Quality of reporting and nature of harms in clinical trials on supervised exercise in patients with rheumatoid arthritis or axial spondyloarthritis

Teuwen, M.M.H.; Vlieland, T.P.M.V.; Weely, S.F.E. van; Schoones, J.W.; Osthoff, A.K.R.; Juhl, C.B.; ... ; Ende, C.H.M. van den

Rheumatology International (2024) 44:25–39
https://doi.org/10.1007/s00296-023-05502-3

Rheumatology
INTERNATIONAL

SYSTEMATIC REVIEW

Quality of reporting and nature of harms in clinical trials on supervised exercise in patients with rheumatoid arthritis or axial spondyloarthritis

Max M. H. Teuwen[1] · Thea P. M. Vliet Vlieland[1] · Salima F. E. van Weely[1] · Jan W. Schoones[2] · Anne-Kathrin Rausch Osthoff[1,3] · Carsten B. Juhl[4,5] · Karin Niedermann[3] · Maaike G. J. Gademan[1,6] · Cornelia H. M. van den Ende[7,8]

Received: 2 October 2023 / Accepted: 25 October 2023 / Published online: 30 November 2023

Abstract

To describe the quality of reporting and the nature of reported harms in clinical studies on the effectiveness of supervised exercises in patients with rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA). We performed a systematic review, searching eight databases up to February 2023. Randomized controlled trials (RCTs) evaluating supervised exercises in adults with RA or axSpA were considered eligible. Data on harms were extracted according to the CONSORT Harms 2022 Checklist. Among others, it was recorded if harms were prespecified or non-prespecified. Moreover, the nature of reported harms was listed. Forty RCTs were included for RA and 25 for axSpA, of which 29 (73%) and 13 (52%) reported information on harms. In 13 (33%) RCTs in RA and four (16%) in axSpA, the collection of harms outcomes was described in the methods section. Prespecified outcomes were reported by eight (RA) and two (axSpA) RCTs. Non-specified harms outcomes were reported by six (RA) and four (axSpA) RCTs. Prespecified harms outcomes included measures of pain, disease activity, inflammation, and structural joint changes. The nature of non-prespecified harms outcomes varied largely, with pain being most common. A considerable proportion of trials on supervised exercise in RA or axSpA does not or inadequately report harms outcomes. Pain was the most commonly reported prespecified or non-specified harm. For a considerate interpretation of the balance between benefits and harms of supervised exercise in RA or axSpA, use of the CONSORT Harms 2022 Checklist for the design, conduct and reporting of trials is advocated.

Keywords Systematic review · Safety · Exercise therapy · Rheumatoid arthritis · Axial spondyloarthritis

✉ Max M. H. Teuwen
m.m.h.teuwen@lumc.nl

Thea P. M. Vliet Vlieland
t.p.m.vliet_vlieland@lumc.nl

Salima F. E. van Weely
s.f.e.van_weelij@lumc.nl

Jan W. Schoones
j.w.schoones@lumc.nl

Anne-Kathrin Rausch Osthoff
rauh@zhaw.ch

Carsten B. Juhl
cjuhl@health.sdu.dk

Karin Niedermann
nika@zhaw.ch

Maaike G. J. Gademan
m.g.j.Gademan@lumc.nl

Cornelia H. M. van den Ende
E.vandenende@maartenskliniek.nl

[1] Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Center, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, The Netherlands

[2] Directorate of Research Policy, Leiden University Medical Center, Leiden, The Netherlands

[3] School of Health Sciences, Institute of Physiotherapy, Zurich University of Applied Sciences, Winterthur, Switzerland

[4] Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

[5] Department of Physiotherapy and Occupational Therapy, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

[6] Department of Clinical Epidemiology, Leiden University Medical Center (LUMC), Leiden, The Netherlands

[7] Department of Research, Sint Maartenskliniek, Nijmegen, The Netherlands

[8] Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands

Introduction

Exercise therapy is a generally proven effective intervention for people with rheumatic and musculoskeletal diseases (RMDs), including those with inflammatory arthritis, such as rheumatoid arthritis (RA) [1, 2], axial spondyloarthritis (axSpA) [3, 4], or both [5]. The reported beneficial effects of exercise therapy in patients with RA or axSpA include improvement of aerobic capacity, muscle strength, and/or overall functional ability, as well as a decrease in pain [1–5]. As such, exercise therapy is included in professional recommendations for the management of RA [6] and axSpA [7]. Despite the documented benefits of exercise therapy, the occurrence of undesired effects, i.e., harms, is also plausible, as exercise therapy could potentially lead to (muscle) pain, exertion, an increase of local or general disease activity or joint damage [8], or to exercise-related injuries. Indeed, anticipated harms or a lack of knowledge on this aspect was found to be barriers for patients to engage in exercise therapy and for professionals to advise or provide it [9, 10]. Previous systematic reviews on the effectiveness of exercise therapy in RA or axSpA concluded that exercise therapy is likely to be safe, although it was noted that safety was scantly described in the selected trials. Indeed, it was noted that there is only a relatively small proportion of trials reporting on any harms outcomes. To advise patients, a thorough insight in the balance between benefits and harms of supervised exercise is needed. For a correct interpretation, it is crucial that both benefits and harms of exercise therapy are adequately documented.

The poor reporting of harms in randomized controlled trials on non-pharmacological care in RMDs was already acknowledged years ago [11]. However, only recently, systematic reviews specifically investigated the potential harms of exercise therapy, based on trials in patients with various conditions including RMDs [12] and osteoarthritis (OA) specifically [13, 14]. The systematic review by Niemeyer et al. [12] included 773 primary trials, 41 of which were done in people with RMDs. They found no increase in risk of serious adverse events (SAEs), but an increase in the risk of non-SAEs related to exercise therapy, concluding that exercise therapy can be recommended as a relatively safe intervention. The two systematic reviews on adverse events (AEs) in hip or knee OA focused on the reporting of harms [13, 14]. It was found that in less than 50% of the 113 trials in knee OA [13] and 14 in hip OA [14], a statement on AEs was included.

The insufficient reporting of harms in trials on exercise therapy is striking as the Consolidated Standards of Reporting Trials (CONSORT) extension for randomized trials of non-pharmacologic treatments, in 2008 [15] and updated in 2017 [16] explicitly mentions the reporting of all important harms or unintended effects in each group. Herewith, it refers to the CONSORT extension for the reporting of harms, first published in 2004 [17] and updated recently [18]. Consistent with the previous version, in the CONSORT Harms 2022 statement, harms are defined as the opposite of benefits, i.e., the totality of possible adverse consequences of an intervention. Key elements of the 2022 update are the distinction between pre-specified and non-specified harms, and the systematic and the non-systematic assessment of harms (i.e., passive or unstructured reporting of harms such as the unprompted self-reporting by participants).

In summary, there is a growing interest in the reporting of harms in trials on exercise therapy in RMDs, yet insight in the quality of reporting and the nature of harms outcomes in trials on the effectiveness of exercise therapy in RA or axSpA is limited. The availability of updated guidelines on the appropriate reporting of harms may help elucidate the areas where the reporting is specifically inadequate. More insights into the specific weaknesses may help improve not only the reporting but also the design and conduct of exercise therapy trials in this field. In addition, insight in the nature of reported harms outcomes might facilitate the development of structured assessments of harms to be used in future trials on the benefits and harms of exercise therapy.

The aims of this systematic literature review are to investigate the quality of reporting on harms outcomes and to describe the nature of reported harms outcomes in studies on the effectiveness of exercise therapy in RA or axSpA patients.

Methods

Study design

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement using those items that were relevant for the research questions in our study [19]. Our study protocol was registered in PROSPERO, an International prospective register of systematic reviews (registered August 29, 2020). Otherwise than described in our study protocol, we decided to restrict our review to studies on the effectiveness on supervised exercise therapy in RA or axSpA, considering two recent systematic reviews about reporting harms outcomes in knee and hip OA [13, 14].

Search strategy

Eligible studies were identified through an search strategy that was developed by a trained librarian (JS) and employed

in a previous systematic review [5] on the effectiveness of exercise therapy and physical activity interventions in RA, axSpA, and knee and hip osteoarthritis (April 2017) (see Supplementary Appendix 1). For the current systematic review, the search was extended with search terms for harms, such as AEs or risk. The final search was performed on February 6, 2023.

The search strategy was developed for PubMed/Medline, using MeSH terms and free text, and then modified for use in Embase (OVID), Web of Science, Emcare (OVID) and PsycINFO (EbscoHOST), Academic Search Premier (EbscoHOST), PEDro, and the Cochrane Library (see Supplementary Appendix 1 for the search strategy details for all databases). This search was intentionally broad with no language or other restrictions being set in order not to miss any potentially relevant studies. The identified records were imported into an application enabling independent selection of publication by multiple reviewers, Rayyan (http://rayyan.qcri.org) by one of the researchers (JS) and duplicates were removed before the start of the study selection [20].

Selection criteria

We included randomized controlled trials (RCTs) comparing an exercise therapy intervention (aerobic, muscle strengthening, range of motion or flexibility, neuromotor (including balance exercises), stretching, or mind–body exercises) with at least six sessions being supervised by a qualified health care professional with a control condition. This criterion of a minimum of six sessions being supervised was deemed appropriate to exclude home-based interventions in combination with a limited number of face-to-face encounters with the therapist for instruction. We included studies that enrolled adult patients with a diagnosis of RA or axSpA and were published in the English language. The diagnostic process may involve clinical assessment or the application of specific classification criteria for RA or axSpA. In the context of axSpA, this approach encompasses both non-radiographic and radiographic forms of the condition. Trials on post-surgical exercise therapy or including patients with multiple diagnoses yet not reporting on RA and axSpA patients separately were not considered eligible. Moreover, studies with a randomized, cross-over design or with randomization on the level of institution (e.g., cluster randomized controlled trials) were excluded.

Selection of studies

The titles and the abstracts identified from the search were subsequently screened for eligibility. First, every record was screened with respect to the inclusion and the exclusion criteria by two of three reviewers (MT, CE, and TVV), independently. Second, the full-text papers of the potentially eligible records were retrieved and screened again independently by two of the three reviewers using the same eligibility criteria. In case a study was reported in multiple publications, information from these publications was taken into account. Publications were considered to be related to the same study based on sample size, recruitment site, general patient characteristics, and/or trial registration number if applicable. Any disagreements on the selection of studies were resolved by discussion among the three researchers.

Data extraction

Data were extracted from the selected studies using a standardized sheet (Supplementary Appendix 2). The data extraction sheet was pilot-tested, and subsequently data extraction from each study was independently performed by two of three reviewers (MT and either CE or TVV). Any disagreements were resolved by discussion among the three researchers. Data extraction was done in two steps, with different levels of detail.

Step 1: general study characteristics, reporting of any harms and details on harms reporting

First, from all the included studies, the following characteristics were extracted for studies on RA and axSpA separately: first author and year of publication, number of treatment arms, and number of patients per treatment arm. If a study was described in multiple papers, the information from the publications other than author and year of publication was combined and, with further references the oldest publication was used.

Moreover, it was recorded if any information on harms was included in the publication (title and abstract, introduction, methods, results (including figures and/or tables), or discussion). For that purpose, multiple terms that were used by authors to label harm outcomes were taken into account, including e.g., harms, side effects, negative effects, AEs, safety, and risk. In addition, outcomes pain, disease activity, inflammation, or radiologic joint damage was considered as potential harms outcomes, but only if the authors explicitly designated these as such in the publication. The same strategy was employed for information on reasons for drop-outs.

In addition to the abovementioned six items recording the presence of any information in specific parts of the publication(s), information on harms outcomes was further extracted using a selection of eight harms-related items from the CONSORT Harms 2022 checklist [18]. The selection of these items was based on their relevance to the specific intervention, i.e., supervised exercise therapy. Thus, in line with the updated and previous version of the CONSORT Harms extension [17, 18], it was recorded whether a hypothesis or study objective regarding harms was formulated. With

regard to data collection, we recorded whether the method and the timing of prespecified and non-prespecified harms outcomes were described and whether active (i.e., collection of harms outcomes by actively asking or assessing) or passive (i.e., collection of harms outcomes by relying on the spontaneously report by study participants or supervisors of exercise therapy) surveillance had taken place [18]. Regarding the results, it was furthermore extracted from the studies whether or not details (timing, duration, or severity) on harms outcomes were presented, and whether the observation of no harms was underpinned by the report on zero events. Finally, for the discussion, it was recorded if a reflection on harms rather than just their mentioning was presented.

Step 2: detailed study characteristics and harms outcomes of a further selection of studies

Second, additional data on the study characteristics (content of intervention and control conditions, intervention duration) and the nature of assessed of harms were extracted in those papers that presented information on harms outcomes in the methods section(s). The rationale for this selection of papers was that, according to the CONSORT Harms checklists, the quality of reporting is mainly determined by the description of the methodology for the ascertainment of harms [17, 18].

Statistical analysis and synthesis

Descriptive analyses were used for the analyses of the extracted information. For each of the 14 items of the list on quality of reporting harms, the proportions of studies meeting that criterion were calculated.

Moreover, any text passages concerning harms outcomes were systematically gathered and documented for studies including relevant information in either the methods or results sections of the manuscript. To ensure data accuracy, the analyses were conducted by MT and checked by CE.

Results

Study selection

The search identified a total of 6903 records. A total of 6722 records were excluded during the initial screening on title and abstract (Fig. 1), with the study pertaining to patients with OA, the intervention not being supervised exercise therapy or a non-randomized study design being the main reasons for exclusion. Of the remaining 181 records, the full-text papers were retrieved. Using the same eligibility criteria, 55 papers reporting on 40 RCTs in RA and 33 papers reporting on 25 RCTs in axSpA were finally included. The characteristics of the 65 selected RCTs and the references to the publications in which they are described are presented in a supplemental table (Supplemental Table 1). From these, the numbers (proportions) of RCTs published in the past 10 years (2013–2023) were 19 (48%) and 19 (76%) in RA and axSpA, respectively.

Quality of reporting on harms

Table 1 shows the quality of reporting about harms outcomes for the 65 selected studies. Most of the included studies reported harm-related information in one or more sections of the manuscript(s): 29 (73%) and 13 (52%) of RCTs in RA and axSpA, respectively.

Title and/or abstract

In 10 (25%) and five (20%) of the studies in RA and axSpA, respectively, harms were addressed in the title and/or the abstract [21–35]. In about half of the cases, this included a specific hypothesis or research aim on harms.

Introduction

Fifteen of the 40 (38%) RA studies and four (16%) of the axSpA studies addressed the issue of harms in the introduction section of the manuscript. A minority of studies (eight (20%) of RA and two (8%) of axSpA studies) included harms outcomes in their objectives [21, 22, 25–30, 36, 37].

Methods

In 13 (33%) of the RA studies and four (16%) of the axSpA studies, the data collection on harms outcomes was described in the methods section [21, 22, 25–32, 36–42]. Of these, eight (20%) of the RA and two (8%) of the axSpA studies reported prespecified harms outcomes [21, 22, 26, 27, 29, 31, 32, 36, 37, 42]. None of the included studies used a prespecified threshold of these outcomes to determine their occurrence in individual patients, but rather evaluated changes in these outcome measures over time on the group level.

Systematic assessment of non-prespecified harms outcomes by means of active surveillance was described in two (5%) RA and one (4%) axSpA studies [38–40]. Active surveillance comprised a planned physical examination by a rheumatologist [38], regular structured assessment of AEs by a nurse [39], or a training diary for the experimental group and a two-weekly assessment of AEs in the control group by phone [40]. Reported methods of passive surveillance comprised asking participants to report to the trial personnel if any AEs occurred [32, 41] or just mentioning that AE were recorded [25, 28–30, 42], and in one of these, a reference to the 2004 CONSORT statement on harms was made [28].

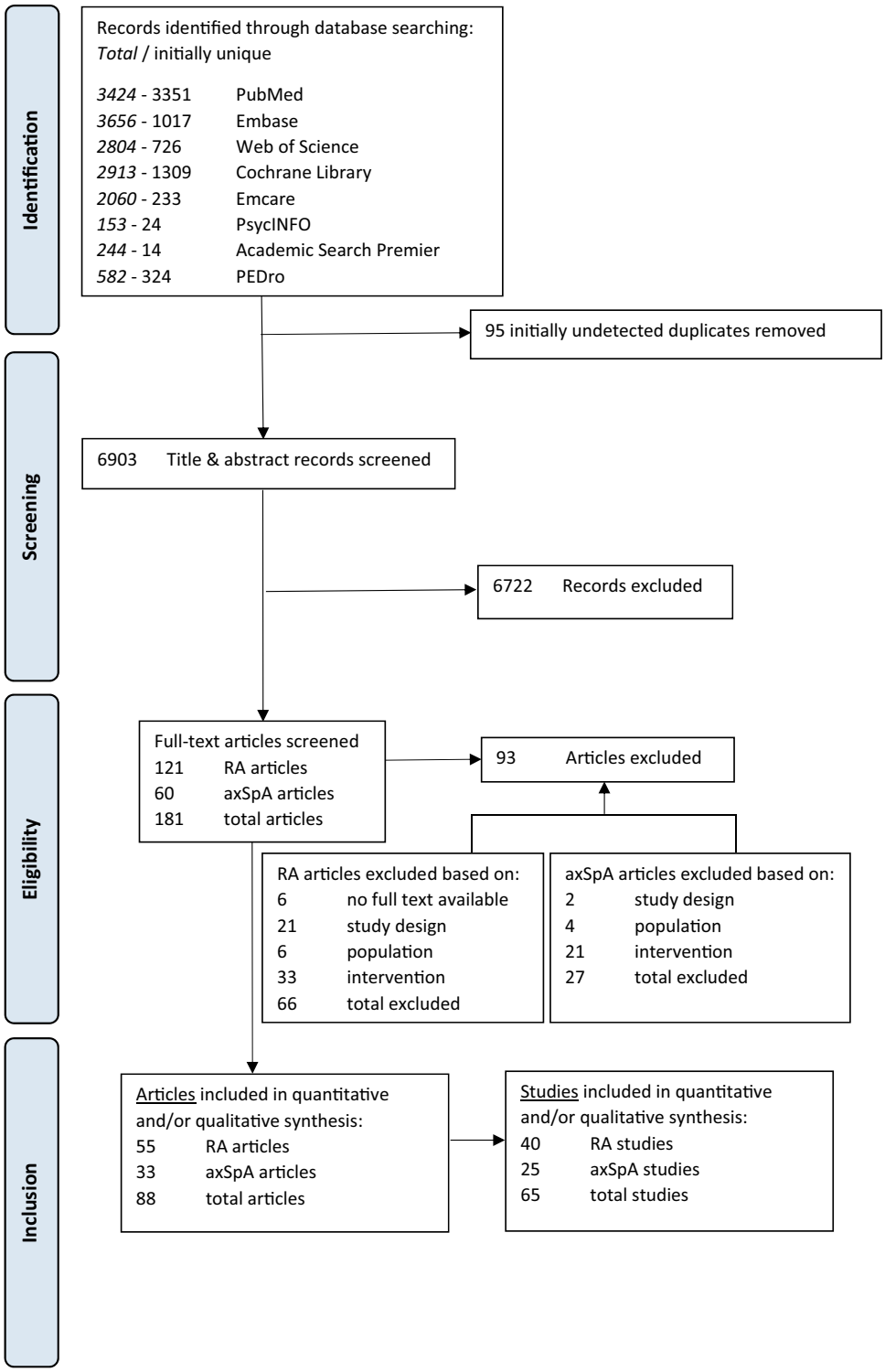

Fig. 1 Flowchart search strategy and screening process

Results and discussion

Information on harms outcomes was included in the results sections (including figures and/or tables) of 18 (45%) of the RA and nine (36%) of the axSpA studies and in the discussion sections of 24 of the RA studies (60%) and eight of the axSpA studies (32%). In some studies, results on harms were only reported in the discussion section [43, 44], whereas some other studies only concluded that the examined intervention was safe without presenting any data [33, 45–47].

Table 1 Quality of reporting of harms outcomes in studies on the effectiveness of supervised exercises in RA or axSpA

Item description[a]		RA ($N=40$) yes, N (%)	axSpA ($N=25$) yes, N (%)
1	**Harms-related information anywhere in the manuscript?**	29 (73)	13 (52)
2	**Harm-related information in the title and/or abstract?**	10 (25)	5 (20)
3	**Harm-related information in the introduction?**	15 (38)	4 (16)
	Specific objectives or hypotheses for harms outcomes?	8 (20)	2 (8)
4	**Information on data collection of harms outcomes in the methods?**	13 (33)	4 (16)
	Prespecified harms outcomes:		
	Method and timing of assessment of harms outcomes described?	8 (20)	2 (8)
	Non-prespecified harms outcomes:		
	Method and timing of systematic assessment (active surveillance[b]) of harms outcomes described?	2 (5)	1 (4)
	Method of passive surveillance of harms outcomes described?	4 (10)	3 (12)
5	**Information on harms outcomes in results section (including figures and/or tables)?**	18 (45)	9 (36)
	Reported details on prespecified harms outcomes?	8 (20)	2 (8)
	Reported details (timing, duration or severity) on non-prespecified harms outcomes?	4 (10)	1 (0)
	Reported information about the number of observed AEs?	16 (40)	7 (28)
6	**Harms-related issues or information in discussion?**	24 (60)	8 (32)
	Reflection on findings on harms outcomes of the study?	19 (48)	2 (8)

Items are derived from the CONSORT Harms statement 2022 [18]

AE adverse event, *RA* rheumatoid arthritis, *axSpA* axial spondyloarthritis

[a]References of all included studies can be found in Supplementary Table 1

[b]Description of data collection of adverse events in the methods section by actively asking or evaluating whether an adverse event occurs

Nature of harms

Table 2 presents the characteristics of the intervention and the nature of harms, of the 17 studies providing sufficient information on the methodology of ascertainment of harms in the methods section. The interventions evaluated in these studies consisted mainly of aerobic and/or muscle strengthening exercises and/or stretching exercises and/or walking exercises, with the exception of one study on hand exercises [32] and one on Tai Chi [25] in RA and one study on Baduanjin Qigong training [30] in axSpA.

Prespecified harms

The description of the methodology for the ascertainment of harms comprised prespecified harms outcomes in the methods section in eight of the 13 selected studies in RA [21, 22, 26, 27, 31, 32, 36, 37] and two of the four studies in axSpA [29, 42]. Prespecified harms predominantly concerned measures of disease activity, pain, and/or biological markers for inflammation. Three studies reported prespecified harms outcome with respect to structural changes (radiographic damage on X-rays, deformity of metacarpal phalangeal joints) [21, 31, 32]. In two studies in axSpA, both from the same author [29, 42], the measurement of harms was described on the individual patient level (absence of a flare-up in disease activity and was defined in terms of stable or decreased self-reported disease activity and acute phase reactants).

Non-prespecified harms

In RA, in six of the 13 selected studies [25, 28, 32, 38, 40, 41], the collection of information on non-prespecified harms was reported. In one study, this was done in combination with the collection of prespecified harms [32]. In two of these six studies [38, 40], active surveillance and in four other passive surveillance were employed. In axSpA, in all four studies reporting on harms outcomes in the methods section [29, 30, 39, 42], the collection of non-prespecified harms was reported. In two of these studies [29, 42], this was combined with the collection of prespecified harms. In one of these four studies [39], active surveillance and in three passive surveillance were reported.

In the five studies reporting on AEs in the intervention group [25, 29, 30, 38, 41], the nature of the following types of non-prespecified AEs in the intervention group was reported: musculoskeletal pain, joint swelling, flare-up, nausea, flue/cold/influenza (more than one study); fall,

Table 2 Description of the methods of collection and nature of harms outcomes and observed results of those studies reporting the collection of harms outcomes in the methods section

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Rheumatoid arthritis ($N=13$)						
Mckenna et al. 2021 [41]	Walking-based exercise ($n=12$); advice on the benefits of exercise ($n=12$)	8	–	–	*Passive surveillance* Participants were advised to seek medical assistance if there was AEs during the intervention e.g., flare-up, fall, or if the participant feels unwell. Primary safety outcomes included the type and frequency of AEs	No SAEs related to the intervention Nature of AEs reported: Musculoskeletal pain (intervention and control groups), RA flare-up (intervention and control groups), nausea (intervention and control groups), cold/flu (intervention and control groups), chest infection (intervention and control groups), fall (intervention and control groups)
Ward et al. 2018 [28]	Group and home-based yoga ($n=13$); usual care ($n=13$)	8	–	–	*Passive surveillance* Primary safety outcomes included the type and frequency of AEs (Ioannidis et al. 2004)	No SAEs were related to the study AEs reported: musculoskeletal pain (intervention and control groups), nausea (intervention group), RA flare-up (intervention and control groups), flu (intervention and control groups), neuralgia (intervention and control groups), surgery (intervention and control groups), infection (control group)
Siqueria et al. 2017 [38]	Water-based (WB) exercise ($n=33$); land-based (LB) exercise ($n=33$); no (C) exercise ($n=34$)	16	–	–	*Active surveillance* The recording of concomitant medications and AEs was performed every 8 weeks by the rheumatologist during the clinical evaluations. For the definition of AE and SAEs international recommendations were followed	SAEs during intervention period: cerebrovascular accident (LB), death (LB) AEs during intervention period: worse due to pain or joint swelling (LB and C), depression (C), morning stiffness (WB, LB, C), low back pain (WB, LB, C), nonrestorative sleep (C), hypertension (WB, LB), influenza (WB)

Table 2 (continued)

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Lamb et al. 2015 [32, 55–57][a]	Hand exercise program ($n=246$); Usual care ($n=244$)	12	Disease activity measures (*N* of tender and swollen joints, degree of joint deformity of MCP joints scored at baseline, 4 and 12 months)	No differences between groups	*Passive surveillance* SAEs (death, life-threatening events, hospitalization, medical intervention, and disability) and AEs reported by clinicians, researchers, or participants were recorded by therapists, research clinicians or participants and classified as related, unrelated, and possibly related to treatment	SAEs were reported, but none were regarded as related to treatment: death (control group), life-threatening condition (Intervention and control group), hospital admission (Intervention and control groups), needing medical intervention (Intervention and control groups), disability accounted for by flares of RA (Intervention and control groups), transient exacerbation of arm pain (intervention group)
Strasser et al. 2011 [27]	Strength and endurance training ($n=20$); stretching exercises ($n=20$)	26	Measures of disease activity (laboratory markers (CRP, ESR), medication, DAS, pain), assessed after intervention	No changes in ESR and CRP. Disease activity and pain decreased in intervention group	–	–
Hsieh et al. 2009 [26]	Supervised aerobic exercise ($n=15$); home-exercise ($n=15$)	8	Severity and extent of arthritis (pain, physician global assessment, laboratory tests), assessed before and after intervention	Intervention group improved in pain and disease activity; no differences between groups	–	–
Lemmey et al. 2009 [40, 58][a]	Progressive resistance training ($n=18$); range of movement training ($n=18$)	24	–	–	*Active surveillance* A training diary was maintained by all patients so that compliance and AEs could be evaluated; additionally, control patients were phoned every two weeks	No training-related injuries or other AEs were reported by subjects in either group
Wang et al. 2008 [25]	Tai Chi exercises ($n=10$); stretching and wellness education ($n=10$)	12	–	–	*Passive surveillance* AEs were recorded	There were no AEs associated with Tai Chi or education and stretching training during the 12-week study period

Table 2 (continued)

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
De Jong et al. 2003 [21, 59–63][a]	Supervised group exercise ($n=158$); usual care ($n=151$)	104	Primary end point of safety was radiographic damage of the large joints (at 12 and 24 months), secondary end point was disease activity (DAS) assessed every 3 months by blinded assessors	No difference in radiographic damage between groups; but a trend toward more damage in the intervention group was observed. Decrease in disease activity in both groups	–	–
Van den Ende et al. 2000 [22]	Intensive exercise program ($n=34$); conservative exercise program ($n=30$)	4	Disease activity (number tender of swollen joints, ESR, pain, evaluated at admission, 3, 6, 12 and 24 weeks after admission by blinded assessor	Decline in disease activity measures in both groups, no significant differences between groups. Pain at 3 weeks was higher in intervention group	–	–
Lyngberg et al. 1994 [37]	Progressive interval training ($n=12$); no training ($n=12$)	12	46 joints were examined for soft tissue swelling, tenderness, and pain during motion and laboratory assessments (ESR); assessed by rheumatologist 2 weeks before and after training	Insignificant changes in disease activity in both groups, but number of swollen joints decreased significantly in intervention group	–	–
Baslund et al. 1993 [36]	Physical training program ($n=9$); no training ($n=9$)	8	Monokines, ESR, CRP	No increases observed	–	–
Hansen et al. 1993 [31]	Self-training ($n=14$); Training in physiotherapy practice ($n=14$); Group training ($n=14$); Group training + Pool ($n=13$); No training ($n=13$)	104	Duration of morning stiffness, number of swollen joints, joint pain, medical treatment, ESR; assessed by physician every 3 months. X-ray every 12 months	No statistical differences between groups	–	–
De Jong et al. 2003 [21, 59–63][a]	Supervised group exercise ($n=158$); usual care ($n=151$)	104	Primary end point of safety was radiographic damage of the large joints (at 12 and 24 months), secondary end point was disease activity (DAS) assessed every 3 months by blinded assessors	No difference in radiographic damage between groups; but a trend toward more damage in the intervention group was observed. Decrease in disease activity in both groups	–	–

Table 2 (continued)

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Van den Ende et al. 2000 [22]	Intensive exercise program ($n=34$); conservative exercise program ($n=30$)	4	Disease activity (number tender of swollen joints, ESR, pain, evaluated at admission, 3, 6, 12 and 24 weeks after admission by blinded assessor	Decline in disease activity measures in both groups, no significant differences between groups. Pain at 3 weeks was higher in intervention group	–	–
Lyngberg et al. 1994 [37]	Progressive interval training ($n=12$); no training ($n=12$)	12	46 joints were examined for soft tissue swelling, tenderness, and pain during motion and laboratory assessments (ESR); assessed by rheumatologist 2 weeks before and after training	Insignificant changes in disease activity in both groups, but number of swollen joints decreased significantly in intervention group	–	–
Baslund et al. 1993 [36]	Physical training program ($n=9$); no training ($n=9$)	8	Monokines, ESR, CRP	No increases observed	–	–
Hansen et al. 1993 [31]	Self-training ($n=14$); training in physiotherapy practice ($n=14$); group training ($n=14$); group training + Pool ($n=13$); no training ($n=13$)	104	Duration of morning stiffness, number of swollen joints, joint pain, medical treatment, ESR; assessed by physician every 3 months. X-ray every 12 months	No statistical differences between groups	–	–
Axial spondyloarthritis ($N=4$)						
Sveaas et al. 2019 [29, 64–66][a]	High-intensity aerobic and strength exercises ($n=50$); usual care ($n=50$)	12	Safety was considered as absence of disease flare-ups after the intervention period, defined as stable or decreased disease activity assessed by ASDAS, BASDAI, CRP, and ESR	All measures (except CRP and ESR) improved statistically significant in favor of the intervention group	*Passive surveillance*: AEs reported by the physiotherapists	AEs reported during exercise in intervention group: Chest pain and nausea Persistent pain
Xie et al. 2019 [30]	Baduanjin qigong training ($n=30$); no training ($n=30$)	12	–	–	*Passive surveillance* All AEs were required to be recorded and reported to the researchers in the intervention and control group	No SAEs were reported by the patients during the observation period Patients in the Baduanjin qigong group reported Mild muscle ache in the thigh and crus during the first 2 weeks of treatment

Table 2 (continued)

Author and publication year	Description of study arms	Duration intervention (weeks)	Prespecified harms outcomes		Non-prespecified harms outcomes	
			Method of collection of harms outcomes	Results on harms outcomes	Method of collection of harms outcomes	Results on harms outcomes
Fang et al. 2016 [39]	Supervised exercise and home-based exercise ($n=24$); home-based exercise ($n=20$)	26	–	–	*Active surveillance* Patients were followed up by telephone by a nurse every two weeks to complete questions on outcomes including AEs	Not described
Sveaas et al. 2014 [42, 67][a]	Endurance and strength training ($n=13$); usual care ($n=15$)	12	Safety was considered as absence of a flare-up in disease activity defined as stable or decreased self-reported disease activity (ASDAS and BASDAI) and acute phase reactants (CRP and ESR)	Increase in ASDAS in two patients of the intervention group On group level decrease in ASDAS in the intervention groups. No differences in CRP and ESR between groups	*Passive surveillance* The report of any AE was included in the definition of safety	Explicit statement that no AEs were observed

AE adverse event, *ASDAS* The Ankylosing Spondylitis Disease Activity Score, *BASDAI* The Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *DAS* Disease Activity Score, *ESR* erythrocyte sedimentation rate, *MCP* metacarpophalangeal joints, *SAE* serious adverse event

[a]Studies comprises of multiple articles. The main article that was first published was used and the other articles are referred to in the references

neuralgia, surgery, morning stiffness, low back pain, hypertension, chest infection, and chest pain (one study).

Discussion

This systematic literature review found that about 50–75% of studies on the effectiveness of supervised exercise therapy in RA or axSpA included any information on harms outcomes in the related manuscript(s). Of these, the majority did not further specify how harms outcomes were defined or monitored. Thus, the majority of the RCTs on the effectiveness of supervised exercise therapy in RA or axSpA lacks detail and consistency of reporting on harms that is imperative to make an accurate evaluation of harms of exercise therapy. Consequently, considering the findings of our review, to date, there is too little information to allow firm conclusions about the absence or the presence of harms of supervised exercise therapy for patients with RA or axSpA.

The issue of poor quality of reporting harms outcomes is well recognized in the literature for pharmacological as well as non-pharmacological interventions in RMDs. Ethgen et al. [11] concluded already in 2005 that the reporting of harms in published randomized, controlled trials of pharmacologic and non-pharmacologic treatment for RA and hip or knee OA was suboptimal and that harms outcomes were less often described less in reports of non-pharmacologic as compared to pharmacologic treatment trials. More recently, two systematic reviews [13, 14] on harms outcomes of exercise therapy in hip and knee OA concluded that less than half of trials included a statement on harms outcomes, in which the proportion is even lower than those observed in the present study. The two latter reviews also concluded that in many trials, the reasons for dropping out were, if applicable, not classified as AEs. The recommendation of the CONSORT 2022 Harms to describe reasons and timing for discontinuation, including if related to participants experiencing harms, might overcome this omission in future.

Remarkably, the number of studies reporting on harms outcomes in the results or discussion sections exceeded the number of studies with harms-related information in the methods section, whereas only a few trials explicitly formulated one or more research questions on harms outcomes. This finding indicates that although authors have failed to address harms according to the reporting guidelines, they are well aware of the relevance of potential harms of exercise therapy. A possible explanation for this inconsistency in reporting on harms is that for some outcomes, exercise therapy can have both positive and negative effects, particularly with respect to disease activity and pain levels [48–51]. In many studies included in our review, the outcomes on disease activity or pain were well defined and systematically assessed and presented, however without any reference to

whether or not they were considered as harms outcomes. In all of these cases, the results were presented on group level. While this approach provides valuable information on the impact of exercise therapy either positive or negative, it is possible that it may mask or overlook episodes of increased disease activity or pain experienced by individual patients in all study arms as possible harm. These effects might have occurred during the trial period but were not adequately captured. To address this issue, it is advisable to establish predetermined thresholds for disease activity measures and pain levels that are considered unacceptable and should be labeled as harm outcomes [18]. By specifying these cut-off points in advance, researchers can better identify and report on any AEs experienced by individual participants during exercise therapy interventions.

In addition to the unclarity about the interpretation of outcomes that were well described and systematically evaluated but not specifically designated as harms outcomes, a number of studies provided results on non-prespecified AEs, but did not mention their planned assessment in the method section. This observation may indicate that reports on harms outcomes in studies on the effectiveness of exercise therapy relatively often rely on spontaneous, self-reported AEs from participants without specific prompting. Although that reporting is in accordance with the guidelines on reporting of exercise therapy interventions such as the Consensus on Exercise Reporting Template (CERT) [52], in exercise therapy trials, the systematic assessment in all study arms is needed. Participants in the non-active study arms might also experience AEs related to non-therapeutic exercising or during the performance of daily activities. Moreover, study arms may vary in terms of participant interaction with trial personnel, which may also include varying intensities of supervision when different exercise therapy interventions are compared [52]. Furthermore, in case of a non-exercise control arm, both trial personnel and participants in the experimental arm(s) may be more inclined to attribute negative effects to the intervention. Thus, an imbalance in the opportunity to report AEs can introduce potential biases and limitations when comparing harm outcomes across different groups and potentially leading to an overestimation of harms in treatment groups.

The results of this review suggest that there is ample room to enhance the quality of harm assessment in studies on the effectiveness of supervised exercise therapy in RA or axSpA. In particular, there is a need for systematic approaches to capture harms outcomes including participant-reported AEs in all study arms [53]. Prespecifying harm outcomes is crucial as it helps researchers to systematically assess and capture any negative effects that may arise from the intervention [54]. Our inventory of the nature of harms could be used as a starting point for a consensual list of harms outcomes that should be prespecified in trials on the effectiveness of supervised exercise therapy in RA or axSpA. Prespecified harms outcomes could encompass, among others, episodes of increased disease activity, severe pain or fatigue, intensification of (pain) medication, and radiological progression in case of longstanding interventions. Structured questionnaires, and regular and consistent monitoring throughout the study duration in all study arms allow comprehensive evaluation of potential harms of exercising and provide a more balanced understanding of its potential risks and benefits. For that purpose, consensus on a set of recommended harms outcomes for exercises, both generic and for specific rheumatic conditions, is needed. By employing rigorous and standardized methods, researchers can minimize bias and ensure a more accurate evaluation of harm outcomes.

Due to the overall poor reporting of harms in the selected studies on exercise therapy interventions in inflammatory arthritis, the potential association between the patients' disease characteristics and the occurrence of harms could not be explored. To address this issue, studies that adequately report on the occurrence, nature, and severity of harms as well as potential risk factors are needed.

This review has some limitations we would like to address. First, we only included studies in English language, resulting in potential missed studies in other languages that could be relevant. Second, in our study, we focused on interventions in which the exercise sessions were all, or at least for a substantial part, supervised. Thereby, the results may not be generalizable to home-based exercise programs. Third, with the quality of reporting of harms in exercise trials in OA already being addressed, we focused on two types of inflammatory RMDs. Therefore, it remains to be established to what extent our findings are generalizable to other forms of RMDs such as fibromyalgia. Finally, we presented only details of harms outcomes from studies describing data collection methods in the methods section(s) of the related paper(s). Although this allows an appropriate interpretation of the presented findings, this policy could have influenced the overview of the nature of harms outcomes we presented.

In summary, this systematic review found that the reporting on harms in RCTs on supervised exercise therapy in inflammatory arthritis is generally insufficient. Although the non-systematic assessment of harms outcomes, such as self-reported participant feedback in the intervention group(s) can offer valuable information in exercise therapy trials, it should be interpreted cautiously. Variations in study arm supervision and participant interaction may have an impact on reporting of harms, introducing potential biases. To improve the assessment of harm outcomes in studies on the effectiveness of exercise therapy, consensus on the most relevant harms outcomes in exercise therapy trials in RMDs, including prespecified thresholds where applicable, is recommended. Moreover, a better implementation of existing

recommendations on the assessment and reporting of harms outcomes during the design, conduct, and reporting of studies is needed. This will help ensure more reliable and robust evaluations of the balance between harms and benefits of exercise therapy in future research.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-023-05502-3.

Author contributions All authors have made substantial contributions to this project, spanning the conception, design, data acquisition, analysis, data interpretation, and/or the development of new software crucial to our work. MMHT, TPMVV, SFEW, JS, A-KRO, CBJ, KN, MGJG, and CHME made substantial contributions to the conception and design. MMHT, TPMVV, JWS and CHME made substantial contributions to the search strategy and selection of studies. MMHT, TPMVV and CHME have made significant contributions to the data extraction and analysis and interpretation of the data. Additionally, all authors were involved in drafting the manuscript and critically revising it to ensure the inclusion of important intellectual content. They have collectively approved the final version for publication. Moreover, the authors have agreed to be accountable for their respective roles in all aspects of the project, demonstrating their commitment to addressing any inquiries related to the accuracy or integrity of any part of the work with appropriate investigation and resolution. All authors take full responsibility for the integrity and accuracy of all aspects of their work.

Funding This project is financially supported by the Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport), The Netherlands; the Netherlands Organisation for Health Research and Development (ZonMw; Project Numbers: 852004018, 852004019); the Dutch Arthritis Society (ReumaNederland); the Royal Dutch Society for Physical Therapy (Koninklijk Nederlands Genootschap voor Fysiotherapie KNGF).

Data availability The data supporting this article will be made available upon reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no known conflicts of interest.

References

1. Ye H, Weng H, Xu Y, Wang L et al (2022) Effectiveness and safety of aerobic exercise for rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. BMC Sports Sci Med Rehabil 14:17. https://doi.org/10.1186/s13102-022-00408-2
2. Hu H, Xu A, Gao C et al (2021) The effect of physical exercise on rheumatoid arthritis: An overview of systematic reviews and meta-analysis. J Adv Nurs 77:506–522. https://doi.org/10.1111/jan.14574
3. Regnaux JP, Davergne T, Palazzo C et al (2019) Exercise programmes for ankylosing spondylitis. Cochrane Database Syst Rev 10:CD011321. https://doi.org/10.1002/14651858.CD011321.pub2
4. Ortolan A, Webers C, Sepriano A et al (2023) Efficacy and safety of non-pharmacological and non-biological interventions: a systematic literature review informing the 2022 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. Ann Rheum Dis 82:142–152. https://doi.org/10.1136/ard-2022-223297
5. Rausch Osthoff A-K, Juhl CB, Knittle K et al (2018) Effects of exercise and physical activity promotion: meta-analysis informing the 2018 EULAR recommendations for physical activity in people with rheumatoid arthritis, spondyloarthritis and hip/knee osteoarthritis. RMD Open 4:e000713. https://doi.org/10.1136/rmdopen-2018-000713
6. England BR, Smith BJ, Baker NA et al (2023) 2022 American College of Rheumatology Guideline for Exercise, Rehabilitation, Diet, and Additional Integrative Interventions for Rheumatoid Arthritis. Arthritis Rheumatol 75:1603–1615. https://doi.org/10.1002/acr.25117
7. Ramiro S, Nikiphorou E, Sepriano A et al (2023) ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 82:19–34. https://doi.org/10.1136/ard-2022-223296
8. de Jong Z, Vliet Vlieland TP (2005) Safety of exercise in patients with rheumatoid arthritis. Curr Opin Rheumatol 17:177–182. https://doi.org/10.1097/01.bor.0000151400.33899.88
9. Veldhuijzen van Zanten JJCS, Rouse PC, Hale ED et al (2015) Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: a review of the literature. Sports Med 45:1401–1412. https://doi.org/10.1007/s40279-015-0363-2
10. Halls S, Law R-J, Jones JG et al (2017) Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis patients. Musculoskelet Care 15:196–209. https://doi.org/10.1002/msc.1157
11. Ethgen M, Boutron I, Baron G et al (2005) Reporting of harm in randomized, controlled trials of nonpharmacologic treatment for rheumatic disease. Ann Intern Med 143:20–25. https://doi.org/10.7326/0003-4819-143-1-200507050-00006
12. Niemeijer A, Lund H, Stafne SN et al (2020) AEs of exercise therapy in randomised controlled trials: a systematic review and meta-analysis. Br J Sports Med 54:1073–1080. https://doi.org/10.1136/bjsports-2018-100461
13. von Heideken J, Chowdhry S, Borg J et al (2021) Reporting of harm in randomized controlled trials of therapeutic exercise for knee osteoarthritis: a systematic review. Phys Ther 101:pzab161. https://doi.org/10.1093/ptj/pzab161
14. James KA, von Heideken J, Iversen MD (2021) Reporting of adverse events in randomized controlled trials of therapeutic exercise for hip osteoarthritis: a systematic review. Phys Ther 101:pzab195. https://doi.org/10.1093/ptj/pzab195
15. Boutron I, Moher D, Altman DG et al (2008) Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 148:295–309. https://doi.org/10.7326/0003-4819-148-4-200802190-00008
16. Boutron I, Altman DG, Moher D et al (2017) CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. Ann Intern Med 167:40–47. https://doi.org/10.7326/M17-0046
17. Ioannidis JP, Evans SJ, Gotzsche PC et al (2004) Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 141:781–788. https://doi.org/10.7326/0003-4819-141-10-200411160-00009
18. Junqueira DR, Zorzela L, Golder S et al (2023) CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. BMJ 381:e073725. https://doi.org/10.1136/bmj-2022-073725
19. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 3:e123–e130. https://doi.org/10.1371/journal.pmed.1000097

20. Ouzzani M, Hammady H, Fedorowicz Z et al (2016) Rayyan-a web and mobile app for systematic reviews. Syst Rev 5:210. https://doi.org/10.1186/s13643-016-0384-4
21. de Jong Z, Munneke M, Zwinderman AH et al (2003) Is a long-term high-intensity safe in patients with exercise program effective and rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum 48:2415–2424. https://doi.org/10.1002/art.11216
22. van den Ende CHM, Breedveld FC, le Cessie S et al (2000) Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 59:615–621. https://doi.org/10.1136/ard.59.8.615
23. Pukšić S, Mitrović J, Čulo M-I et al (2021) Effects of yoga in daily life program in rheumatoid arthritis: a randomized controlled trial. Complement Ther Med 57:102639. https://doi.org/10.1016/j.ctim.2020.102639
24. McMeeken J, Stillmann B, Story I, Kent P (1999) The effects of knee extensor and flexor muscle training on the timed–up–and—go test in individuals with rheumatoid arthritis. Physiother Res Int 4:55–67. https://doi.org/10.1002/pri.1999.4.1.55
25. Wang C (2008) Tai Chi improves pain and functional status in adults with rheumatoid arthritis: results of a pilot single-blinded randomized controlled trial. Med Sport Sci 52:218–229. https://doi.org/10.1159/000134302
26. Hsieh L-F, Chen S-C, Chuang C-C et al (2009) Supervised aerobic exercise is more effective than home aerobic exercise in female Chinese patients with rheumatoid arthritis. J Rehabil Med 41:332–337. https://doi.org/10.2340/16501977-0330
27. Strasser B, Leeb G, Strehblow C et al (2011) The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol 30:623–632. https://doi.org/10.1007/s10067-010-1584-2
28. Ward L, Stebbings S, Athens J et al (2018) Yoga for the management of pain and sleep in rheumatoid arthritis: a pilot randomized controlled trial. Musculoskelet Care 16:39–47. https://doi.org/10.1002/msc.1201
29. Sveaas SH, Bilberg A, Berg IJ et al (2019) High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients. Br J Sports Med 54:292–297. https://doi.org/10.1136/bjsports-2018-099943
30. Xie Y, Guo F, Lu Y et al (2019) A 12-week Baduanjin Qigong exercise improves symptoms of ankylosing spondylitis: a randomized controlled trial. Complement Ther Clin Pract 36:113–119. https://doi.org/10.1016/j.ctcp.2018.12.007
31. Hansen TM, Hansen G, Langgaard AM et al (1993) Longterm physical training in rheumatoid arthritis. a randomized trial with different training programs and blinded observers. Scand J Rheumatol 22:107–112. https://doi.org/10.3109/03009749309099253
32. Lamb SE, Williamson EM, Heine PJ et al (2015) Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 385:421–429. https://doi.org/10.1016/S0140-6736(14)60998-3
33. Altan L, Korkmaz N, Dizdar M et al (2012) Effect of Pilates training on people with ankylosing spondylitis. Rheumatol Int 32:2093–2099. https://doi.org/10.1007/s00296-011-1932-9
34. Cetin SY, Calik BB, Ayanc A, Kabul EG (2020) The effectiveness of 10-Tai Chi movements in patients with ankylosing spondylitis receiving anti-tumor necrosis factor α therapy: a randomized controlled trial. Eur J Integr Med 39:101208. https://doi.org/10.1016/j.eujim.2020.101208
35. Karahan AY, Tok F, Yildirim P et al (2016) The effectiveness of exergames in patients with ankylosing spondylitis: a randomized controlled trial. Adv Clin Exp Med 25:931–936. https://doi.org/10.17219/acem/32590
36. Baslund B, Lyngberg K, Andersen V et al (1993) Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arhtritis. J Appl Physiol 75:1691–1695. https://doi.org/10.1152/jappl.1993.75.4.1691
37. Lyngberg KK, Harreby M, Benizen H et al (1994) Elderly rheumatoid arthritis patients on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehabil 75:1189–1195. https://doi.org/10.1016/0003-9993(94)90003-5
38. Siqueira US, Orsini Valente LG, de Mello MT et al (2017) Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention—the HydRA trial. Am J Phys Med Rehabil 96:167–175. https://doi.org/10.1097/PHM.0000000000000564
39. Fang H, Cai W, Pan Y et al (2016) Six-month home-based exercise and supervised training in patients with ankylosing spondylitis. Int J Clin Exp Med 9:6635–6641
40. Lemmey AB, Marcora SM, Chester K et al (2009) Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 61:1726–1734. https://doi.org/10.1002/art.24891
41. McKenna SG, Donnelly A, Esbensen BA et al (2021) The feasibility of an exercise intervention to improve sleep (time, quality and disturbance) in people with rheumatoid arthritis: a pilot RCT. Rheumatol Int 41:297–310. https://doi.org/10.1007/s00296-020-04760-9
42. Sveaas SH, Berg IJ, Provan SA et al (2014) Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PLoS ONE 30:e108688. https://doi.org/10.1371/journal.pone.0108688
43. Seneca T, Hauge EM, Maribo T (2015) Comparable effect of partly supervised and self-administered exercise programme in early rheumatoid arthritis—a randomised, controlled trial. Dan Med J 62:A5127
44. Gurpinar B, Ilcin N, Savci S, Akkoc N (2021) Do mobility exercises in different environments have different effects in ankylosing spondylitis? Acta Reumatol Port 46:297–316
45. Cima SR, Barone A, Porto JM, Carvalho de Abreu DC (2013) Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int 33:725–732. https://doi.org/10.1007/s00296-012-2447-8
46. Flint-Wagner HG, Lisse J, Lohman TG et al (2009) Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. J Clin Rheumatol 15:165–171. https://doi.org/10.1097/RHU.0b013e318190f95f
47. de Souza MC, Jennings F, Morimoto H et al (2017) Swiss ball exercises improve muscle strength and walking performance in ankylosing spondylitis: a randomized controlled trial. Rev Bras Reumatol 57:45–55. https://doi.org/10.1016/j.rbre.2016.09.009
48. Schünemann HJ, Brennan S, Akl EA et al (2023) The development methods of official GRADE articles and requirements for claiming the use of GRADE—a statement by the GRADE guidance group. J Clin Epidemiol 159:79–84. https://doi.org/10.1016/j.jclinepi.2023.05.010
49. Peter WF, Swart NM, Meerhoff GA et al (2021) Clinical practice guideline for physical therapist management of people with rheumatoid arthritis. Phys Ther 101:pzab127. https://doi.org/10.1093/ptj/pzab127
50. Gensler LS (2016) Physical activity in axial spondyloarthritis-tails from bench to bedside. Clin Rheumatol 35:1443–1445. https://doi.org/10.1007/s10067-016-3264-3
51. Thomas JL (2013) Helpful or harmful? Potential effects of exercise on select inflammatory conditions. Phys Sportsmed 41:93–100. https://doi.org/10.3810/psm.2013.11.2040
52. Slade SC, Dionne CE, Underwood M et al (2016) Consensus on exercise reporting template (CERT): explanation and elaboration

statement. Br J Sports Med 50:1428–1437. https://doi.org/10.1136/bjsports-2016-096651
53. Ioannidis JP (2009) Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med 169:1737–1739. https://doi.org/10.1001/archinternmed.2009.313
54. Mayo-Wilson E, Fusco N, Hong H et al (2019) Opportunities for selective reporting of harms in randomized clinical trials: selection criteria for non-systematic adverse events. Trials 20:553. https://doi.org/10.1186/s13063-019-3581-3
55. Williams M, Williamson EM, Heine PJ et al (2015) Strengthening and stretching for rheumatoid arthritis of the hand (SARAH). A randomised controlled trial and economic evaluation. Health Technol Assess 19:1–222. https://doi.org/10.3310/hta19190
56. Williamson E, McConkey C, Heine P et al (2017) Hand exercises for patients with rheumatoid arthritis: an extended follow-up of the SARAH randomised controlled trial. BMJ Open 7:e013121. https://doi.org/10.1136/bmjopen-2016-013121
57. Hall AM, Copsey B, Williams M et al (2017) Mediating effect of changes in hand impairments on hand function in patients with rheumatoid arthritis: exploring the mechanisms of an effective exercise program. Arthritis Care Res (Hoboken) 67:982–988. https://doi.org/10.1002/acr.23093
58. Lemmey AB, Williams SL, Marcora SM et al (2012) Are the benefits of a high-intensity progressive resistance training program sustained in rheumatoid arthritis patients? A 3-year followup study. Arthritis Care Res (Hoboken) 64:71–75. https://doi.org/10.1002/acr.20523
59. de Jong Z, Munneke M, Zwinderman AH et al (2004) Long term high intensity exercise and damage of small joints in rheumatoid arthritis. Ann Rheum Dis 63:1399–1405. https://doi.org/10.1136/ard.2003.015826
60. de Jong Z, Munneke M, Lems WF et al (2004) Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum 50:1066–1076. https://doi.org/10.1002/art.20117
61. Munneke M, de Jong Z, Zwinderman AH et al (2005) Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. Arthritis Rheum 53:410–417. https://doi.org/10.1002/art.21165
62. van den Hout WB, de Jong Z, Munneke M et al (2005) Cost-utility and cost-effectiveness analyses of a long-term, high-intensity exercise program compared with conventional physical therapy in patients with rheumatoid arthritis. Arthritis Rheum 53:39–47. https://doi.org/10.1002/art.20903
63. de Jong Z, Munneke M, Kroon HM et al (2009) Long-term follow-up of a high-intensity exercise program in patients with rheumatoid arthritis. Clin Rheumatol 28:663–671. https://doi.org/10.1007/s10067-009-1125-z
64. Sveaas SH, Dagfinrud H, Berg IJ et al (2020) High-intensity exercise improves fatigue, sleep, and mood in patients with axial spondyloarthritis: secondary analysis of a randomized controlled trial. Phys Ther 100:1323–1332. https://doi.org/10.1093/ptj/pzaa086
65. Sveaas SH, Dagfinrud H, Johansen MW et al (2020) Longterm effect on leisure time physical activity level in individuals with axial spondyloarthritis: secondary analysis of a randomized controlled trial. J Rheumatol 47:1189–1197. https://doi.org/10.3899/jrheum.190317
66. Bilberg A, Dagfinrud H, Sveaas SH (2022) Supervised intensive exercise for strengthening exercise health beliefs in patients with axial spondyloarthritis: a multicenter randomized controlled trial. Arthritis Care Res (Hoboken) 74:1196–1204. https://doi.org/10.1002/acr.24556
67. Sveaas SH, Berg IJ, Fongen C et al (2018) High-intensity cardiorespiratory and strength exercises reduced emotional distress and fatigue in patients with axial spondyloarthritis: a randomized controlled pilot study. Scand J Rheumatol 47:117–121. https://doi.org/10.1080/03009742.2017.1347276