



Review

The anti-inflammatory effects of exercise on autoimmune diseases: A 20-year systematic review

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Abstract

Background: The anti-inflammatory effect of exercise may be an underlying factor in improving several autoimmune diseases. The aim of this systematic review was to examine the evidence on the role of exercise training in mitigating inflammation in adolescents and adults with autoimmune disease.

Methods: PubMed, Web of Science, and Embase databases were systematically reviewed for related studies published between January 1, 2003, and August 31, 2023. All randomized and non-randomized controlled trials of exercise interventions with autoimmune disease study participants that evaluated inflammation-related biomarkers were included. The quality of evidence was assessed using the Tool for the assessment of Study quality and reporting in Exercise scale and Cochrane bias risk tool.

Results: A total of 14,565 records were identified. After screening the titles, abstracts, and full texts, 87 were eligible for the systematic review. These studies were conducted in 25 different countries and included a total of 2779 participants (patients with autoimmune disease, in exercise or control groups). Overall, the evidence suggests that inflammation-related markers such as C-reactive protein, interleukin 6, and tumor necrosis factor α were reduced by regular exercise interventions. Regular exercise interventions combined with multiple exercise modes were associated with greater benefits.

Conclusion: Regular exercise training by patients with autoimmune disease exerts an anti-inflammatory influence. This systematic review provides support for the promotion and development of clinical exercise intervention programs for patients with autoimmune disease. Most patients with autoimmune disease can safely adopt moderate exercise training protocols, but changes in inflammation biomarkers will be modest at best. Acute exercise interventions are ineffective or even modestly but transiently pro-inflammatory.

Keywords: Autoimmune diseases; Cytokines; Inflammation; Physical activity; Training

1. Introduction

Autoimmune diseases are conditions characterized by immune dysregulation leading to tissue damage in the host. Autoimmune disease rates are increasing rapidly in many parts of the world due to environmental and lifestyle factors.¹ Most

autoimmune diseases require lifelong treatment and significantly impact affected individuals and their families, society, and healthcare costs.² Physical inactivity is one of the risk factors for the progression of autoimmune diseases.³ Exercise training is recommended for patients with autoimmune disease in combination with medication and clinical care to improve quality of life, cardiorespiratory capacity, and muscle strength, and to alleviate symptoms such as pain and depression.^{3–5}

Inflammation palliation is an important goal in the treatment of autoimmune diseases. All autoimmune diseases share common features, including elevated circulating inflammatory

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markers such as interleukin (IL)-6, tumor necrosis factor α (TNF- α), and C-reactive protein (CRP) under basal or resting conditions.⁶ Regular exercise training has been linked in numerous studies with an anti-inflammatory effect.⁷ Possible mechanisms of the anti-inflammatory effects of exercise include increased release of hormones (cortisol and adrenaline) and myokines that downregulate the production of pro-inflammatory cytokines by immune cells. Exercise training also mobilizes regulatory T (Treg) cells, natural killer cells, and other immune cells that release the anti-inflammatory cytokine IL-10. Exercise training is typically associated with decreased visceral adipose tissue volume. This is important because an increase in visceral adipose tissue caused by physical inactivity and overeating leads to an expansion of resident inflammatory innate and adaptive immune cells that undergird systemic inflammation.^{7,8} Taken together, exercise training is important for overall immune health through its effects on immune cell recruitment and enhanced surveillance, antimicrobial activities, and reduced systemic inflammation.⁹

In the period from 2003 to 2013, there were few systematic reviews of published papers on exercise training and autoimmune diseases. One systematic review focused on the effects of acute (a single bout) and regular (repeated bouts) exercise on various inflammatory markers in patients with chronic inflammatory disease.⁶ This review concluded that regular exercise programs reduced chronic inflammation and that single bouts of recommended amounts of moderate-to-vigorous exercise were associated with a variable but modest increase in some inflammation biomarkers. Recent systematic reviews and meta-analyses from 2013 to 2023, most of which included a specific autoimmune disease, reported variable results for the effects of exercise on inflammatory biomarkers. For example, a systematic review for multiple sclerosis (MS) found limited effects of exercise on inflammation,¹⁰ whereas a systematic review for rheumatic diseases reported that exercise significantly attenuated some inflammatory-related markers, such as the erythrocyte sedimentation rate, but not CRP.¹¹ In addition, recent systematic reviews favored the selection of exercise programs that could be quantified in terms of intensity, and thus excluded exercise

intervention studies using modes such as calisthenics, yoga, Pilates, and Tai Chi.

Despite the existing literature suggesting that exercise training has an anti-inflammatory effect, no previous investigation has systematically reviewed all types of exercise interventions for the most common autoimmune diseases. Therefore, the aim of this systematic review was to summarize the anti-inflammatory effects of various forms of acute and regular exercise interventions for autoimmune diseases. It assessed the characteristics of exercise programs for specific autoimmune diseases, evaluated the effectiveness of different exercise programs on inflammatory outcomes, identified the types of autoimmune diseases most influenced by exercise programs, and formulated recommendations for further research.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was pre-registered in the International Database of Prospectively Registered Systematic Reviews (ID #CRD42023426627). The search strategy was based on the Participants, Intervention, Comparisons, Outcomes, and Study Design worksheet for systematic reviews. The inclusion and exclusion criteria are provided in [Table 1](#).

2.1. Data sources and searches

This review focused on published studies examining the anti-inflammatory effects of exercise interventions in patients with autoimmune disease. The search strategy was developed through discussions between team members and physicians in the departments of rheumatology, endocrinology, neurology, and gastroenterology. A broad search of 3 databases (PubMed, Web of Science, and Embase) was undertaken for articles containing terms for autoimmune diseases combined with exercise and inflammation. No limitations were applied regarding outcomes. We limited the relevant literature to English articles published from January 1, 2003 to August 31, 2023 (see [Supplementary Table 1](#) for the details of the search strategy).

Table 1
Selection criteria.

Category	Inclusion criteria	Exclusion criteria
Population	Subjects diagnosed with autoimmune diseases, no age or gender restrictions	Subjects had a combination of other non-autoimmune diseases
Intervention	Exercise interventions, such as aerobic training, resistance training, high-intensity interval training, yoga, calisthenics, and traditional Chinese exercise, were conducted	Studies included non-exercise interventions or a combined exercise and non-exercise intervention
Comparator	Studies had a control group (including healthy or patient control) or self-control	—
Outcome	Inflammation-related markers, such as pro- and anti-inflammatory cytokines, C-reactive protein, and immune cell ratios, were included in the results	No analysis or description of inflammatory-related biomarkers was performed
Study design	Studies with an experimental design, including randomized controlled trials and non-randomized controlled trials	Protocols, reviews, case reports, pilot studies, follow-up studies, and observational studies were excluded

2.2. Eligibility criteria

2.2.1. Design

Experimental studies, including both randomized controlled trials (RCTs) and non-RCTs (NRCTs), were considered eligible for inclusion. Studies were included if they investigated the effect of exercise (both acute and regular exercise) on inflammation-related biomarkers in patients with autoimmune disease. Trials were included if the effect was measured following the completion of the exercise program. Case reports and follow-up trials were excluded.

2.2.2. Participants

The patients in the included studies were diagnosed with autoimmune diseases, including MS, rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIMs), type 1 diabetes (T1D), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), systemic sclerosis (SSc), Takayasu arteritis (TA), pemphigus foliaceus, Sjogren syndrome, psoriasis, psoriatic arthritis, Hashimoto's disease, Guillain-Barre syndrome, myasthenia gravis, and combinations of same. Studies were excluded if subjects had autoimmune diseases combined with non-autoimmune diseases.

2.2.3. Intervention

The studies included in this review were not limited by the type of exercise intervention. Acute exercise was defined as a single bout or an exercise program. Regular exercise was defined as repeated bouts of exercise.¹² If a study assessed the effects of both regular and acute exercise, the study was reviewed twice. Aerobic training (AT) was defined as exercise designed to improve cardiorespiratory fitness. Resistance training (RT) was defined as exercise designed to improve both muscle size and strength. Exercise intensity was systematically assessed in the included studies in accordance with the guidelines of the American College of Sports Medicine.¹³ Studies were excluded if the protocol contained a combined exercise and non-exercise intervention.

2.2.4. Outcomes

The inflammation-related biomarkers in the included studies were pro- and anti-inflammatory cytokines, such as IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-17, transforming growth factor- β , TNF- α , interferon, granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory protein-1, calprotectin and CRP, as well as immune cell ratios including leukocytes, lymphocytes, monocytes, neutrophils, natural killer cells, Tregs, B regulatory cells, and dendritic cells.

2.3. Study selection

Results from the literature search were exported to Endnote references manager (Clarivate Analytics, Philadelphia, PA, USA), which was then used to de-duplicate the retrieved articles. After removal of duplicates, 2 review authors (BL and XJ) independently examined titles and abstracts against the

eligibility criteria. All articles selected in this process were obtained in full text. All full-text articles were also assessed independently by BL and XJ. Disagreement among review authors regarding eligibility was discussed among the entire group of reviewers until consensus was reached.

2.4. Data extraction

Following the screening process, relevant data from the included articles were extracted into Excel 2019 (Microsoft, Redmond, WA, USA) by BL and XJ. Data were initially extracted by XJ, with BL ensuring the accuracy of the extracted data. Extracted data included study characteristics (design), participant characteristics (sample size, gender, and age), exercise intervention (type, duration, frequency, and intensity), and outcomes (inflammation-related markers and their changes).

2.5. Quality and risk of bias assessment

A quality assessment of the included studies using the Tool for the assessment of Study quality and reporting in EXercise (TESTEX) scale¹⁴ was performed independently by BL and XJ. The TESTEX scale was developed specifically for exercise specialists to assess the quality of exercise studies and has been used in other systematic reviews/meta-analyses of exercise studies.^{5,15} Each TESTEX item was assigned a value of either 0 (absent or inadequately described) or 1 (present or explicitly described) for a maximum score of 15 points (5 for study quality and 10 for reporting). Discrepancies in scoring between reviewers were discussed and resolved when possible. Final scores were determined by consensus among team members when discrepancies could not be resolved. In addition, a Cochrane risk of bias assessment tool was used for the RCTs included in this review. A Cochrane risk of bias assessment evaluates RCTs based on several categories, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues". These categories were graded as "high risk of bias", "low risk of bias", and "unclear risk of bias". Each article was independently assessed by BL and XJ.

3. Results

3.1. Study selection

A total of 14,565 records were identified by the searches. Following the removal of duplicates and irrelevant articles, 736 full-text articles were assessed for eligibility. Following the full-text screening process, 87 articles were eligible and were included in the systematic review. The search procedure is summarized in Fig. 1.

3.2. Study characteristics

3.2.1. Participants

A total of 87 studies^{16–102} published between January 1, 2003, and August 31, 2023, provided results for 2779 patients

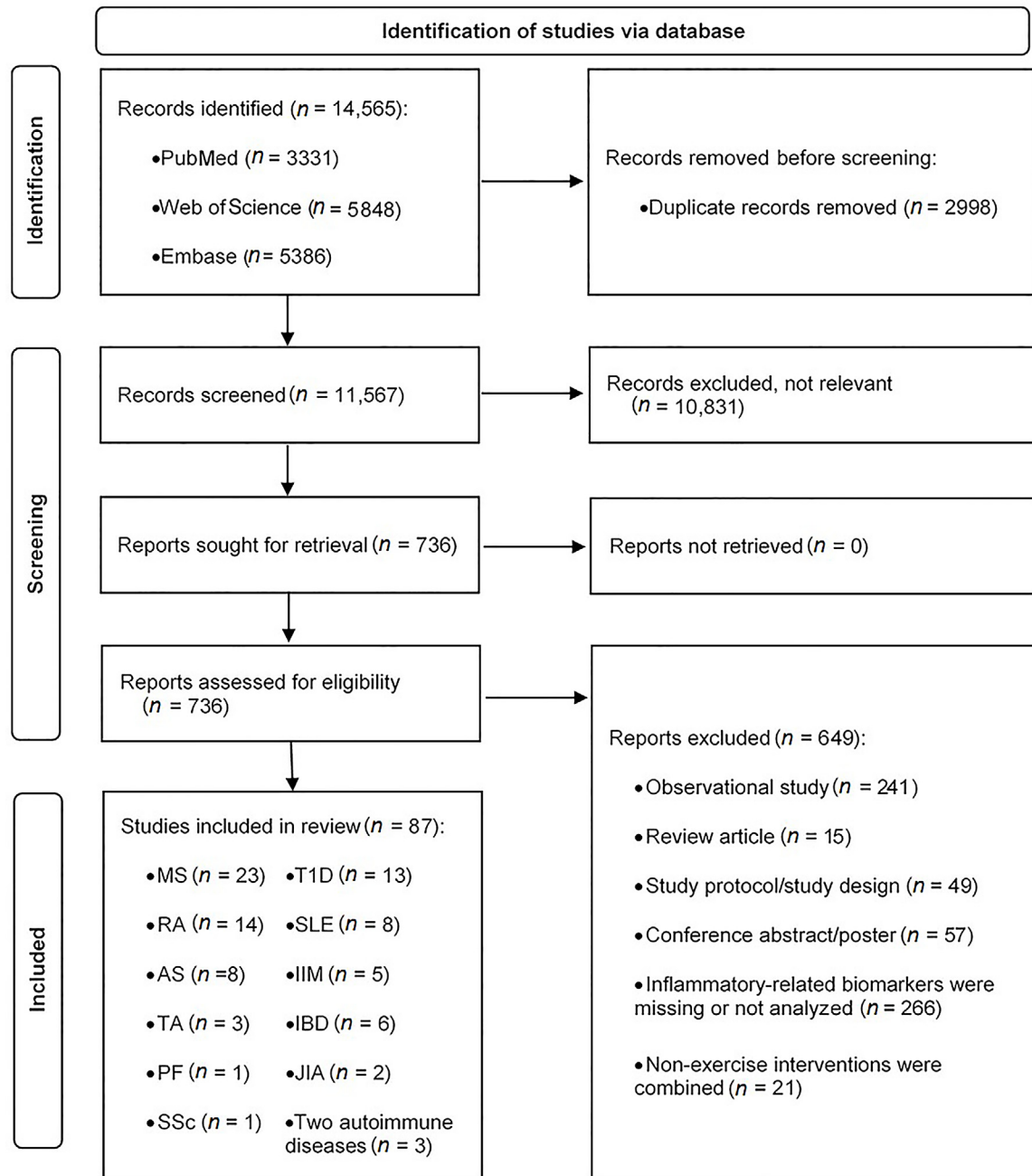


Fig. 1. Flowchart of the search and selection of studies. AS = ankylosing spondylitis; IBD = inflammatory bowel diseases; IIM = idiopathic inflammatory myopathies; JIA = juvenile idiopathic arthritis; MS = multiple sclerosis; PF = pemphigus foliaceus; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; T1D = type 1 diabetes; TA = Takayasu arteritis.

with autoimmune diseases. The most common autoimmune disease studied was MS,^{16–38} followed by RA,^{39–52} T1D,^{53–65} SLE,^{66–73} AS,^{74–81} IIM,^{82–86} IBD,^{87–92} TA,^{93–95} JIA,^{96,97} pemphigus foliaceus,⁹⁸ and SSc.⁹⁹ Three studies included patients with more than 1 autoimmune disease (RA and SLE,¹⁰⁰ RA and JIA,¹⁰¹ MS and AS,¹⁰² respectively). Age and gender, organized in Tables 2 and 3, are significant factors in the effectiveness of exercise interventions as well as in the development of autoimmune diseases.¹ There were 12 studies^{54,55,58–62,87,91,92,96,97} that enrolled adolescents. Eight studies^{18,25,35,41,50,54,81,82} reported the median and range of

participant age. One study³⁹ did not report the gender. Another study⁸⁶ did not report the age or gender. These studies were conducted in 25 countries (12 studies from Brazil,^{16,49,53,67,69–71,73,75,93,95,98} 9 studies from Iran,^{17,25,26,31–33,37,58,68} 9 studies from the USA,^{22,38,42,54,55,59–62} 7 studies from Turkey,^{35,39,43,63,74,77,102} 6 studies from Sweden,^{28,40,50,82–84} 5 studies each from Germany,^{21,27,30,36,89} and Ireland,^{19,41,56,57,88} 4 studies from the UK,^{51,52,64,100} 3 studies each from Czech Republic,^{76,78,86} the Netherlands,^{90,92,99} and Norway,^{66,81,101} 2 studies each from Australia,^{47,85} Belgium,^{23,34} Canada,^{24,87} China,^{79,94}

Table 2
Characteristics of the included regular exercise intervention studies.

Study	Autoimmune disease	Subjects (sample size, age, group, gender)	Exercise intervention	Inflammation-related biomarkers
Alvarenga-Filho et al. (2016) ¹⁶	MS	$n = 18, 38.5 \pm 10.2$ years, 8 Ex/10 Con, 3 M/15 F	Combined RT and AT	IL-6↓, TNF-α↓, IL-22↓
Bahmani et al. (2022) ¹⁷	MS	$n = 20, 27.1 \pm 2.9$ years, 10 Ex/10 Con, 20 F	AT	CRP↓, TNF-α↓, IL-6↓, IL-1β↓
Bansi et al. (2013) ¹⁸	MS	$n = 28, 52$ years, 28 Ex, 10 M/18 F	AT	—
Barry et al. (2019) ¹⁹	MS	$n = 9, 35.5 \pm 2.1$ years, 9 Ex, 1 M/8 F	AT	IL-10↑
Briken et al. (2016) ²¹	MS	$n = 42, 50.0 \pm 7.5$ years, 32 Ex/10 Con, 17 M/25 F	AT	—
Castellano et al. (2008) ²²	MS	$n = 11, 40 \pm 10$ years, 11 Ex, 3 M/8 F	AT	TNF-α↑, IFN-γ↑
Deckx et al. (2016) ²³	MS	$n = 45, 48.1 \pm 11.2$ years, 29 Ex/16 Con, 19 M/26 F	Combined RT and AT	CD80 ⁺ pDC↑, CD62L ⁺ pDC↑
Faramarzi et al. (2020) ²⁵	MS	$n = 94, 18–50$ years, 47 Ex/47 Con, 94 F	Combined RT, AT, stretching, balance training, and Pilates	IL-6↓, hs-CRP↓, PTX3↑, IFN-γ↑
Golzari et al. (2010) ²⁶	MS	$n = 20, 33.0 \pm 7.7$ years, 10 Ex/10 Con, 20 F	Combined RT, AT, and stretching	IL-17↓, IFN-γ↓
Joisten et al. (2021) ²⁷	MS	$n = 68, 50.3 \pm 10.2$ years, 68 Ex (35 HIIT/33 AT), 42 F/26 M	HIIT, AT	NLR↓
Kierkegaard et al. (2016) ²⁸	MS	$n = 20, 36.3 \pm 7.6$ years, 20 Ex, 4 M/16 F	RT	TNF-α↓
Kjølhede et al. (2016) ²⁹	MS	$n = 32, 43.4 \pm 7.5$ years, 16 Ex/16 Con, 8 M/24 F	RT	—
Mähler et al. (2018) ³⁰	MS	$n = 17, 51 \pm 10$ years, 17 EX, 6 M/11 F	AT	CD39 ⁺ Tregs↑, CD31 ⁺ Tregs↓, IL-17A ⁺ CD4 ⁺ cells↓
Mokhtarzade et al. (2017) ³²	MS	$n = 40, 31.7 \pm 3.0$ years, 22 Ex/18 Con, 40 F	AT	TNF-α↓
Mokhtarzade et al. (2021) ³³	MS	$n = 42, 35.7 \pm 8.6$ years, 21 Ex/21 Con, 11 M/31 F	Combined RT and AT	—
Nieste et al. (2023) ³⁴	MS	$n = 28, 45.4 \pm 11.0$ years, 28 Ex, 6 M/22 F	AT	CRP↑
Ozkul et al. (2018) ³⁵	MS	$n = 36, 34.3$ years, 18 Ex/18 Con, 8 M/28 F	Combined AT and Pilates	—
Schulz et al. (2004) ³⁶	MS	$n = 28, 39.5 \pm 9.8$ years, 15 Ex/13 Con, 9 M/19F	AT	—
Tadayon Zadeh et al. (2020) ³⁷	MS	$n = 30, 32.1 \pm 2.6$ years, 15 Ex/15 Con, 30 F	Combined AT and RT	IL-6↓, CRP↓, IL-10↑
White et al. (2006) ³⁸	MS	$n = 10, 47 \pm 12$ years, 10 Ex, 10 F	RT	IL-4↓, IL-10↓, CRP↓, IFN-γ↓
Acar et al. (2016) ³⁹	RA	$n = 28, 55.1 \pm 11.8$ years, 28 Ex	Combined AT and RT	CRP↓
Andersson et al. (2020) ⁴⁰	RA	$n = 49, 69.5 \pm 2.6$ years, 24 Ex/25 Con, 9 M/40 F	Combined AT and RT	IL-10↓, Tregs↓, Bregs↓
Azeez et al. (2020) ⁴¹	RA	$n = 52, 34–74$ years, 28 Ex /24 Con, 8 M/44 F	Combined AT and RT	CRP↓
Bartlett et al. (2018) ⁴²	RA	$n = 12, 64 \pm 7$ years, 12 Ex, 1 M/11 F	HIIT	CD16 ⁺ monocytes↓
Gautam et al. (2019) ⁴⁴	RA	$n = 72, 43.9 \pm 2.4$ years, 36 Ex/36 Con, 16 M/56 F	Yoga	CRP↓, IL-6↓, IL-17A↓, TNF-α↓, TGF-β↑
Gautam et al. (2020) ⁴⁵	RA	$n = 66, 44.3 \pm 9.0$ years, 33 Ex/33 Con, 13 M/53 F	Yoga	IL-6↓, TNF-α↓, TGF-β↑
Joo et al. (2022) ⁴⁶	RA	$n = 37, 49.9 \pm 7.9$ years, 24 Ex/13 Con, 37 F	RT	—
Law et al. (2015) ⁴⁷	RA	$n = 9, 57 \pm 14$ years, 9 Ex, 1 M/8 F	Combined AT and RT	—
Lozada-Mellado et al. (2022) ⁴⁸	RA	$n = 60, 44.4 \pm 11.0$ years, 30 Ex/30 Con, 60 F	Combined AT and RT	TNF-α↓, TNF-β↓
Sarajlic et al. (2018) ⁵⁰	RA	$n = 29, 60–67$ years, 29 Ex	Combined AT and RT	CRP↓
Stavropoulos-Kalinoglou et al. (2013) ⁵¹	RA	$n = 36, 53.9 \pm 9.9$ years, 18 Ex/18 Con, 8 M/28 F	Combined AT and RT	CRP↓
Wadley et al. (2014) ⁵²	RA	$n = 19, 55.5 \pm 10.1$ years, 12 Ex/7 Con, 6 M/13 F	AT	—
Farinha et al. (2018) ⁵³	T1D	$n = 28, 24.5 \pm 5.0$ years, 28 Ex (9 HIIT/ 9 RT/10 HIIT+RT), 15 M/ 13 F	HIIT, RT, or combined HIIT and RT	—
Minnock et al. (2022) ⁵⁷	T1D	$n = 10, 31.6 \pm 3.7$ years, 10 Ex, 4 M/ 6 F	Combined AT and RT	—
Nazari et al. (2023) ⁵⁸	T1D	$n = 40, 11.1 \pm 2.3$ years, 20 EX/ 20 Con, 19 M/ 21 F	Combined AT and RT	—
Turner et al. (2014) ⁶⁴	T1D	$N = 8, 38 \pm 17$ years, 8 Ex, 7 M/ 1 F	RT	IL-6↑
Clarke-Jenssen et al. (2005) ⁶⁶	SLE	$n = 6, 47.0 \pm 3.8$ years, 6 Ex, 6F	AT	—
Hashemi et al. (2022) ⁶⁸	SLE	$n = 24, 25.9 \pm 5.8$ years, 14 Ex/ 10 Con, 24 F	Combined AT and RT	TNF-α↓, IL2↓, IL-4↓, IL-5↓
Perandini et al. (2014) ⁶⁹	SLE	$n = 8, 35.8 \pm 6.5$ years, 8 Ex, 8 F	AT	sTNFR2↓, IL-10↓
Soriano-Maldonado et al. (2018) ⁷²	SLE	$n = 58, 44.0 \pm 13.9$ years, 26 Ex/ 32 Con, 58 F	AT	—
Timóteo et al. (2018) ⁷³	SLE	$n = 14, 37.4 \pm 12.6$ years, 5 Ex/ 9 Con, 14 F	Combined RT, AT, and stretching	—

(continued on next page)

Table 2 (Continued)

Study	Autoimmune disease	Subjects (sample size, age, group, gender)	Exercise intervention	Inflammation-related biomarkers
Aydın et al. (2016) ⁷⁴	AS	$n = 37, 34.6 \pm 7.9$ years, 37 Ex, 20 M/ 17 F	Calisthenic exercise	—
de Souza et al. (2017) ⁷⁵	AS	$n = 60, 44.4 \pm 9.9$ years, 30?Ex/ 30 Con, 44 M/ 16 F	RT	—
Hulejová et al. (2012) ⁷⁶	AS	$n = 26, 36.0 \pm 6.5$ years, 26 Ex, 18 M/ 8 F	Combined RT, postural corrections, and stretching	—
Kisacik et al. (2016) ⁷⁷	AS	$n = 24, 39.9 \pm 10.0$ years, 24 Ex, 24 F	Combined dance and Pilates	TNF- α ↓
Levitova et al. (2016) ⁷⁸	AS	$n = 40, 36.8 \pm 1.1$ years, 40 Ex, 27 M/ 13 F	Combined core spinal traction and RT	Calprotectin↓
Ma et al. (2020) ⁷⁹	AS	$n = 84, 36.1 \pm 5.2$ years, 42?Ex/ 42 Con, 59 M/ 25 F	Tai Chi	CRP↓
Nolte et al. (2021) ⁸⁰	AS	$n = 29, 39.2 \pm 13.7$ years, 16 Ex/ 13 Con, 15 M/ 14 F	Combined AT and RT	—
Sveaas et al. (2020) ⁸¹	AS	$n = 100, 47.2$ years, 50 EX/ 50 Con, 47 M/ 53 F	Combined HIIT and RT	—
Alexanderson et al. (2007) ⁸²	IIM	$n = 9, 53$ years, 9 Ex, 4 M/ 5 F	RT	—
Alexanderson et al. (2014) ⁸³	IIM	$n = 19, 60.0 \pm 3.8$ years, 10 Ex/ 9 Con, 5 M/?14 F	RT	—
Arnardottir et al. (2003) ⁸⁴	IIM	$n = 7, 60.4 \pm 12.5$ years, 7 Ex, 7 M	Combined AT and RT	—
Coudert et al. (2022) ⁸⁵	IIM	$n = 14, 65 \pm 14$ years, 14 Ex, 14 M	Combined AT and RT	IL-12p70↓, MIP-1 β ↓, TNF- α ↓, IL-17A↓, sICAM-1↓
Švec et al. (2022) ⁸⁶	IIM	$n = 23, 23$ Ex	Combined RT and stability training	IL-7↓, IL-9↓, CCL-5↓, TNF- α ↓
Bjelica et al. (2023) ⁸⁷	IBD	$n = 10, 15.4 \pm 1.2$ years, 10 EX, 9 M/ 1 F	Combined AT and RT	—
Cronin et al. et al. (2019) ⁸⁸	IBD	$n = 20, 25.0 \pm 6.5$ years, 13 Ex/ 7 Con, 15 M/ 5 F	Combined AT and RT	—
Klare et al. (2015) ⁸⁹	IBD	$n = 30, 41.1 \pm 14.1$ years, 15 Ex/ 15 Con, 8 M/ 22 F	AT	Leukocytes↓
Lamers et al. (2021) ⁹⁰	IBD	$n = 37, 54.0 \pm 11.9$ years, 18 Ex/ 19 Con, 15 M/ 22 F	AT	IL-6↑, IL-8↑, IL-10↑
Legeret et al. (2019) ⁹¹	IBD	$n = 21, 13.3 \pm 3.0$ years, 21 Ex, 11 M/ 10 F	Exercise games (dance)	CRP↓
Scheffers et al. (2023) ⁹²	IBD	$n = 15, 9.5 \pm 4.0$ years, 8 Ex/ 7 Con, 9 M/ 6 F	Combined AT and RT	Calprotectin↓
Astley et al. (2021) ⁹³	TA	$n = 14, 18.3 \pm 3.8$ years, 5 Ex/ 9 Con, 4 M/ 10 F	Combined AT and RT	IL-1 β ↓
Li et al. (2020) ⁹⁴	TA	$n = 278, 36.8 \pm 8.6$ years, 140 Ex/ 138 Con, 145 M/ 133 F	RT	TNF- α ↓, CRP↓
Oliveira et al. (2017) ⁹⁵	TA	$n = 6, 35.3 \pm 6.6$ years, 6 Ex, 6 F	AT	TNF- α ↓
Timóteo et al. (2019) ⁹⁸	PF	$n = 19, 34.11 \pm 15.70$ years, 9 Ex/ 10 Con, 8 M/ 11 F	Combined RT and stretching	IL-17↓, IL-22↓, IL-15↓, IFN- γ ↓
Sandstad et al. (2015) ¹⁰¹	RA and JIA	$n = 18, 32.9 \pm 8.2$ years, 9 Ex/ 9 Con, 18 F	HIIT	—
Taspinar et al. (2015) ¹⁰²	AS and MS	$n = 73, 34.7 \pm 7.9$ years, 73 Ex, 39 M/ 34 F	Calisthenic exercise	—

Notes: Ages are presented as mean \pm SD or median. \uparrow , increase or obtain a higher value; \downarrow , impair or obtain a lower value; —, unchanged.

Abbreviations: AS = ankylosing spondylitis; AT = aerobic training; Bregs = B regulatory cells; CCL = chemokine ligand; CD = cluster of differentiation; Con = control group; CRP = C-reactive protein; Ex = exercise group; F = female; HIIT = high-intensity interval training; hs-CRP = high-sensitivity CRP; IBD = inflammatory bowel diseases; IFN- γ = interferon- γ ; IIM = idiopathic inflammatory myopathies; IL = interleukin; JIA = juvenile idiopathic arthritis; M = male; MIP = macrophage inflammatory protein; MS = multiple sclerosis; NLR = neutrophil-to-lymphocyte ratio; pDC = plasmacytoid dendritic cells; PF = pemphigus foliaceus; PTX = pentraxins; RA = rheumatoid arthritis; RT = resistance training; sICAM = soluble intercellular adhesion molecule; sIL-6R = soluble IL-6 receptor; SLE = systemic lupus erythematosus; sTNFR = soluble TNF receptor; T1D = type 1 diabetes; TA = Takayasu arteritis; TGF = transforming growth factor; TNF = tumor necrosis factor; Tregs = T regulatory cells.

Table 3
Characteristics of the included acute exercise intervention studies.

Study	Autoimmune disease	Subjects (sample size, age, group, gender)	Exercise intervention	Inflammation-related biomarkers
Berkowitz et al. (2019) ²⁰	MS	$n = 15, 33.8 \pm 7.8$ years, 15 Ex, 15 F	AT (moderate) AT (vigorous)	IL-6↑ IL-10↓
Briken et al. (2016) ²¹	MS	$n = 42, 50.0 \pm 7.5$ years, 32 Ex/10 Con, 17 M/25 F	AT	—
Castellano et al. (2008) ²²	MS	$n = 11, 40 \pm 10$ years, 11 Ex, 3 M/8 F	AT	—
Devasahayam et al. (2021) ²⁴	MS	$n = 14, 54.1 \pm 8.5$ years, 14 Ex, 4 M/10 F	AT	IL-6↑
Joisten et al. (2021) ²⁷	MS	$n = 68, 50.3 \pm 10.2$ years, 68 Ex (35 HIIT/33 AT), 42 F/26 M	HIIT or AT	PLR↑ (HIIT)
Kjølhede et al. (2016) ²⁹	MS	$n = 32, 43.4 \pm 7.5$ years, 16 Ex/16 Con, 8 M/24 F	RT	—
Majdinasab et al. (2018) ³¹	MS	$n = 35, 28.5 \pm 4.0$ years, 35 Ex, 35 F	AT	TNF-α↓, IL-6↑ (immediately after AT), TNF-α↑ (1-h post)
Ercan et al. (2023) ⁴³	RA	$n = 40, 45.3 \pm 9.6$ years, 40 Ex, 11 M/29 F	AT	IL-6↑
Law et al. (2015) ⁴⁷	RA	$n = 8, 60 \pm 12$ years, 8 Ex, 2 M/6 F	Combined AT and RT	—
Pereira Nunes Pinto et al. (2017) ⁴⁹	RA	$n = 17, 55.6 \pm 6.4$ years, 17 Ex, 17 F	RT	IL-1ra↑, IL-10↑, IL-6↑, IL-1β↓
Galassetti et al. (2006) ⁵⁴	T1D	$n = 12, 13.7$ years, 12 Ex, 7 M/5 F	AT	IL-6↑
Galassetti et al. (2006) ⁵⁵	T1D	$n = 20, 13.7 \pm 0.3$ years, 20 Ex, 12 M/8 F	AT	IL-6↑
Minnock et al. (2020) ⁵⁶	T1D	$n = 12, 31.8 \pm 5.3$ years, 12 Ex, 6 M/6 F	AT RT Combined AT and RT	<i>IL6, TNFa, and MCP1</i> mRNA↑ <i>IL6, TNFa, and MCP1</i> mRNA↑ <i>IL6, TNFa, and MCP1</i> mRNA↑
Rosa et al. (2008) ⁵⁹	T1D	$n = 21, 13.0 \pm 0.3$ years, 21 Ex, 13 M/8 F	AT	IL-6↑, TNF-α↑, IL-4↑, IL-12p70↑, GM-CSF↑, MCP-1↑, MIP-1α↑
Rosa et al. (2010) ⁶⁰	T1D	$n = 47, 13.8 \pm 0.4$ years, 47 Ex, 22 M/25 F	AT	IL-6↑
Rosa et al. (2011) ⁶¹	T1D	$n = 49, 13.9 \pm 0.2$ years, 49 Ex, 29 M/20 F	AT	IL-6↑
Rosa et al. (2011) ⁶²	T1D	$n = 23, 13.9 \pm 0.3$ years, 23 Ex, 13 M/10 F	AT	—
Salman et al. (2008) ⁶³	T1D	$n = 19, 22.1 \pm 2.8$ years, 19 Ex, 19 M	AT	CD3 ⁺ CD4 ⁺ T cells ↓, NK cells ↑
Żebrowska et al. (2018) ⁶⁵	T1D	$n = 14, 26.0 \pm 5.9$ years, 14 Ex, 7 M/7 F	AT HIIT	TGF-β↑ TGF-β↑, TNF-α↓
da Silva et al. (2013) ⁶⁷	SLE	$n = 27, 29.4 \pm 2.2$ years, 27 Ex, 27 F	AT	—
Perandini et al. (2014) ⁶⁹	SLE	$n = 8, 35.8 \pm 6.5$ years, 8 Ex, 8 F	AT	IL-10↓
Perandini et al. (2015) ⁷⁰	SLE	$n = 23, 33.0 \pm 5.6$ years, 23 Ex, 23 F	AT (moderate) AT (vigorous)	IL-6↓ sTNFR1↓, TNF-α↑
Perandini et al. (2016) ⁷¹	SLE	$n = 8, 33.5 \pm 3.3$ years, 8 Ex, 8 F	AT	<i>TLR3, IFNG, GATA3, FOXP3, STAT4</i> mRNA↓
Oliveira et al. (2017) ⁹⁵	TA	$n = 11, 33.5 \pm 5.7$ years, 11 Ex, 11 F	AT	—
Rochette et al. (2018) ⁹⁶	JIA	$n = 12, 12.3 \pm 2.8$ years, 12 Ex, 4 M/8 F	AT	Calprotectin↑
Rochette et al. (2018) ⁹⁷	JIA	$n = 12, 12.3 \pm 2.8$ years, 12 Ex, 4 M/8 F	AT	IL-6↓, sIL-6R↓ (24-h post)
Hargadóttir et al. (2010) ⁹⁹	SSc	$n = 11, 59 \pm 3$ years, 11 Ex, 3 M/8 F	AT	Leukocytes↑, IL-6↑
Pool et al. (2004) ¹⁰⁰	RA and SLE	$n = 13, 34.1 \pm 5.0$ years, 13 Ex, 13 F	AT	CD4 ⁺ T lymphocytes↓ (RA and SLE) CD4 ⁺ /CD8 ⁺ T lymphocytes↓(RA)

Notes: Ages are presented as mean \pm SD or as median. ↑, increase or obtain a higher value; ↓, impair or obtain a lower value; —, unchanged.

Abbreviations: AT = aerobic training; CCL = chemokine ligand; CD = cluster of differentiation; Con = control group; Ex = exercise group; F = female; FOXP3 = Forkhead box p3; GATA3 = GATA binding protein 3; GM-CSF = granulocyte-macrophage colony-stimulating factor; HIIT = high-intensity interval training; IFNG = interferon gamma; IL = interleukin; JIA = juvenile idiopathic arthritis; M = male; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; mRNA = messenger RNA; MS = multiple sclerosis; NK = natural killer; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; RA = rheumatoid arthritis; RT = resistance training; sIL-6R = soluble IL-6 receptor; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; STAT = signal transducer and activator of transcription; sTNFR = soluble TNF receptor; T1D = type 1 diabetes; TA = Takayasu arteritis; TGF = transforming growth factor; TLR = Toll-like receptor; TNF = tumor necrosis factor.

France,^{96,97} India,^{44,45} and Switzerland;^{18,91} and 1 study each from Denmark,²⁹ Israel,²⁰ Republic of Korea,⁴⁶ Mexico,⁴⁸ Poland,⁶⁵ South Africa,⁸⁰ and Spain⁷²).

3.2.2. Exercise interventions

In these studies, 66 studies^{16–19,21–23,25–30,32–42,44–48,50–53,57,58,64,66,68,69,72–95,98,101,102} were conducted regular exercise interventions, 28 studies^{20–22,24,27,29,31,43,47,49,54–56,59–63,65,67,69–71,95–97,99,100} were acute, and 7 studies^{21,22,27,29,47,69,95} investigated the effects of both acute and regular (reviewed twice). For regular exercise interventions, 32 trials^{16,23,25,26,33,35,37,39–41,47,48,50,51,53,57,58,68,73,76–78,80,81,84–88,92,93,98} used a combination of exercise, 17 trials used AT,^{17–19,21,22,27,30,32,34,36,52,66,69,72,89,90,95} 9 trials used RT,^{28,29,38,46,64,75,82,83,94} while 4 studies^{27,42,53,101} used high-intensity interval training (HIIT). The frequency of exercise was 3–5 times per week. For acute exercise interventions, 22 trials^{20–22,24,31,43,54,55,59–63,67,69–71,95–97,99,100} used AT, 2 trials^{29,49} used RT, 2 trials^{27,65} used HIIT and AT, and 2 trials^{47,56} used combined exercise. Other interventions were yoga,^{44,45} Pilates,^{25,35,77} Tai Chi,⁷⁹ stretching,^{25,26,73,76,98} and calisthenic exercise.^{74,102} Detailed exercise protocols were summarized in Tables 2, 3, and Supplementary Table 2. Safety related information was extracted from participants who withdrew from the exercise intervention, including reasons for dropping out and any adverse events that occurred during the exercise intervention. The relevant information is available in Supplementary Table 2.

3.3. Main findings of the reviewed studies

3.3.1. MS

In the regular exercise intervention trials for people with MS, the intervention programs included AT, RT, HIIT, and combined exercise. Nine intervention protocols^{17–19,21,22,30,32,34,36} were AT, 3 studies^{28,29,38} were RT, 1 study²⁷ was HIIT and AT, and 7 studies^{16,23,25,26,33,35,37} were a combination of exercises. Exercise interventions generally ranged from 8 to 12 weeks, with a minimum of 4 days and a maximum of 6 months. The frequency of exercise interventions was 2–5 times per week. Seven of 20 studies found that exercise had anti-inflammatory effects with reductions in CRP, IL-6, and TNF- α in the peripheral circulation and increases in IL-10 (3 AT, 1 RT, and 3 combined exercise).^{16,17,19,25,28,33,37} Two exercise interventions reported changes in the number of dendritic cells²³ and the ratio of Tregs.³⁰ Two studies^{26,38} reported an exercise-induced decrease in interferon- γ , but another study²⁵ showed an increase. Seven studies^{18,21,27,29,32,35,36} reported no effects of exercise interventions on inflammation-related markers (4 AT, 1 RT, and 2 combined exercise). Among the acute exercise intervention studies for MS, 5 studies^{20–22,24,31} were AT, 1 study²⁹ was RT, and 1 study²⁷ was HIIT and AT. Only one of these studies showed a decrease in TNF- α immediately after AT in patients with MS.³¹ Three studies^{21,22,29} found no anti-inflammatory effects (2 AT and 1 RT). In contrast, 4 acute exercise interventions^{20,24,27,31} (3 AT, 1 HIIT) reported increases in IL-6 and TNF- α

(1-h post AT) in the peripheral circulation and decreases in IL-10. Patients with MS exhibited improvements in clinical disability,^{22,26} fatigue,^{16,28,33,35,38} mood,^{28,30,32} cognition,²⁸ quality of life,^{28,33,36} exercise capacity,^{22,25,28,29,33,35} physical fitness,^{17,36} cardiorespiratory fitness,¹⁸ muscle strength,^{26,28,29,38} and balance²⁶ after exercise interventions.

3.3.2. RA

In the regular exercise intervention trials for people with RA, the intervention programs included AT, RT, yoga, HIIT, and combined exercise. Seven intervention protocols^{39,40,43,47,48,50,51} were combined exercise, 2 studies^{44,45} were yoga, 1 study⁵² was AT, 1 study⁴⁶ was RT, and 1 study⁴² was HIIT. Exercise interventions generally ranged from 8 to 24 weeks, with a maximum of 2 years. The frequency of exercise interventions was 2–5 times per week. Seven of 12 studies found that regular exercise had anti-inflammatory effects with decreases in CRP, IL-6, and TNF- α in the peripheral circulation and increases in IL-10 (5 combined exercise and 2 yoga).^{39,41,44,45,48,50,51} One study⁴⁰ with combined exercise reported changes in the ratios of both Tregs and B regulatory cells. However, 4 studies^{42,46,47,52} found no effect of exercise interventions on inflammation-related markers (1 AT, 1 RT, 1 HIIT, and 1 combined exercise). Two acute exercise intervention studies^{47,49} found no anti-inflammatory effects (1 combined exercise and 1 RT), and 1 acute AT intervention study⁴³ reported an increase in IL-6. Patients with RA exhibited improvements in disease activity^{39,42,45,52} and fatigue^{40,41} following exercise. Additionally, patients demonstrated significant enhancements in cardiorespiratory fitness,^{42,47,51,52} exercise capacity,^{40–42} and muscle strength^{40,46,47} after engaging in exercise.

3.3.3. T1D

Three regular exercise intervention trials^{53,57,58} (10–12 weeks, 3 sessions per week) for people with T1D reported no changes in inflammation biomarkers. One regular RT exercise intervention trial⁶⁴ increased IL-6. Of the 9 acute exercise intervention trials in T1D, 7 studies^{54,55,59–63} were AT, 1 study⁶⁵ was AT and HIIT, and 1 study⁵⁶ included AT, RT, and combined exercise interventions. One study reported that acute AT exercise intervention increased the ratio of natural killer cells,⁶³ and another study⁶⁵ showed a decrease in TNF- α . Seven studies showed pro-inflammatory effects after acute exercise interventions, including the elevation of IL-6 in the peripheral circulation^{54,55,59–61,64} and in the muscle.⁵⁶ It is noteworthy that the subjects in 6 of these studies were adolescents.^{54,55,59–62} After combined AT and RT exercise intervention, patients with T1D experienced a decrease in blood glucose levels and an improvement in glycemic control.^{56,57} Additionally, patients showed significant improvements in muscle strength and cardiorespiratory fitness.⁵⁷

3.3.4. SLE

In 5 regular (2–4 months, 2–3 sessions per week) exercise intervention trials (3 trials^{66,69,72} used AT, 2 trials^{68,73}

used combined exercise) with female patients with SLE, only 1 study⁶⁸ showed a reduction of TNF- α , IL-2, IL-4, and IL-5 after 8-week combined exercise. Four studies^{66,69,72,73} reported no changes in inflammation biomarkers. Leukocyte gene expression in patients with SLE compared to healthy controls following an acute 30-min bout of exercise (70% peak O₂ consumption (VO_{2peak})) was less organized, which suggests a deficiency in the normal exercise-induced immune transcriptional response.⁷¹ Exercise intervention improves quality of life and physical function,⁶⁶ cardiorespiratory fitness,⁷² flexibility, strength, and pain⁷³ in patients with SLE.

3.3.5. AS

Five regular (2–6 months, 2–5 sessions per week) exercise intervention trials^{74–76,80,81} for patients with AS generally reported no changes in inflammation biomarkers. One Tai Chi intervention study⁷⁹ found a decrease in CRP, and 2 investigating combined exercise reported a reduction in TNF- α ⁷⁷ and calprotectin⁷⁸ in the peripheral circulation. Patients with AS exhibited improvements in disease activity,^{76,78–81} quality of life,^{77,81} mood,^{74,77,81} as well as reduced pain^{78,79,81} after exercise. Furthermore, patients demonstrated a greater improvement in functional capacity,^{74,76,77,79,80} cardiorespiratory fitness, and muscle strength^{75,80,81} after exercise intervention.

3.3.6. IIM

Of 5 regular (7–26 weeks, 2–5 sessions per week) exercise intervention (2 RT,^{82,83} 3 combined exercise^{84–86}) trials for people with IIM, 2 studies^{85,86} reported reductions in plasma TNF- α , IL-7, IL-9, IL-17A, IL-12p70, macrophage inflammatory protein-1 β , chemokine ligand-5, and soluble intercellular adhesion molecule-1. The other studies reported no changes in inflammation biomarkers.^{82–84} Exercise intervention also improved disability, stability, aerobic capacity, and muscle strength in patients with IIM.^{83,86}

3.3.7. IBD

Five regular (4 days–16 weeks, 3–5 sessions per week) exercise intervention trials (AT, combined exercise, active video games) for patients with IBD reported a decrease in the blood leukocyte count,⁸⁹ serum CRP,⁹¹ calprotectin,⁹² or no change in inflammation biomarkers.^{87,88} However, plasma cytokine IL-6, IL-8, and IL-10 increases following 4 bouts of prolonged walking were modest and similar in study participants with or without IBD, and both groups experienced no changes in fecal calprotectin.⁹⁰ Patients with IBD exhibited an improved quality of life and reduced fatigue following exercise.⁹² Additionally, they exhibit a decrease in body fat percentage⁸⁸ and improved cardiorespiratory fitness and muscle strength.^{87,88} The acute exercise intervention did not change IBD disease activity in patients with ulcerative colitis, but it did increase in patients with Crohn's disease.⁹⁰

3.3.8. TA

AT, RT, and combined AT and RT regular (each 12 weeks, 2–3 sessions per week) exercise intervention trials for patients with TA showed reductions in serum CRP and plasma TNF- α ^{94,95} and IL-1 β .⁹³ After exercise, patients with TA experience alleviated TA symptoms,⁹⁴ reduced visceral adiposity,⁹³ and significant improvements in physical activity levels as well as muscle strength and function.^{93,95}

3.3.9. Other autoimmune diseases

One 12-week RT exercise intervention NRCT study⁹⁸ (3 sessions per week, 70% 1 repetition maximum) with patients with pemphigus foliaceus showed reductions in plasma IL-17, IL-22, IL-15, and IFN- γ . Most patients with SSc were unable to complete a maximal cardiopulmonary exercise test, and thus acute changes in inflammation biomarkers were difficult to interpret relative to healthy controls.⁹⁹ The normal increase in blood CD8⁺ concentrations following an acute, maximal incremental cycling bout was blunted in patients with both RA and SLE.¹⁰⁰ Two exercise intervention studies^{101,102} in patients with combined autoimmune diseases (RA and JIA, MS and AS, respectively) showed no changes in inflammation biomarkers.

3.4. Quality and risk of bias

In the studies that were included in this review, 39 studies were RCTs^{17,18,21,23,25–27,29,30,32–37,40,41,44,45,48,52,53,56,58,68,74,75,79–81,83,85,88,89,92–94,101,102} and 48 were NRCTs.^{16,19,20,22,24,28,31,39,39,42,43,46,47,49–51,54,55,57,59–67,69–73,76–78,82,84,86,87,90,91,95–100} The quality assessments of RCTs and NRCTs were in [Supplementary Table 3](#). The quality of the included studies ranged from 3 to 13 (maximum 15), with an average quality score of 7.39 points. The average quality score of included RCT studies was 9.13 points. The risk of bias for randomization was low in 28 of 39 studies^{17,21,23,27,29,30,32,34,35,40,41,44,45,48,53,58,74,79–81,83,85,88,89,92–94,102} and unclear in 11 studies.^{18,25,26,33,36,37,52,56,68,75,101} For allocation concealment, 11 of 39 studies had a low risk,^{21,23,25,29,32,34,40,48,56,81,88} 24 studies^{17,18,26,27,30,33,35–37,41,44,45,52,53,68,74,75,79,80,89,93,94,101,102} were unclear, and 4 studies^{58,83,85,92} had a high risk. Due to the nature of the exercise interventions, it was difficult to blind participants to the intervention programs. For blinding of participants and personnel, only 1 study³⁰ was low risk, 17 studies^{17,18,21,26,27,36,37,40,41,48,52,53,56,74,79,85,94} were equivocal, and 21 studies^{23,25,29,32–35,44,45,58,68,75,80,81,83,88,89,92,93,101,102} were high risk. For blinding of outcome assessment, 17 of 39 achieved low risk,^{18,23,25,32,35,40,44,45,48,53,75,81,83,85,93,94,102} 14 of 39 were unclear,^{17,26,29,33,36,37,41,52,56,68,74,79,89,101} and 8 of 39 had high risk.^{21,27,30,34,58,80,88,92} For risk of bias on incomplete outcome data, 31 studies^{18,21,23,25,26,29,32–35,37,39,41,44,45,48,52,53,58,74,75,80,81,83,88,89,92–94,101,102} were low risk and 8 studies^{17,27,36,40,56,68,79,85} were unclear. Risk of bias was low in regard to selective reporting and other related areas in all studies. The graph and summary on risk of bias for the included RCTs are shown in [Supplementary Figs. 1 and 2](#).

4. Discussion

4.1. Exercise characteristics and main findings

This systematic review showed that acute and regular exercise interventions have a differential response on inflammation biomarkers in patients with autoimmune diseases. The exercise-induced effect on inflammation is also dependent on the type and severity of the autoimmune diseases (as summarized in Fig. 2). According to the literature we reviewed, changes in inflammatory markers and disease-related symptoms were not synchronized. For example, exercise interventions with similar protocols had inconsistent effects on inflammatory markers and disease symptoms in patients with AS and MS. Consistent with other studies, acute exercise modestly and transiently increases the inflammatory response and regular exercise has an anti-inflammatory effect.^{6,7} Most of the regular exercise intervention studies employed moderate exercise training protocols due to safety concerns and patient limitations. Acute moderate- to high-intensity exercise increases inflammatory biomarkers, possibly due to exercise-induced muscle micro injury. This finding is consistent with the study conducted by Contrepois et al.¹⁰³ The review also analyzed the effects of exercise interventions on inflammatory markers in various autoimmune disease symptoms. Furthermore, exercise interventions can alleviate the complications of autoimmune diseases. For instance, exercise can enhance joint mobility and improve the quality of life for patients with RA. However, the pathogenesis of autoimmune disease is complex, and for many of them it remains unclear.

4.1.1. MS and RA

Thirty-seven of the 87 papers included in this systematic review were exercise interventions for MS and RA. The inflammation response to exercise interventions for these 2 types of autoimmune diseases has been investigated extensively and systematically reviewed.^{10,11} The reviews related to exercise interventions for these 2 types of diseases focused on exercise intervention programs that could be quantified in terms of intensity and workload (e.g., AT and RT). The systematic review of studies in patients with MS concluded that despite exercise-induced improvements in quality of life, no significant changes were measured for inflammation.¹⁰ A review of studies in patients with RA showed regular exercise-related improvements in disease activity scores and small beneficial effects on the erythrocyte sedimentation rate but no effect on CRP.¹¹ The current review employed a broader inclusion of exercise training protocols for patients with autoimmune diseases and showed that the best effects on inflammation were from studies that utilized combined exercise interventions. The combined exercise interventions for MS combined AT and RT, and some studies added Pilates, stretching, and balance training.^{25,26,35} Notably, exercise interventions for RA demonstrating anti-inflammatory effects were usually in the form of individual and group classes with high participation rates.^{39,42,44,45,48} These combined exercise training studies support an individualized and clinical team-based approach. In general, most regular combined exercise

interventions in patients with RA report no worsening of or improvements in disease activity scores with variable and modest anti-inflammatory effects. More meaningful improvements in inflammation biomarkers may require higher exercise workload volumes and significant weight loss that exceed the capabilities of patients with both MS and RA.

4.1.2. SLE

The leukocytes of SLE patients, regardless of disease activity, exhibited a decrease in inflammatory gene expression immediately after acute aerobic exercise, followed by an increase during recovery.⁷¹ Additionally, less organized gene networks were observed in SLE patients, indicating a potential deficiency in triggering a normal exercise-induced immune transcriptional response. SLE patients may have high levels of inflammation-related transcripts, which could result in lower exercise-induced changes in transcript levels compared to disease-induced changes. Furthermore, the immunosuppressive medications used by SLE patients may make them less sensitive to exercise-induced immune-related transcriptional responses. Exercise may also alleviate disease-related inflammatory responses by reducing body weight and body fat percentage in patients with SLE.¹⁰⁴

4.1.3. T1D

Although exercise intervention has been established as effective for type 2 diabetes, fewer studies have been reported for T1D, and the effects on inflammatory factors were not significant. However, exercise interventions can improve glycemic homeostasis and increase muscle strength in patients with T1D. Combined resistance and AT at a moderate intensity improved blood glucose homeostasis and growth hormone in children with T1D.⁵⁸ In addition, in patients with T1D, a recent study suggests that exercise combined with dietary interventions may be more effective for alleviating symptoms.¹⁰⁵

4.1.4. Other autoimmune diseases

The anti-inflammatory effects of acute and regular exercise interventions were studied in other autoimmune disease groups, including those with AS, IIM, IBD, TA, FS, JIA, and SSc (Tables 2 and 3). Acute exercise bouts generally did not evoke clinically important changes in inflammation biomarkers, and this is in part due to the moderate exercise workloads used in these studies. The effect of regular exercise training on inflammation biomarkers in other autoimmune disease groups is variable, and any improvements are modest at best. Combined exercise interventions may have some effects on inflammation in patients with autoimmune diseases. The effective exercise intervention for patients with AS was Tai Chi, dance therapy, and Pilates or core muscle stabilization and balance training,^{77–79} and for IIM, it was strength and stability training.⁸⁶ Pathways related to aerobic metabolism are altered in patients with IIM after endurance exercise.¹⁰⁶ Thus, study results may be due in part to the type of autoimmune diseases and related effects on physiological function. For example, RT may not be appropriate for patients with IBD because RT increases intra-abdominal pressure, which may

worsen symptoms of diarrhea or abdominal pain. In contrast, 1 study has shown that breathing exercises combined with meditation, which help regulate intra-abdominal pressure, may relieve IBD symptoms.¹⁰⁷ The metabolic modulating effect of exercise is one of the ways in which exercise interventions are thought to alleviate symptoms in patients with autoimmune diseases.

4.1.5. Immune homeostasis in exercise

Acute exercise induces inflammation by modifying factors such as adrenaline, IL-6, and TNF- α in the microenvironment. This, in turn, improves the recognition and response to abnormalities such as foreign pathogens and internal malignant cells.¹⁰⁸ Exercise not only enhances positive immune function but also enhances regulatory modalities such as IL-1 receptor antagonist, vascular growth factor D, and immune checkpoints. These facilitate a compensatory anti-inflammatory response resulting in a more robust immune homeostasis.¹⁰³ However, the findings regarding the effect of exercise on immune function are still controversial. For instance, cytotoxic T lymphocyte-associated antigen-4 is a crucial immune checkpoint that negatively regulates T cells. The agonist is clinically used to treat RA and juvenile RA. Nevertheless, Gautam et al.⁴⁵ found that T lymphocyte-associated antigen-4 was reduced after yoga exercise in patients with RA.⁴⁵ The mechanism and effect of this change are unclear. Autoimmune diseases occur when the immune system fails to regulate itself, leading to an abnormal immune response by T cells or antibodies against normal cells and tissues. The mechanisms behind this are complex and require further research to be elucidated.

4.2. Limitations and implications

RCTs of exercise interventions were not available for all types of autoimmune diseases, and there were fewer high-quality RCTs from 2003 to 2013. The quality of the literature included in this systematic review was variable. There was only 1 exercise intervention trial each for both FS and SSc. There were no acute exercise intervention trials for AS and IIM, and fewer regular exercise interventions for T1D. Some of the included trials had imprecise definitions of the duration and intensity of exercise interventions and did not describe how exercise intensity was monitored. Some studies did not adequately address the characteristics of the exercise intervention (periodicity, incremental load) and used acute exercise or a small number of sessions. Therefore, more well-controlled and organized RCTs are needed to investigate the effects of regular exercise interventions.

In addition, the inflammatory markers selected for the included studies were inconsistent. For example, some studies assessed the inflammatory response using CRP and cytokines, whereas others measured the degree of inflammation using white blood cell counts or the proportion of certain immune cells. In addition, there was a paucity of literature using inflammation as a primary outcome in autoimmune diseases exercise intervention studies.

Third, the language of the included studies was English, so fewer studies of traditional Chinese exercise, such as Tai Chi, were included. Only 3 databases were selected for the study, and no other databases were thoroughly searched for studies related to autoimmune diseases exercise interventions. This systematic review did not include direct analysis of trial data,

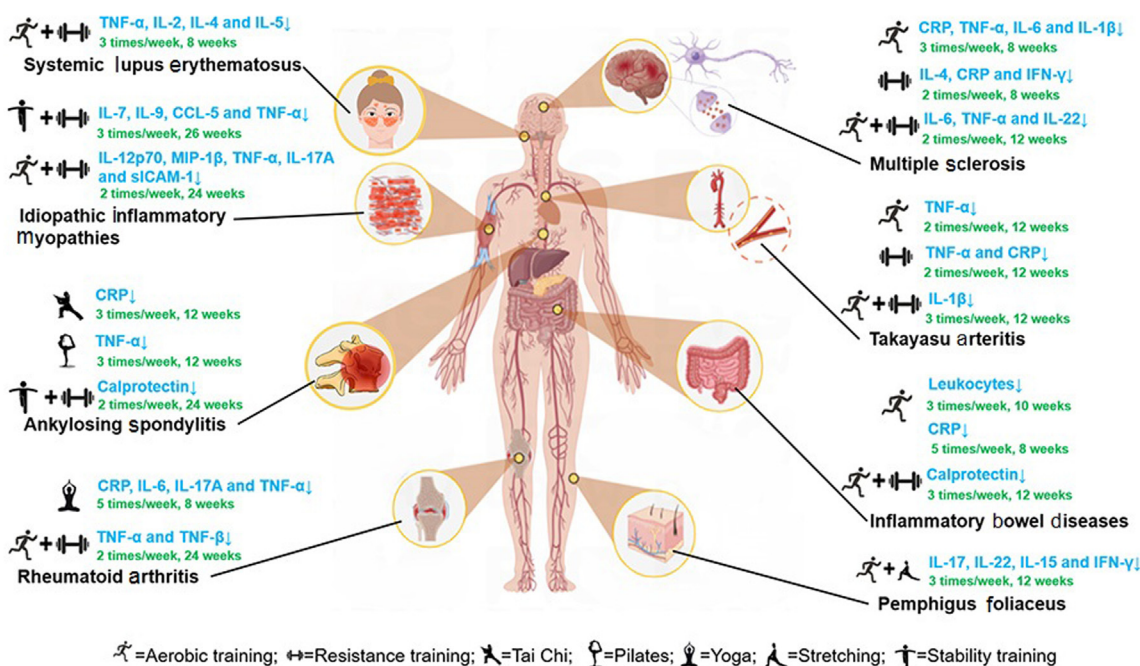


Fig. 2. Anti-inflammatory effects of regular exercise on autoimmune diseases. ↑ = increase; ↓ = decrease; CCL = chemokine ligand; CRP = C-reactive protein; IFN- γ = interferon- γ ; IL = interleukin; MIP = macrophage inflammatory protein; sICAM = soluble intercellular adhesion molecule; TNF- α = tumor necrosis factor- α .

and the authors of the included trials were not contacted to provide data for statistical analysis.

5. Conclusion

From an anti-inflammatory perspective, regular interventions that combine multiple exercise modes individualized to patients with autoimmune diseases are recommended. Most patients with autoimmune disease can safely adopt moderate exercise training protocols, but changes in inflammation biomarkers will be modest at best. Regular exercise training, especially when combined with aerobic and RT, is an effective countermeasure to autoimmune diseases. Acute exercise interventions are ineffective or even modestly but transiently pro-inflammatory.

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Authors' contributions

BL made contributions to the conception and design, study selection, data extraction, risk of bias assessment, data analysis, and drafting of the manuscript; DX contributed to the literature search, study selection, data extraction, risk of bias assessment, data analysis, drafting of the manuscript, and participated in the conception and design of the study and contributed to the revision of the manuscript; XJ contributed to the literature search, study selection, data extraction, risk of bias assessment, data analysis, and drafting of the manuscript; XC, RL, and SZ contributed to the study selection, data extraction, risk of bias assessment, data analysis, and drafting of the manuscript; YM contributed to the literature search; DCN participated in the conception and design of the study and contributed to the revision of the manuscript; PC made contributions to the conception and design. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2024.02.002.

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