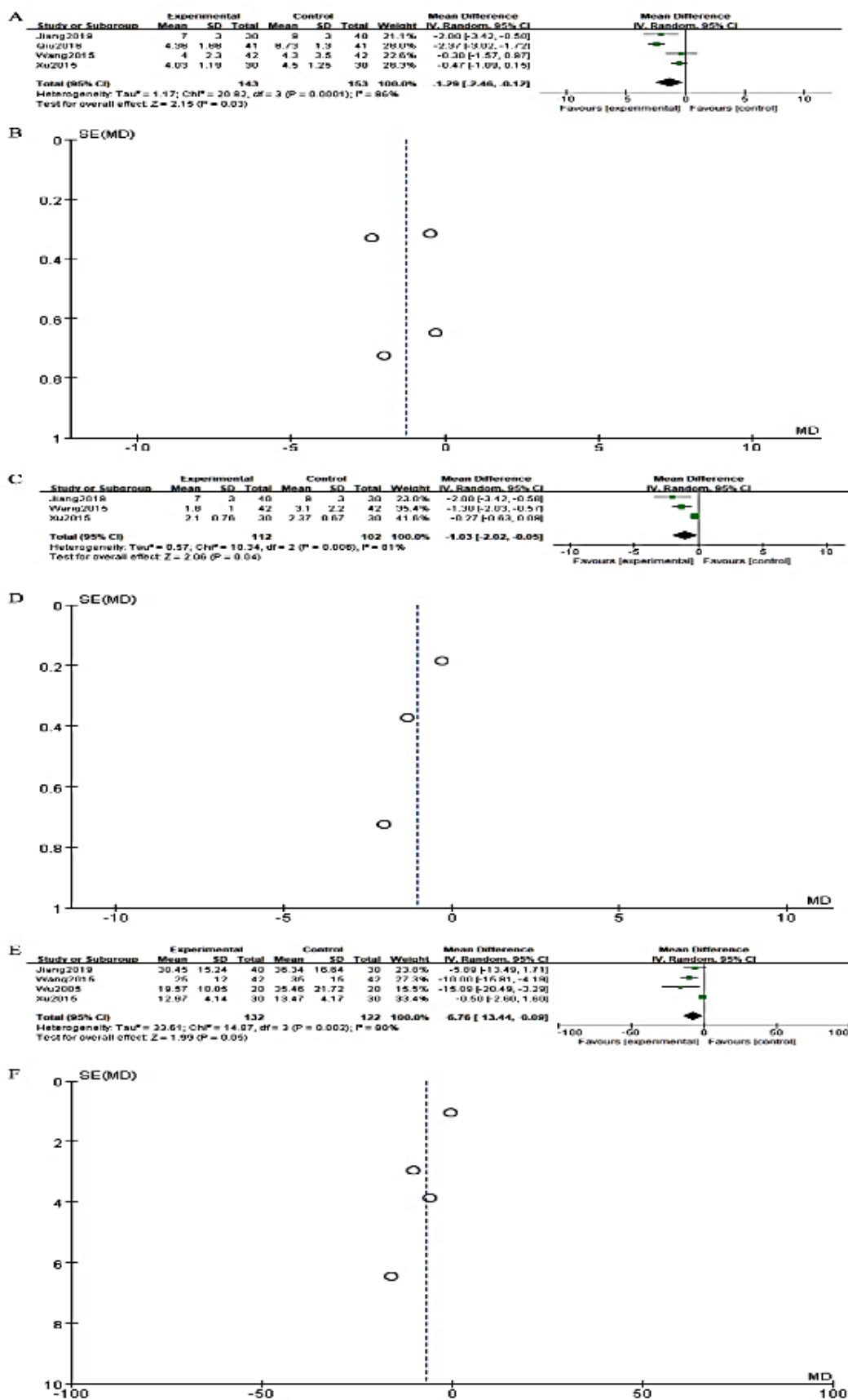
**Analysis of publication bias**

The funnel chart was drawn on the basis of VAS score, joint symptoms, range of motion of disease, average grip strength of both hands and HAQ score, and the publication bias was

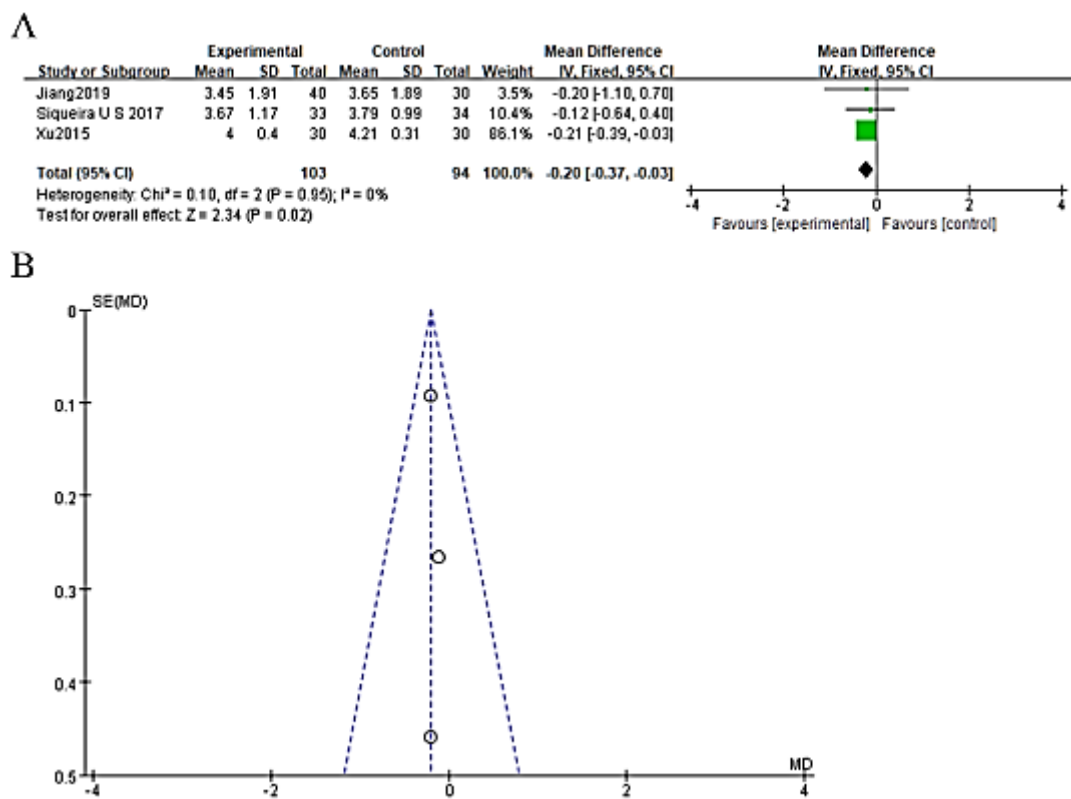
analyzed (Figure 4). The results indicated that almost all funnel charts were symmetrical, while a few were asymmetrical, suggesting that a publication bias was observed in the contained literature, which may be explained by the heterogeneity of the studies and the limited number of contained examples.

**DISCUSSION**

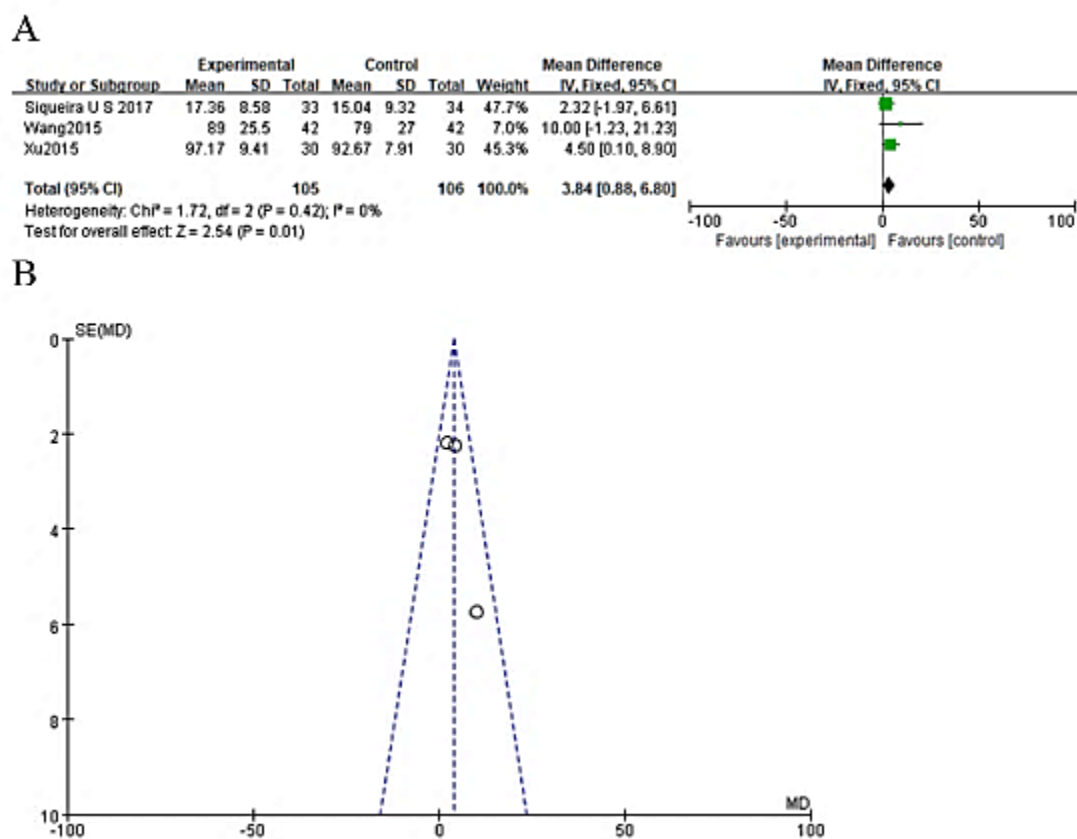
Rheumatoid arthritis is a chronic autoimmune joint disease caused by multi-joint inflammation, pain, limitation of activity and long-term lack of exercise. It often leads to decreased muscle strength, muscle atrophy, aggravating joint dysfunction and deformity, resulting in the loss of self-care, ability to work in most patients, and great pain to patients and families. Exercise therapy is a kind of physiotherapy which has been widely used in clinics and has shown good results [21,22]. Exercise therapy is a training method based on biomechanics and neurodevelopment, using instruments, bare hands or the patient's own strength to enable patients get back systemic or local motor function and sensory function recovery [21,23]. The most common strategy is to solve the problem of motor dysfunction, so exercise therapy has become the core treatment of rehabilitation.



**Figure 4:** A: Forest Plot of TJC comparison; B: Funnel Plot of TJC comparison; C: Forest Plot of SJC comparison; D: Funnel Plot of SJC comparison; E: Forest Plot of morning stiffness time; F: Funnel Plot of morning stiffness time

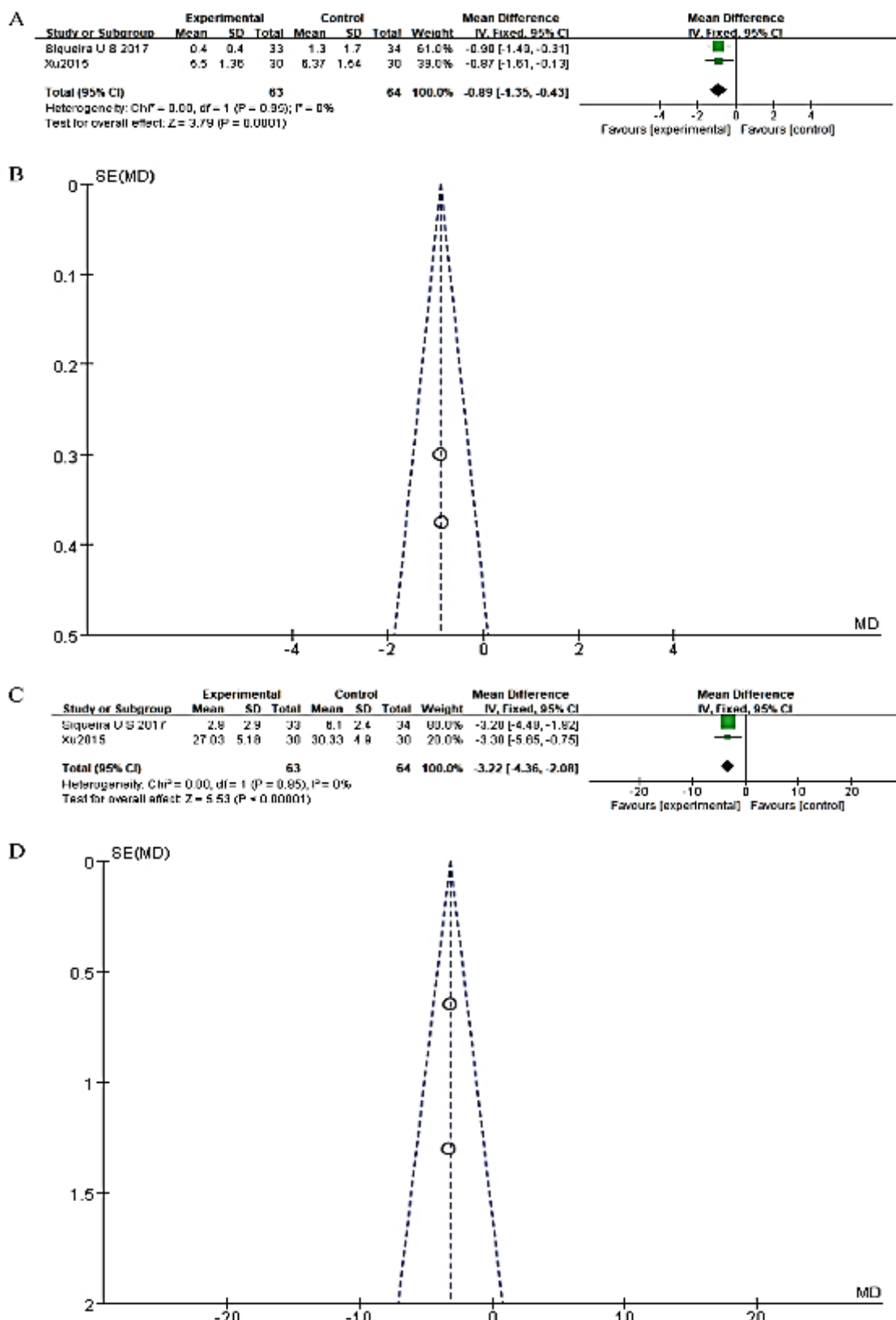


**Figure 5:** Forest analysis map of the comparison of DAS28 scores. A: Forest Plot; B: Funnel Plot



**Figure 6:** Forest analysis map of the comparison of average grip strength of hands A. Forest Plot. B. Funnel Plot





**Figure 7:** Forest analysis map of comparison of HAQ scores. A: Forest Plot of HAQ scores. B: Funnel Plot of HAQ scores. C: Forest Plot of PGA scores. D: Funnel Plot of PGA scores

Previous studies have shown that regular and proper exercise can accelerate the renewal of immune cells, replace aging and dysfunctional T

cells with new T cells, maintaining and increasing the diversity of T cell differentiation and decreasing muscle glycogen. The level of

inflammatory factors would also be decreased by increasing the differentiation and proliferation of regulatory T cells [22]. The release of catecholamines and cortisol increases the number and phagocytic activity of neutrophils in the circulatory system, exerting an anti-infective capacity. Meanwhile, the killing activity of NK cells and IL-2 production are enhanced, thus improving or maintaining the immune response function. In addition, appropriate aerobic exercise intervention can enhance the effect of the vaccine by enhancing the function of some immune cells (mainly T cells), and regulating the plasticity of immune cells [23]. For the elderly and obese people, as well as some patients with cancer and chronic viral diseases, aerobic exercises are a powerful behavioral intervention which can successfully improve the function of the immune system and enhance body health [24].

In order to maintain the normal function of the joint and enhance the recovery of the function of the diseased joint, exercise intervention on RA patients were carried out, with RA supplemented with joint function rehabilitation exercise training. Based on conditions, a specific training plan was made for different stages of acute activity and stability, especially in the stability stage, focusing on the functional recovery of the wrist and knee joint. Sports trainings should be carried out according to capacity, step by step, and from less to more. Patients were also instructed to protect their joints in their daily lives to avoid aggravating pain or damaging the joints or causing/aggravating joint deformities due to incorrect posture or improper force. Clinical observation has shown that timely and moderate exercise relaxes tense muscles, reduces spasm, promotes local blood circulation of joints, prevents the accumulation of painful inflammatory substances, and promotes the dissipation of inflammation [25]. The bioelectricity produced by muscle contraction during exercise contributes to the disposition of calcium ions, thereby reducing pain. In addition, active exercise puts patients' attention on exercise, thus reducing their attention to pain, enhancing their tolerance to pain, and reducing the degree of pain. In combination with the results of this meta-analysis are 7 clinically-controlled studies with containing 483 samples. The meta-analysis of VAS was carried out, suggesting that the VAS score of the study group was significantly lower. It has also shown that the pain symptoms of patients with RA can be alleviated by exercise intervention, mainly because exercise improves blood circulation, relaxes muscles, relieves inflammation, and reduces the degree of pain in patients. For these patients, attention was paid to

controlling the intensity of the exercise as well as attention to self-protection during exercise. Pain is the most obvious symptom in patients with RA. Severe pain can make the joints unable to move. So in order to relieve pain, patients usually maintain a bad limb position, and their daily living activities can be improved if joint pain is effectively reduced.

Morning stiffness is also a common clinical symptom of RA patients, manifested as tightness or stiffness in the joints in the morning. The duration of morning stiffness is often correlated with RA disease activity. The mechanism of morning stiffness is not very clear, but it is generally believed that it is caused by an increase in joint tissue fluid at night. Meta-analysis was performed on the TJC, SJC, and morning stiffness time in this study. Based on the random effect model, the study group had significantly lower TJC scores, SJC scores, and morning stiffness times. It is suggested that exercise intervention can shorten the time of morning stiffness and relieve symptoms in patients with RA. The decrease in TJC score and SJC score in the study group is mainly due to the improvement in local blood circulation. The gradual levels of inflammatory factors and the relaxation of body and mind after the application of healthy exercise training. The reasons for shortening the time of morning stiffness in the study group are probably after getting up in the morning, the joint tissue fluid flows back into the blood, and the morning stiffness can be alleviated properly. Secondly, targeted joint exercise training promotes venous and lymphatic reflux, eliminates joint swelling, enhances joint function, increased the range of motion, and improve stiffness and ankylosis [26]. Then, appropriate exercise can relax tense muscles, promote local blood circulation, reduce the feeling of joint stiffness and adhesion, and shorten the time of morning stiffness.

Clinically, RA easily invades the small joints of both hands and knee joints. However, because of pain, both hands and knee joints are in a state of bracing for a long time, which is easy to cause muscle atrophy of hands and knees, tendon and other soft tissue contracture, resulting in decreased function of both hands and knee joints in patients with RA. Although drugs can control the progress of the disease, it has no obvious effect on the deterioration of the functions of both hands and knee joints [27]. Further development may destroy joint function and cause loss of joint function, which seriously affects the normal work and life of RA patients. DAS28 objective evaluation of RA activity of the comprehensive index is the evaluation of disease improvement

[28]. If DAS28 > 1.2 indicates a good response to treatment; RA mainly involves the proximal interphalangeal joint and metacarpophalangeal joint. Therefore, the average grip strength of both hands is used to reflect the functional status. Based on the DAS28 scores of 28 joints and the average grip strength of both hands, a meta-analysis was performed in this study. DAS28 scores of the study group were lower, and the average grip strength of the study group was significantly higher, according to the fixed effect model analysis. This indicates that conventional drug therapy in combination with healthy exercise training can not only reduce the disease activity of RA patients and delay the progression of the disease, but also significantly improves the hand function of RA patients. A recent study has showed that drug therapy in combination with exercise therapy when treating RA needs to be adhered to for a long time, otherwise the therapeutic effect that has been produced may decrease [29].

As one of the important indicators to measure the basic daily behavior of RA patients, the HAQ score not only reflects the quality of life of RA patients, but also indirectly reflects the degree of their functional limitations [30]. The PGA reflects the degree to which the disease affects health and daily life, with higher scores indicating poorer functionality. In this study, a meta-analysis was conducted on the HAQ scores and PGA scores, and it revealed that the HAQ and PGA scores of the study group were significantly better, indicating that on the basis of conventional drug treatment, combined health exercise training can significantly enhance the quality of life of RA patients. The application of healthy exercise training significantly improves the patient's condition, helping them adjust their mentality, so they can return to a normal way of living as soon as possible. This result is consistent with two foreign results on the treatment of RA with exercise therapy. A meta-analysis on the treatment of RA with aerobic exercise indicated that aerobic exercise can improve the life quality [31]. Another meta-analysis of the efficacy of resistance exercise in RA patients indicated that resistance training significantly improved muscle strength, and decreased HAQ score and erythrocyte sedimentation rate [32].

### Limitations of this study

As a result of the strict inclusion and exclusion criteria, the final number of contained studies was relatively small, and no further subgroup analysis of heterogeneous studies was performed. Also, in all the studies, follow-up times were not consistent, so some limitations

existed, which need to be followed up by scholars to offer more support in the clinical application of routine drug therapy in combination with health exercise training in patients with RA.

## CONCLUSION

Conventional drug therapy in combination with healthy exercise training may become a clinical treatment choice for patients with RA. On the basis of drug therapy, the combination with exercise therapy enhances the recovery of joint function of RA patients, improves their clinical symptoms and limb disability, and alleviates disease progression, the benefits being fewer side effects and long-term use.

## DECLARATIONS

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### Funding

None provided.

### Ethical approval

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Conception and design (T Liu, X Zhou), Collection and assembly of data (T Liu, C Huang), Data analysis

and interpretation (T Liu, C Huang, L Zhou, R Zong, and X Zhou). All authors participated in drafting, revision and approval of the manuscript for publication.

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