2022-03-10

The effect of exercise training programs with aerobic components on Creactive protein, erythrocyte sedimentation rate and selfassessed disease activity in people with ankylosing spondylitis: A systematic review and metaanalysis

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10.1111/1756-185x.14315
International Journal of Rheumatic Diseases
Wiley

The effect of exercise training programmes with aerobic components on C-reactive protein, erythrocyte sedimentation rate and self-assessed disease activity in people with ankylosing spondylitis: a systematic review and meta-analysis

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Running title: Exercise and Ankylosing Spondylitis.

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Acknowledgements

This study was completed to partially fulfil the degree of Master of Science (Sport and Health Sciences) from the University of Exeter, United Kingdom.

Abstract

Aim

To examine the effect of exercise training programmes with aerobic components on C-reactive protein, erythrocyte sedimentation rate and self-assessed disease activity in people with ankylosing spondylitis compared to non-aerobic rehabilitation.

Methods

A systematic review was undertaken of PubMED, Cochrane Library, Embase and Web of Science databases. Articles evaluating the effect of exercise training programmes with aerobic components on C-reactive protein, erythrocyte sedimentation rate or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in adults (>17 years) with ankylosing spondylitis were included. Control groups were defined as non-aerobic rehabilitation, including usual care or physiotherapy.

Results

Thirteen articles met inclusion criteria for qualitative and meta-analysis, involving 366 participants undertaking exercise and 361 controls. Exercise programmes included modalities such as running, aerobic walking and swimming, and were between three weeks and three months in duration. Exercise programmes significantly reduced C-reactive protein (weighted mean difference [WMD]: -1.09; 95% CI: -2.08 to -0.10; p=0.03; n=5) and the BASDAI (WMD: −0.78; 95% CI: −0.98 to -0.58; p<0.001; n=13) compared to non-aerobic rehabilitation. BASDAI subgroup analysis revealed greater improvements compared to usual care than structured physiotherapy. Exercise programmes did not reduce erythrocyte sedimentation rate (WMD: 0.16; 95% CI: -2.15 to 2.47; p=0.89; n=4).

Conclusion

Exercise training programmes with aerobic components reduced C-reactive protein and improved self-assessed disease activity in people with ankylosing spondylitis. Further research is required to investigate the effects of differing aerobic exercise modes, intensities and durations.

Key words

Inflammation, arthritis, pain, fatigue, physical activity.

1 – Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic condition characterised by inflammation of the spinal vertebrae and sacroiliac joints.[1] Associated with the human leukocyte antigen B27 positive rate in worldwide populations, estimates of prevalence range between 18.6 to 39.9 cases per 10,000 people depending on geographical region.[2] AS is more common in males with an estimated ratio of 2:1,[3] with symptoms including pain and fatigue and advanced cases resulting in spinal ankylosis.[3] AS has also been associated with comorbidities such as cardiovascular and cerebrovascular disease,[4] factors contributing to an increased mortality hazard ratio of 1.6.[5]

The aetiology and pathogenesis of AS are thought to involve a combination of factors including microbiota imbalance and endocrinal abnormity, resulting in the injurious overproduction of pro-inflammatory cytokines.[6] Whilst there is no cure for AS, the reduction of inflammatory biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is considered important for rehabilitative progression, being positively associated with both disease severity[7] and the self-reported Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[8,9] Pertinently, aerobic exercise has been evidenced to reduce CRP within healthy middle-aged and older adults,[10] while

observational studies have shown inverse associations between inflammatory biomarkers and aerobic fitness in healthy men.[11] Aerobic exercise could potentially therefore be an important adjuvant therapy for people with AS. However, exercise recommendations for people with AS[12] are ambiguous, with no guidance on factors such as mode, intensity or duration – advice that reflects the equivocality of existing evidence. Two recent systematic reviews[13,14] along with a 2019 Cochrane review,[15] concluded that exercise training programmes did not reduce levels of CRP or ESR compared to usual care, although seemingly incongruently, measures of the BASDAI improved. These reviews however, synthesised all modes of exercise including aerobic, range of motion and resistance training, quantitatively analysing and basing conclusions on heterogenous exercise programmes. More relevantly, a further meta-analysis[16] examined the effects of aerobic exercise on CRP and the BASDAI in people with AS, finding no improvement compared to physiotherapy. However, only studies that monitored intervention exercise intensity were eligible for inclusion, resulting in the omission of several otherwise germane studies that did not assess this factor. Consequently, evidence regarding the effects of aerobic exercise on inflammation and disease activity remains inconclusive.

Therefore, the current systematic review and meta-analysis aims to comprehensively evaluate and quantify the effect of exercise training programmes with aerobic components on CRP, ESR, and the BASDAI in people with AS compared to non-aerobic rehabilitative control groups.

2 – Methods

This review was reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[17] recommendations, (PRISMA checklist,

Appendix A). A summary of review protocol was registered in PROSPERO, registration number CRD42021244678.

2.1 – Searches

A systematic literature search of PubMed, Web of Science, Cochrane Library and Embase databases from inception to March 27th, 2021, was undertaken to identify original articles and review papers. Search terms were formulated with reference to the PICO model (Population, Intervention, Comparison, Outcomes). To maximise search sensitivity and ensure that no relevant results were missed, it was decided not to include terms relating to comparators and outcomes. Key phrases for database screening were; ankylosing spondylitis + exercise; axial spondyloarthritis + exercise; ankylosing spondylitis + physical activity; axial spondyloarthritis + physical activity. Backwards and forward citation chasing was also undertaken with identified reviews from 2018 onwards.[13-16]

2.2 – Article type

Included articles were randomised and non-randomised controlled trials, fully published in English language. Pilot studies were included if participants received exercise and control group allocation. All types of grey literature were excluded.

2.3 – Participants

Eligible participants were aged 18 and above, described as having AS or radiographic axial spondyloarthritis (r-axSpA) as diagnosed by either the modified New York AS criteria, or Axial Spondyloarthritis and AS criteria. Studies including participants with non-radiographic axial spondylitis were included if combined with AS or r-axSpA participants.

2.4 – Interventions

Exercise programmes of at least two weeks in duration that focused solely on aerobic exercise, or that included aerobic exercise as part of a broader programme, were included. There were no restrictions on programme mode, intensity and frequency. Combined interventions with non-physical activity components were excluded, for example cryotherapy with exercise. Comparators were defined as non-aerobic rehabilitation, including no intervention, usual care or comparative programmes of physiotherapy / flexibility exercises.

2.5 – Outcomes

Studies measuring changes in systemic inflammatory biomarkers C-reactive protein (mg/l) and erythrocyte sedimentation rate (mm/h) were included due to their positive association with disease activity[9] and severity.[7] Patient assessed disease activity was quantified using the BASDAI composite self-report questionnaire (0-10). The BASDAI contains 6 questions answered on a 10 cm visual analogue scale, pertaining to pain in the spine and peripheral joints, fatigue and stiffness. BASDAI scores of >4 indicate suboptimal disease management,[18] with the minimum clinically significant change evidenced to be 1.1.[19]

2.6 – Search strategy

Following identification of articles through database searches and removal of duplicates, titles and abstracts were screened, and full texts examined if appropriate. Titles, abstracts and full texts were analysed by two researchers independently. A third researcher was designated to resolve disagreements regarding study inclusion, but was

not required. The search strategy was managed using Mendeley desktop software version 1.19.8.

2.7 – Data extraction

Data extraction consisted of the following for each study; lead author and date, aspects of study design including trial type, exercise mode, duration, frequency and length of intervention and control group activities. Participant characteristics were sample size, age, sex, pharmacotherapy and classification criteria. Mean / standard deviation for all outcome measures pre and post intervention were extracted for both exercise group and comparator, along with statistical analysis procedures.

2.8 – Bias assessment

Methodological quality of studies was assessed independently by two researchers using the Physiotherapy Evidence Database (PEDro) Scale. Based on the Delphi list,[20] the PEDro scale is evidenced to be a valid quality assessment tool for physical therapy and exercise trials.[21] The PEDro scale is a checklist of 10 questions pertaining to internal validity, assessing factors such as randomisation, blinding, key outcomes and intention-to-treat analysis, with a further item considering external validity not included in the final calculation. A higher PEDro score indicates greater quality. Items 5 (subject blinding) and 7 (assessor blinding) were deemed non-applicable within the present study given the nature of the intervention, therefore a score of 8 was considered highest quality and lowest risk of bias.

2.9 – Data analysis

A systematic evaluation was undertaken involving factors such as study characteristics, methodology and individual study results, followed by meta-analysis. Quantitative

analysis involved calculation of mean pre to post intervention changes for each study and outcome. This method was chosen in preference to comparison of final values to remove between-person variability. Changes in standard deviation were calculated by applying an imputed correlation coefficient followed by sensitivity analysis. Where reported, median values were analysed as mean. For studies that contained two relevant exercise groups and a suitable comparator, exercise group scores were combined with the formula presented in the Cochrane Handbook of Systematic Reviews.[22]

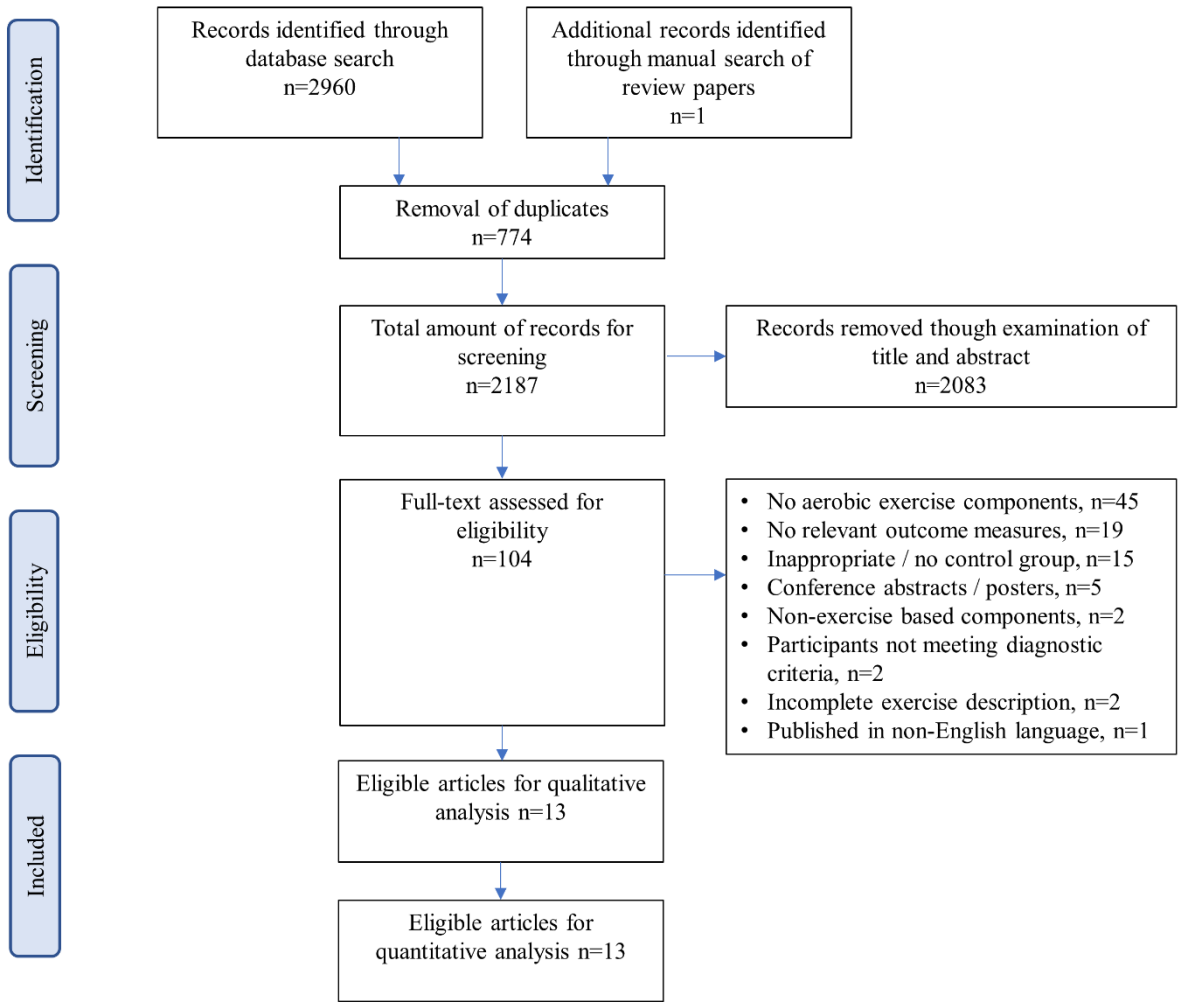
Meta-analysis was undertaken for all outcomes with pooled data using an inverse variance weighting method (one divided by the standard error squared) with a fixed effects model. This established weighted mean differences (WMD) and 95% confidence intervals (95% CI) between exercise and control groups. A fixed effects model was chosen a-priori due to expected clinical homogeneity (similar participants and outcome measures). RevMan version 5.4 was used to perform statistical analysis and produce forest plots, with $P < 0.05$ considered statistically significant. I^2 values (%) were calculated and interpreted according to the thresholds suggested in the Cochrane Handbook of Systematic Reviews;[22] 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% substantial heterogeneity and 75% to 100% considerable heterogeneity. Heterogeneity was further explored using subgroup analysis to establish potential effects of comparator and exercise programme duration. Sensitivity analysis was undertaken by repeating meta-analyses with a random effects model for main outcomes CRP, ESR and BASDAI, and also by removing studies with high risk of bias. Publication bias was assessed with visual funnel plot examination.

3 – Results

3.1 – Study identification and selection

2960 articles were identified through database searches, and one additional article was identified from manual searches of retrieved review papers. Following removal of duplicates, 2187 articles were screened. 104 underwent full text examination after reviewing titles and abstracts, with 13 original articles meeting inclusion criteria for qualitative and quantitative analysis. A PRISMA flow chart of literature identification, screening and reasons for exclusion can be seen in Figure 1.

Figure 1 – Flow diagram of literature identification, inclusion and reasons for exclusion



3.2 – Study / participant characteristics (Table 1)

Of the 13 included articles, 10 were randomised controlled trials,[23-32] two were non-randomised controlled trials,[33,34] and one was a randomised pilot study with exercise and control group allocation.[35] Six studies involved aerobic exercise uniquely in the

form of aerobic walking[29], running,[26,31] swimming / aerobic walking,[23] running / Nordic walking,[25] and exergaming.[30] Three studies combined aerobic exercise (high-intensity interval training [HIIT]),[32,35] and walking / cycling / swimming[28]) with strengthening exercises, while one study[27] combined aerobic aquatic and flexibility exercises. The remaining studies combined aerobic exercise (treadmill running,[24,33] and cycling / aerobic walking[34]) with both strengthening and flexibility exercises. Non-aerobic rehabilitative control groups comprised of usual care / treatment, no intervention and / or physiotherapy. Seven studies[23,26-29,31,33] included structured physiotherapy / range of movement exercises within the control group. All studies reported measurements of the BASDAI, while five included measurements of CRP[26,28,29,32,35] and four ESR.[28,29,32,35] Biomarker measurement procedure was described in three studies,[29,32,35] with blood samples undertaken according to "laboratory policy"[32] or "standard techniques,"[29] with one study[35] reporting undertaking ESR measurements with the Westergren method. One study[35] reported taking blood samples between 14 and 48 hours after final exercise, and two after four hours of fasting.[32,35]

Duration of exercise programmes ranged from three weeks to three months, with the most common duration being 12 weeks. Exercise duration and frequency ranged between 30 minutes twice weekly[26] to 60 minutes five times weekly.[27] Aerobic exercise intensity was monitored in eight studies[23,26,28,29,31-33,35] ranging between 55-85%[31] and 90-95% (interval protocol)[32,35] maximum heart rate. All exercise programmes were described as supervised either fully or in part, generally by qualified physiotherapists, with compliance to unsupervised elements commonly monitored through telephone communication or participant logs. Exercise programmes took place in a variety of settings including homes,[24,28,33,34] hospitals,[34,35] fitness centres,[32,33] swimming

pools[23,27,28] and unspecified outdoor locations.[23,26,29]

Studies involved 727 participants, of which exercise groups consisted of 366, and control groups 361. The minimum study sample size was 19 participants[28] (nine exercise, 10 controls), while the maximum was 106 participants[26] (53 exercise, 53 controls). Pharmacotherapy received by participants included tumour necrosis factor inhibitor therapy in ten studies,[24-27,29-32,34,35] disease modifying anti-rheumatic drugs in six,[23,25,27-30] and non-steroidal anti-inflammatory drugs in eight.[25,27,28,30-33,35] Two studies,[29,31] also included participants receiving corticosteroid treatment. Only two studies[32,35] included participants meeting the Axial Spondyloarthritis and AS criteria, with the remaining the modified New York criteria. All studies included both male and female participants, with a higher percentage of female participants in three studies.[31,32,35]

Table 1 – Study characteristics

Study				Participants				Intervention		
Author, date	Type	PEDro Quality score	Outcomes	Group allocation, number, mean age (SD)	Gender ratio % female	Medical therapy	Classification criteria	Exercise type / intensity	Duration / frequency / setting	Comparator
Karapolat et al. 2009	RCT	5	BASDAI	EG 1: n=13, 50.2 (±12.4) EG 2: n=12, 46.9 (±13.4) CG: n=12, 48.4 (±9.5)	EG 1, 27.0 EG 2, 70.4 CG, 66.7	DMARDS	NYC	EG1 - Freestyle swimming. EG2 - Aerobic walking (60-70% HR max)	6 weeks, 30 minutes thrice weekly. Pool / outdoor	Usual care with ROM
Gunendi et al. 2010	NRCT	4	BASDAI	EG: n=16, 45.6 (±12.4) CG: n=16, 43.4 (±12.0)	EG, 18.8 CG, 31.3	NSAIDS	NYC	Treadmill (60-80% HR max), strengthening, flexibility	3 weeks, 5 times weekly. Gym / home	Physiotherapy
Masiero et al. 2011	RCT	6	BASDAI	EG: n=20, 47.5 (±18.0) CG: n=22, 47.5 (±12.6)	EG, 25.0 CG, 18.2	TNF-I	NYC	Cycling / treadmill running and walking strengthening and flexibility	2 months, 60 minutes twice weekly. Home + unspecified setting	No intervention
Kjeken et al. 2013	RCT	6	BASDAI	EG: n=46, 49.4 (±10.3) CG: n=49, 48.6 (±9.4)	EG, 21.7 CG, 46.9	NSAIDS DMARDS TNF-I	NYC	Moderate – high intensity interval running / walking	3 weeks, 2 hours thrice weekly. Unspecified setting	Usual treatment
Niederman et al. 2013	RCT	7	CRP / BASDAI	EG: n=53, 50.1 (±11.9) CG: n=53, 47.6 (±12.4)	EG, 36.0 CG, 36.0	29% TNF-I	NYC	Cardiovascular training – Aerobic walking (65-85% HR max)	12 weeks, 30 mins, twice weekly. Outdoor	Usual care / ROM

Dundar et al. 2014	RCT	7	BASDAI	EG: n=35, 42.3 (±11.3) CG: n=34, 43.1 (±11.7)	EG, 16.7 CG, 20.7	NSAIDS DMARDS TNF-I	NYC	Aerobic aquatic exercises / ROM	4 weeks, 60 minutes 5 times weekly. Pool	Physiotherapy
Hsieh et al. 2014	RCT	6	CRP / ESR / BASDAI	EG: n=9, 36.2 (±11.7) CG: n=10, 42.1 (±8.8)	EG, 50.0 CG, 42.9	NSAIDS DMARDS	NYC	Fast walking, swimming, cycling, (50-80% VO2 peak) + strengthening	3 months, 5 times weekly. Home / pool	ROM
Masiero et al. 2014	NRCT	5	BASDAI	EG: n=22, 49.1 (±11.8) CG: n=23, 46.2 (±10.3)	EG, 20.0 CG, 9.1	TNF-I	NYC	Cycling / walking strengthening and flexibility	6 weeks, 60 minutes twice weekly. Home / unspecified setting	Usual treatment
Sveass et al. 2014	RPS	6	CRP / ESR / BASDAI	EG: n=10, 46.6 (±13.6) CG: n=14, 49.9 (±11.1)	EG, 80.0 CG, 29.0	NSAIDS TNF-I	ASAS	High intensity interval training (90-95% HR max, 4x4 minute bouts interspersed with 3 minutes active rest) + 1 day endurance	12 weeks, 50 minutes, thrice weekly. Hospital	Usual treatment
Jennings et al. 2015	RCT	7	CRP / ESR / BASDAI	EG: n=35, 42.9 (±9.9) CG: n=35, 40.2 (±9.3)	EG, 34.6 CG, 52.1	CS DMARDS TNF-I	NYC	Aerobic walking (anaerobic threshold heartrate)	12 weeks, 80 mins, thrice weekly. Outdoor	Usual care / ROM

Karahan et al. 2016	RCT	6	BASDAI	EG: n=28, 36.1 (±12.4) CG: n=29, 36.6 (±11.3)	EG, 25.0 CG, 30.4	NSAIDS DMARDS TNF-I	NYC	Aerobic "Exergaming"	8 weeks, 30 minutes, 5 times weekly. Unspecified setting	No intervention
Basakci et al. 2020	RCT	4	BASDAI	EG: n=17, 46.6 (±11.9) CG: n=14, 42.9 (±11.1)	EG, 52.9 CG, 71.4	NSAIDS TNF-I CS	NYC	Treadmill running (55-80% HR max)	12 weeks, 40 minutes thrice weekly. Unspecified setting	Usual care with ROM
Sveaas et al. 2020	RCT	7	CRP / ESR / BASDAI	EG: n=50, 45.1 (±11.5) CG: n=50, 47.2 (±11.3)	EG, 50.0 CG, 56.0	NSAIDS TNF- I	ASAS	High intensity interval training (90-95% HR max, 4x4 minute bouts interspersed with 3 minutes active rest) + 1 day running / cycling	3 months, 50 minutes thrice weekly. Hospital / fitness centre	Usual care

Abbreviations: RCT – Randomised controlled trial; NRCT – Non-randomised controlled trial; RPS – Randomised pilot study; PEDro – Physiotherapy evidence database; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; CRP – C-reactive protein; ESR – Erythrocyte sedimentation rate; EG – Exercise group; CG – Control group; NSAIDS – Non-steroidal anti-inflammatory drugs; DMARDS – Disease modifying anti-rheumatic drugs; TNF-I – Tumour necrosis factor inhibitor; CS – corticosteroid;; NYC – New York criteria; ASAS – Axial spondyloarthritis and ankylosing spondylitis criteria; ROM – Range of Motion

3.3 – Quality assessment; PEDro scale (Table 2)

Overall, four studies were rated as having low risk of bias (7-8 points),[26,27,29,32] seven as having moderate risk (5-6 points)[23-25,28,30,34,35] and two studies as having high risk (0-4 points).[31,33.] The most common methodological limitations were lack of genuine intention-to-treat analysis (defined as all participants initially allocated to groups were included in statistical analysis) and lack of therapist blinding. Additionally, three studies[23,25,31] failed to obtain key outcomes for 85% of participants, while three did not conceal group allocation.[31,33,34] All studies showed no significant participant differences at baseline for either outcome, and included point estimates and variability in the form of mean and standard deviation or median and range / inter-quartile range. Only one study[33] did not undertake between group statistical comparisons. Further common study limitations included lack of a-priori power calculation for the sample size, potentially increasing the possibility of type II error, while studies commonly failed to control for external exercise participation. Generally, study quality did not vary with publication date. Overall, evidence was deemed to be of moderate to good quality, with a mean PEDro score of 5.8 / 8.

Table 2 – PEDro scale quality assessment

Table to show itemised study quality assessment using the PEDro quality scale. 0 = item not present; 1 = item present; N/A = non-applicable. Higher total scores indicate lower risk of bias.

	Eligibility Specified †	Randomised	Allocation concealed	Comparable at baseline	Subjects blinded ‡	Therapist blinded	Assessor blinded §	Key outcomes obtained for 85%	Intention to treat analysis	Between group comparisons	Point estimates and variability	Total / 8
Karapolat et al. 2009	Yes	1	1	1	N/A	0	N/A	0	0	1	1	5
Gunendi et al. 2010	Yes	0	0	1	N/A	0	N/A	1	1	0	1	4
Masiero et al. 2011	Yes	1	1	1	N/A	0	N/A	1	0	1	1	6
Kjeken et al. 2013	Yes	1	1	1	N/A	0	N/A	0	1	1	1	6
Niederman et al. 2013	Yes	1	1	1	N/A	0	N/A	1	1	1	1	7
Dundar et al. 2014	Yes	1	1	1	N/A	0	N/A	1	1	1	1	7
Hsieh et al. 2014	Yes	1	1	1	N/A	0	N/A	1	0	1	1	6
Masiero et al. 2014	Yes	0	0	1	N/A	0	N/A	1	1	1	1	5

Sveass et al. 2014	Yes	1	1	1	N/A	0	N/A	1	0	1	1	6
Jennings et al. 2015	Yes	1	1	1	N/A	0	N/A	1	1	1	1	7
Karahan et al. 2016	Yes	1	1	1	N/A	0	N/A	1	0	1	1	6
Basakci et al. 2020	Yes	1	0	1	N/A	0	N/A	0	0	1	1	4
Sveass et al. 2020	Yes	1	1	1	N/A	0	N/A	1	1	1	1	7

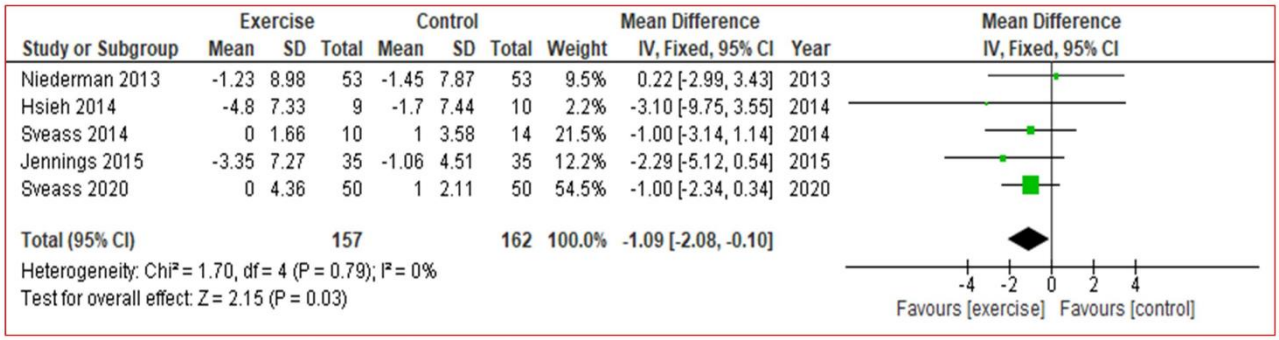
† Item 1 not included in final score calculation / ‡ Non-applicable for exercise interventions / § BASDAI – self-report outcome measure / biomarkers

3.4 – Effect of exercise on inflammatory biomarkers

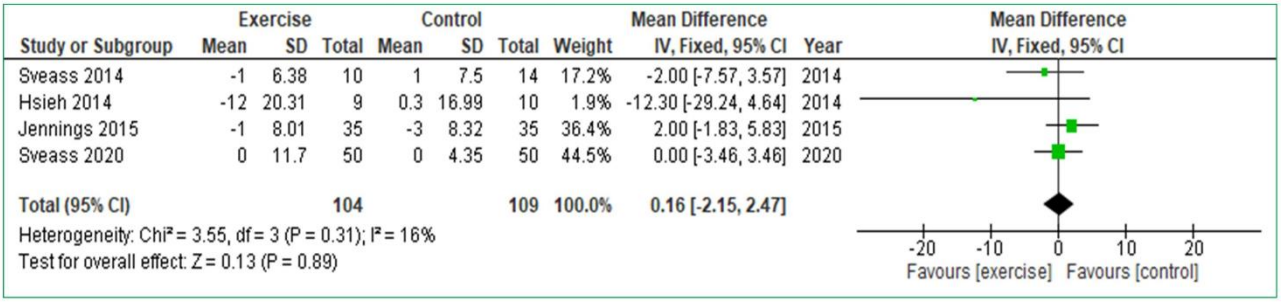
Only one study[32] reported a beneficial effect of exercise programmes on CRP compared to a control group (usual care [median difference -1 mg/l, p=0.041]) following analysis of covariance. No studies reported improvements in ESR; although universally neither CRP nor ESR were exacerbated. All five studies scored at least 6 / 8 on the PEDro scale, indicating the evidence regarding biomarkers to be of good quality. Meta-analysis was undertaken to explore the effects of exercise on CRP and ESR (Figure 2). Results indicated a significant effect of exercise on CRP (WMD: -1.09; 95% CI: -2.08 to -0.10; p=0.03; n=5), but no significant effect on ESR (WMD: 0.16; 95% CI: -2.15 to 2.47; p=0.89; n=4).

Figure 2 – Meta analysis: Effect of exercise on CRP and ESR

CRP



ESR



3.5 – Effect of exercise on self-assessed disease activity - BASDAI

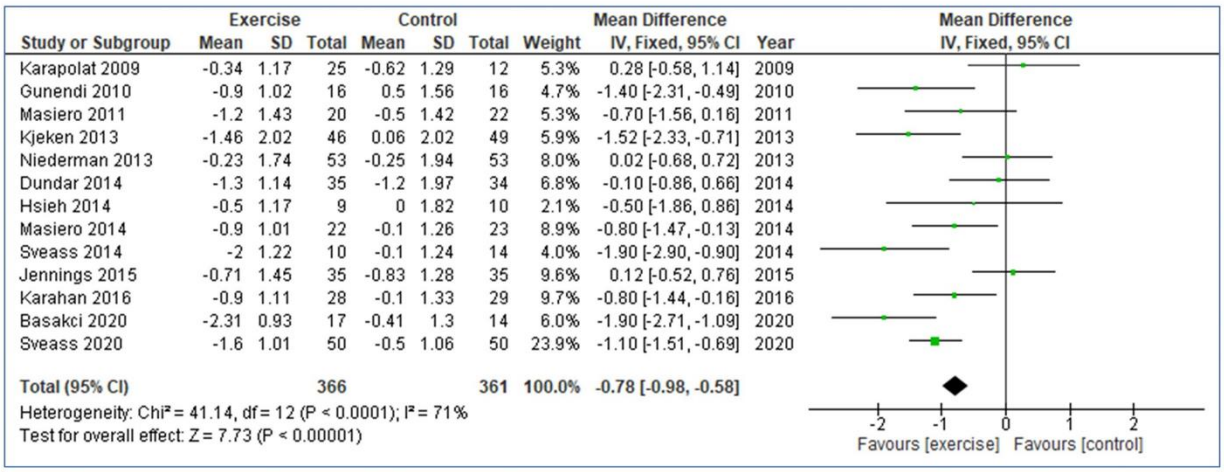
Of the 13 studies reporting pre and post intervention measures of the BASDAI, five[25,30-32,35] evidenced improvements compared to non-aerobic rehabilitation. One study with two parallel exercise groups[23] reported improvements in group 1 (swimming), compared to controls, but not group 2 (aerobic walking). However, when combined there was no significant improvement. Meta-analysis (Figure 3) evidenced that exercise programmes with aerobic components reduced BASDAI scores (WMD: -0.78; 95% CI: -0.98 to -0.58; $p<0.001$; n=13) compared to non-aerobic rehabilitation. Substantial study heterogeneity was observed ($I^2=72\%$, $p<0.001$).

3.5.1 – BASDAI subgroup analysis

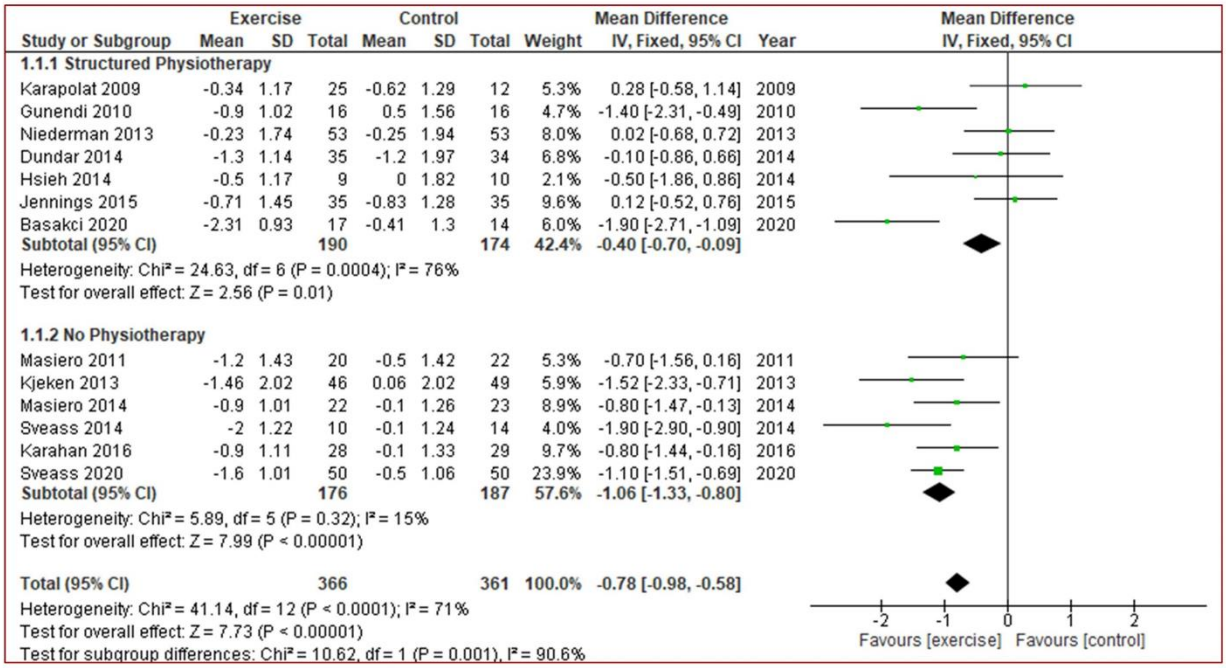
BASDAI comparator subgroup analysis (Figure 3) suggested a statistically significant subgroup effect (I^2=90.6%; p=0.001) indicating exercise training programmes yielded greater BASDAI improvements compared to no physiotherapy (usual care / treatment / no intervention) than to structured physiotherapy. Although exercise training programmes showed BASDAI improvements against both comparators, exercise compared to no physiotherapy demonstrated improvements of near clinical significance (WMD: -1.06; 95% CI: -1.33 to -0.80; p<0.001; n=6). Unexplained substantial heterogeneity (I^2=76%; p=0.0004) remained within the structured physiotherapy comparator group. Further analysis evidenced no subgroup effect for programme duration (<12 weeks / ≥12 weeks [I^2=0%; p=0.55]), although significant heterogeneity remained in both subgroups (Appendix B).

Figure 3 – Meta analysis: Effect of exercise on the BASDAI / BASDAI subgroup analysis – comparator

BASDAI



BASDAI subgroup analysis – comparator (structured physiotherapy v no physiotherapy)



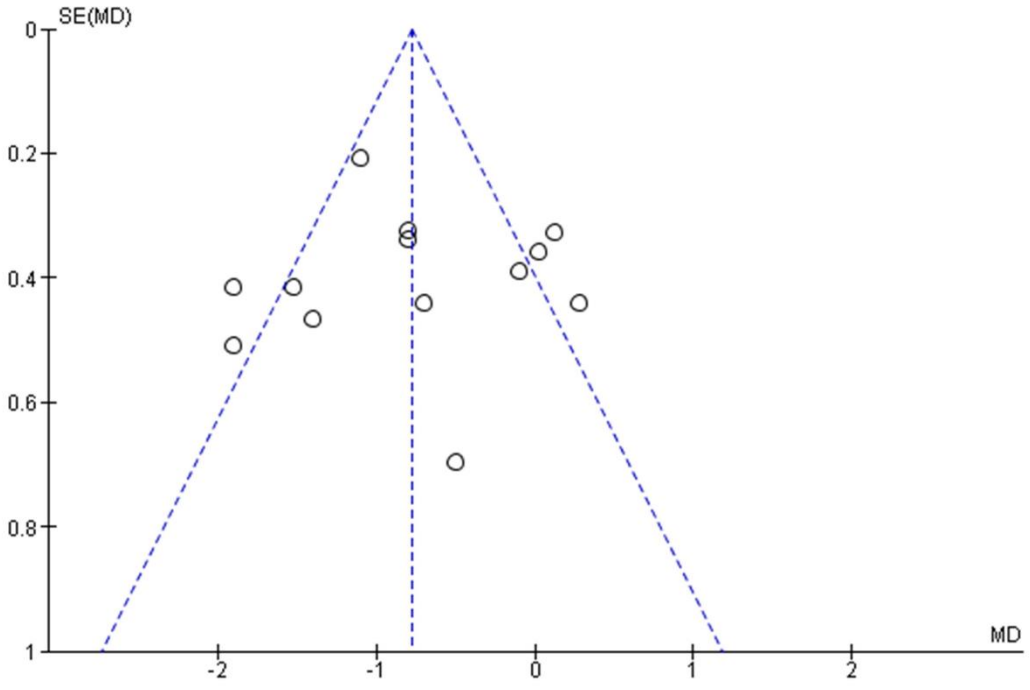
3.6 – Sensitivity analysis

Repeated meta-analysis with a random effects model was undertaken for main outcomes CRP, ESR and the BASDAI. Results evidenced larger confidence intervals in the presence of study heterogeneity than the fixed effects model. However, the inference from results was similar for both methods. Additionally, BASDAI meta-analysis was repeated, removing studies deemed to be at high risk of bias. Results indicated a reduced, but still significant effect of exercise (WMD: -0.66; 95% CI: -0.88 to -0.44; $p<0.001$; n=10).

3.7 – Publication bias

Visual funnel plot analysis (Figure 4) demonstrated no asymmetry that would indicate publication bias.

Figure 4 – Funnel plot to evaluate publication bias



4 – Discussion

This study provides evidence that exercise training programmes with aerobic components reduce CRP and self-assessed disease activity in people with AS, compared to non-aerobic rehabilitation. Similar reductions however were not evidenced in ESR.

CRP / ESR

Despite four out of five studies not evidencing significant improvements,[26,28,29,35] pooled data meta-analysis revealed that aerobic exercise programmes significantly reduced levels of CRP in people with AS. These results are congruent with studies involving healthy populations[10,36] that have evidenced aerobic exercise training related CRP reductions. However, results contrast previous meta-analyses of people with AS, [13,14,15] that combined a variety of exercise training modalities and found no CRP improvements. Therefore, the inclusion of only programmes with aerobic components would appear to be of importance. A single aerobic exercise session can stimulate acute transient increases in the plasma levels of inflammatory cytokines such as Interleukin-6 (IL-6)[36]. IL-6 is considered to be an important stimulus for the hepatic synthesis of CRP[37] and is highly associated with the pathogenesis of inflammatory conditions.[38] However, long-term aerobic exercise training is theorised to reduce both this acute inflammatory response, and also IL-6 basal levels.[36] Perandini et al[39] examined the inflammatory effects of a 12-week aerobic exercise programme in people with systemic lupus erythematosus. It was found that exercise training reduced resting levels of IL-6, tumour necrosis factor alpha and interleukin-10, and blunted acute inflammatory responses. Within the same population, Barnes et al.[40] evidenced that levels of pro-inflammatory cytokines were lower in more physically active patients. Whilst this evidence is of importance to people with inflammatory conditions, it is unclear whether

exercise related reductions in inflammatory cytokines were a consequence of ameliorated underlying pathological mechanisms, or other factors such as reduced adipose tissue.[37] With regard to AS, current evidence of the effects of aerobic exercise on IL-6 is limited, but constitutes a valuable area for further research.

It should also be noted, that due to ambiguous reporting of blood sample collection timing in studies within this review, acute cytokine responses could have influenced post-intervention CRP and ESR measurements. Acute inflammatory responses can take up to six days to return to baseline following exercise.[36] Therefore, any premature measurements could have led to erroneous results.

Additionally, aerobic exercise modality could have partially counterbalanced potential anti-inflammatory mechanisms. All five studies that measured inflammatory outcomes included either increased intensity walking or treadmill running. Increased mechanical stress has been evidenced to induce spondyloarthritis in tumour necrosis factor transgenic models,[41] and could possibly play a role in the onset and inflammatory progression of human spondyloarthritis.[42] Non-weight bearing aerobic exercise training programmes such as swimming, therefore, could offer even greater anti-inflammatory benefit. Interestingly, one study[23] that compared both swimming and aerobic walking to a control group, evidenced self-assessed disease activity improvements in only the aquatic group. Unfortunately however, inflammatory measurements were not also undertaken.

Despite the reductions in CRP, similar improvements in ESR were not found. However, similar discordance between CRP and ESR has been evidenced in people with various inflammatory health conditions, attributed to differences in cytokine stimulation and factors such as gender, adiposity, smoking and alcohol consumption.[43]

Furthermore, while regular physical activity in the general population has been consistently negatively correlated with CRP, this relationship with ESR has yet to be convincingly established.[44] Congruently, interventional exercise studies with both healthy and clinical populations have generally reported inconclusive results regarding the effects of exercise on ESR.[37]

BASDAI

This study also revealed BASDAI improvements of near clinical significance.[19] As an evidenced positive correlate of inflammatory biomarkers[9], improvements could have been a consequence of reduced CRP. However, due to only one study[32] evidencing improvements in both BASDAI and CRP, it should be considered that a number of additional factors could have been influential. Aerobic exercise has been evidenced to reduce fatigue in people with rheumatoid arthritis, theorised to be a result of increased aerobic capacity.[45] As aerobic capacity is integral to physical fitness and human functioning, the consequent reduction in fatigue would appear to be a justifiable hypothesis. However, studies that measured both aerobic capacity and the BASDAI in people with AS[26,28,29,31,32,35] did not universally report contemporaneous improvements. Therefore, more evidence is required to substantiate this potential association. Additionally, aerobic exercise has been theorised to reduce pain and fatigue in people with AS through stimulated interaction between opioid and serotonergic mechanisms, thereby promoting analgesia,[46] while changes in existing comorbidities such as fibromyalgia or ulcerated colitis could also have been influential.

BASDAI reductions could also have been influenced by exercise improving general wellbeing through affective response. Relevant hypotheses in this area include improved capacity to cope with stressful situations,[47] and opportunities for social

interaction and enjoyment.[48] Subgroup analysis indicating no dose response for exercise programme duration would appear to substantiate these psychological hypotheses. In agreement, previous reviews[13-15] have commonly evidenced BASDAI improvements following various exercise modes, durations and intensities. It would seem possible therefore, that BASDAI improvements may not be solely dependent on exercise mode or dose, but simply participation. Furthermore, comparator analysis evidenced greater improvements in participants not undertaking structured physiotherapy sessions. As physiotherapy has been evidenced to reduce BASDAI measurements in people with AS, possibly through the reduction of functional impairment,[49] exercise having a lesser effect on people already undertaking this form of rehabilitation is unsurprising. It is encouraging however, that aerobic exercise appears to offer additional benefit.

Study limitations

This study provides the most specific evidence to date regarding the effects of aerobic exercise training on CRP and the BASDAI in people with AS. However, more explicit conclusions regarding mode, duration and intensity cannot be delineated due to methodological heterogeneity, combined exercise programmes and relative paucity of literature. Particularly, the number of studies within this review that measured inflammatory parameters was limited. Nevertheless, these studies were all deemed to be of low risk of bias, indicating the evidence to be good quality. Additionally, the inclusion of the BASDAI as a measure of disease activity could be debated, due to the generally accepted susceptibility of self-reported outcome measures to various forms of bias including selective recall and social desirability.

Implications for clinical practice

BASDAI improvements of near clinical significance along with CRP reductions

indicate that aerobic exercise training should be considered for people with AS, although the mechanisms by which these benefits occur are not yet clearly defined. Given that cardiovascular disease is an associated comorbidity of AS,[4] and that aerobic exercise has been evidenced to reduce cardiovascular risk factors in healthy populations,[50] the prescription of aerobic exercise as an adjuvant therapy would seem to be of importance. However, whilst results of this study are encouraging with regard to the safety of this form of exercise training, preceding examination of potential adverse effects and events should be undertaken.

Implications for future research

Methodologically sound studies are required to evidence the effects of differing aerobic exercise training modes, intensities and durations, including non-weight bearing exercise on inflammatory markers and clinical parameters. To this end, due to the encouraging, as yet limited evidence of the effects of HIIT on people with AS,[32,35] future research would be advised to further examine the potential benefits of this form of exercise. Additionally, studies examining the potential mechanisms by which aerobic exercise can reduce inflammation in people with AS are recommended.

5 – Conclusion

Exercise training programmes with aerobic components reduced CRP and improved self-assessed disease activity in people with AS. More quality studies are required to examine the effects of differing aerobic exercise modes, intensities and durations to further elucidate these benefits.

Conflicts of interest

None to declare.

References

1. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N. Engl. J. Med. 2016 Jun 30;374(26):2563-74.
2. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology. 2014 Apr 1;53(4):650-7.
3. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007 Apr 21;369(9570):1379-90.
4. Szabo SM, Levy AR, Rao SR, Kirbach SE, Lacaille D, Cifaldi M, Maksymowych WP. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: A population-based study. Arthritis Rheum. 2011 Nov;63(11):3294-304.
5. Exarchou S, Lie E, Lindström U, Askling J, Forsblad-d'Elia H, Turesson C, Kristensen LE, Jacobsson LT. Mortality in ankylosing spondylitis: results from a nationwide population-based study. Ann. Rheum. Dis. 2016 Aug 1;75(8):1466-72.
6. Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X, Qiu G, Cao X, Weng X. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019 Aug 5;7(1):1-6.
7. de Vries MK, van Eijk IC, van der Horst-bruinsma IE, Peters MJ, Nurmohamed MT, Dijkmans BA, Hazenberg BP, Wolbink GJ. Erythrocyte sedimentation rate, C-reactive protein level, and serum amyloid A protein for patient selection and monitoring of anti–tumor necrosis factor treatment in ankylosing spondylitis. Arthritis. Care. Res. 2009 Nov 15;61(11):1484-90.

8. Garrett SL, Kennedy LG, Whitelock HC, Jenkinson T, Gaisford P, O'hea J, Calin A. A new approach to defining disease status in as-the Bath Ankylosing-Spondylitis Disease-Activity Index (BASDAI). Brit. J. Rheumatol. 1993 Jan 1 (vol. 32, pp. 23-23). Walton street journals dept, Oxford, England OX2 6DP: Oxford University Press, United Kingdom.
9. Yildirim K, Erdal A, Karatay S, Melikoglu MA, Ugur M, Senel K. Relationship between some acute phase reactants and the Bath Ankylosing Spondylitis Disease Activity Index in patients with ankylosing spondylitis. South. Med. J. 2004 Apr 1;97(4):350-4.
10. Zheng G, Qiu P, Xia R, Lin H, Ye B, Tao J, Chen L. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. Front. Ageing. Neurosci. 2019 Apr 26;11:98.
11. Kullo IJ, Khaleghi M, Hensrud DD. Markers of inflammation are inversely associated with V^{O2} max in asymptomatic men. J. Appl. Physiol. 2007 Apr 1.
12. Van Der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, Regel A, Ciurea A, Dagfinrud H, Dougados M, van Gaalen F. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann. Rheum. Dis. 2017 Jun 1;76(6):978-91.
13. Hu X, Chen J, Tang W, Chen W, Sang Y, Jia L. Effects of exercise programmes on pain, disease activity and function in ankylosing spondylitis: A meta-analysis of randomized controlled trials. Eur. J. Clin. Invest. 2020 Dec;50(12):e13352.
14. Pécourneau V, Degboé Y, Barnetche T, Cantagrel A, Constantin A, Ruyssen-Witrand A. Effectiveness of exercise programs in ankylosing spondylitis: a

meta-analysis of randomized controlled trials. Arch. Phys. Med. Rehab. 2018 Feb 1;99(2):383-9.

15. Regnaux JP, Davergne T, Palazzo C, Roren A, Rannou F, Boutron I, Lefevre-Colau MM. Exercise programmes for ankylosing spondylitis. Cochrane Db. Syst. Rev. 2019(10).
16. Verhoeven F, Guillot X, Prati C, Mougin F, Tordi N, Demougeot C, Wendling D. Aerobic exercise for axial spondyloarthritis-its effects on disease activity and function as compared to standard physiotherapy: A systematic review and meta-analysis. Int. J. Rheum. Dis. 2019 Feb;22(2):234-41.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372.
18. Tubach F, Pham T, Skomsvoll JF, Mikkelsen K, BjØrneboe O, Ravaud P, Dougados M, Kvien TK. Stability of the patient acceptable symptomatic state over time in outcome criteria in ankylosing spondylitis. Arthrit. Care Res. 2006 Dec 15;55(6):960-3.
19. Kviatkovsky MJ, Ramiro S, Landewé R, Dougados M, Tubach F, Bellamy N, Hochberg M, Ravaud P, Martin-Mola E, Awada H, Bombardier C. The minimum clinically important improvement and patient-acceptable symptom state in the BASDAI and BASFI for patients with ankylosing spondylitis. J. Rheumatol. 2016 Sep 1;43(9):1680-6.
20. Verhagen AP, De Vet HC, De Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of

randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J. Clin. Epidemiol. 1998 Dec 1;51(12):1235-41.

21. Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: a systematic review. Phys. Ther. 2008 Feb 1;88(2):156-75.
22. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019 Sep 23.
23. Karapolat HA, Eyigor S, Zoghi ME, Akkoc YE, Kirazli YE, Keser GÖ. Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study. Eur. J. Phys. Rehabil. Med. 2009 Dec 1;45(4):449-57.
24. Masiero S, Bonaldo L, Pigatto M, Nigro AL, Ramonda R, Punzi L. Rehabilitation treatment in patients with ankylosing spondylitis stabilized with tumor necrosis factor inhibitor therapy. A randomized controlled trial. J. Rheumatol. 2011 Jul 1;38(7):1335-42.
25. Kjeken I, Bø I, Rønningen A, Spada C, Mowinckel P, Hagen KB, Dagfinrud H. A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial. J. Rehabil. Med. 2013 Mar 5;45(3):260-7.
26. Niedermann K, Sidelnikov E, Muggli C, Dagfinrud H, Hermann M, Tamborrini G, Ciurea A, Bischoff-Ferrari H. Effect of cardiovascular training on fitness and perceived disease activity in people with ankylosing spondylitis. Arthritis Care Res. 2013 Nov;65(11):1844-52.

27. Dundar U, Solak O, Toktas H, Demirdal US, Subasi V, Kavuncu VU, Evcik D. Effect of aquatic exercise on ankylosing spondylitis: a randomized controlled trial. Rheumatol. Int. 2014 Nov 1;34(11):1505-11.
28. Hsieh LF, Chuang CC, Tseng CS, Wei JC, Hsu WC, Lin YJ. Combined home exercise is more effective than range-of-motion home exercise in patients with ankylosing spondylitis: a randomized controlled trial. Biomed Res. Int. 2014 Jan 1;2014.
29. Jennings F, Oliveira HA, de Souza MC, da Graça Cruz V, Natour J. Effects of aerobic training in patients with ankylosing spondylitis. J. Rheumatol. 2015 Dec 1;42(12):2347-53.
30. Karahan AY, Tok F, Yıldırım P, Ordahan B, Türkoğlu G, Şahin N. The effectiveness of exergames in patients with ankylosing spondylitis: a randomized controlled trial. Adv. Clin. Exp. Med. 2016;25:931–936.
31. Basakci Calik B, Pekesen Kurtca M, Gur Kabul E, Telli Atalay O, Taskin H, Yigit M, Tasci M, Cobankara V. Investigation of the effectiveness of aerobic exercise training in individuals with ankylosing spondylitis: Randomized controlled study. Mod. Rheumatol. 2021 Mar 4;31(2):442-50.
32. Sveaas SH, Bilberg A, Berg IJ, Provan SA, Rollefstad S, Semb AG, Hagen KB, Johansen MW, Pedersen E, Dagfinrud H. High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients. Br. J. Sports Med. 2020 Mar 1;54(5):292-7.
33. Günendi Z, Dinçel AS, Erdoğan Z, Aknar Ö, Yanpal S, Göğüş F, Atalay F. Does exercise affect the antioxidant system in patients with ankylosing spondylitis?. Clin. Rheumatol. 2010 Oct 1;29(10):1143-7.

34. Masiero S, Poli P, Bonaldo L, Pigatto M, Ramonda R, Lubrano E, Punzi L, Maffulli N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: a controlled clinical trial with a 12-month follow-up. Clin. Rehabil. 2014 Jun;28(6):562-72.
35. Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vøllestad N, Fongen C, Olsen IC, Michelsen A, Ueland T, Aukrust P. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PloS One. 2014 Sep 30;9(9):e108688.
36. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J. Am. Coll. Cardiol. 2005 May 17;45(10):1563-9.
37. Metsios GS, Moe RH, Kitas GD. Exercise and inflammation. Best. Pract. Res. Clin. Rheumatol. 2020 Apr 2:101504.
38. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation. Nat. Rev. Rheumatol. 2015 Feb;11(2):86-97.
39. Perandini LA, Sales-de-Oliveira D, Mello SB, Camara NO, Benatti FB, Lima FR, Borba E, Bonfa E, Sá-Pinto AL, Roschel H, Gualano B. Exercise training can attenuate the inflammatory milieu in women with systemic lupus erythematosus. J. Appl. Physiol. 2014 Sep 15;117(6):639-47.
40. Barnes JN, Nualnim N, Sugawara J, Sommerlad SM, Renzi CP, Tanaka H. Arterial stiffening, wave reflection, and inflammation in habitually exercising systemic lupus erythematosus patients. Am. J. Hypertens. 2011 Nov 1;24(11):1194-200.

41. Jacques P, McGonagle D. The role of mechanical stress in the pathogenesis of spondyloarthritis and how to combat it. Best Pract. Res.: Clin. Rheumatol. 2014 Oct 1;28(5):703-10.
42. Gracey E, Burssens A, Cambré I, Schett G, Lories R, McInnes IB, Asahara H, Elewaut D. Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. Nat. Rev. Rheumatol. 2020 Apr;16(4):193-207.
43. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, Yale SH. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. WMJ. 2016 Dec;115(6):317-21.
44. Alende-Castro V, Alonso-Sampedro M, Vazquez-Temprano N, Tuñez C, Rey D, García-Iglesias C, Sopeña B, Gude F, Gonzalez-Quintela A. Factors influencing erythrocyte sedimentation rate in adults: new evidence for an old test. Medicine. 2019 Aug;98(34).
45. Rongen-van Dartel SA, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van Den Hout WB, van den Ende CH, Neuberger G, Reid A, van Riel PL, Fransen J. Effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis. Arthritis Care Res. 2015 Aug;67(8):1054-62.
46. Lima LV, Abner TS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. J. Physiol. 2017 Jul 1;595(13):4141-50.
47. Weinberg RS, Gould D. Foundations of sport and exercise psychology, 7E. p408 Human kinetics; 2019.
48. Raedeke TD. The relationship between enjoyment and affective responses to exercise. J. Appl. Sport Psychol. 2007 Feb 14;19(1):105-15.

49. Gravaldi LP, Bonetti F, Lezzerini S, De Maio F. Effectiveness of Physiotherapy in Patients with Ankylosing Spondylitis: A Systematic Review and Meta-Analysis. InHealthcare 2022 Jan (Vol. 10, No. 1, p. 132). Multidisciplinary Digital Publishing Institute.
50. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. Front. Cardiovasc. Med. 2019 Jun 4;6:69.

Appendices

Appendix A – PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5,6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	7,8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7,8

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7,8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10
Study characteristics	17	Cite each included study and present its characteristics.	10-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16-18
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	19-22
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	19-22
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	19-22
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	21
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	23
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	23
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	19-22
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	24

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	25,27
	23c	Discuss any limitations of the review processes used.	27
	23d	Discuss implications of the results for practice, policy, and future research.	27,28
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4,5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4,5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A; None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A; None
Competing interests	26	Declare any competing interests of review authors.	28
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix B - Meta analysis: BASDAI subgroup analysis 2 – Programme duration (<12 weeks / ≥ 12 weeks)