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One-year effectiveness of long-term exercise therapy in people with axial spondyloarthritis and severe functional limitations

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Abstract

Objective: To evaluate the effectiveness of long-term, personalized, supervised exercise therapy on functional ability compared with usual care in people with axial spondyloarthritis (axSpA) and severe functional limitations.

Methods: Participants were randomly 1:1 assigned to the intervention [maximal 64 sessions, with 14 additional optional sessions of supervised active exercise therapy (e.g. aerobic and muscle strengthening) with individualized goal-setting, education and self-management regarding physical activity] or usual care (care determined by clinician(s) and participants themselves). Primary endpoint was the change in the Patient-Specific Complaints activity ranked 1 [PSC1 (0–10)] at 52 weeks. Secondary endpoints were the PSC activities ranked 2 and 3, the Bath Ankylosing Spondylitis Functional Index, 6-min walk test, Patient Reported Outcome Measurement Information System-Physical Function-10 and the Short Form-36 Physical and Mental Component Summary Score (SF-36 PCS and MCS). Statistical comparisons comprised independent student t-tests and linear mixed models, based on intention-to-treat.

Results: 214 participants [49% female, age 52 (S.D. 12) years], were randomized to the intervention ($n = 110$) or usual care ($n = 104$) group. In the intervention group 93% started treatment, using on average 40.5 sessions (S.D. 15.1). At 52 weeks, the difference in change in PSC1 between groups favoured the intervention group [mean difference (95% CI); −1.8 (−2.4 to −1.2)]. Additionally, all secondary outcomes, except the SF-36 MSC, showed significantly greater improvements in the intervention group with effect sizes ranging from 0.4 to 0.7.

Conclusion: Long-term, supervised exercise therapy proved more effective than usual care in improving functional disability and physical quality of life in people with axSpA and severe functional limitations.

Trial registration: Netherlands Trial Register NL8238, included in the International Clinical Trial Registry Platform (ICTRP) (https://trialsearch.who.int/Trial2.aspx?TrialID=NL8238).

Keywords: spondyloarthritis, physical therapy, physical function, exercise, randomized trial.

Rheumatology key messages

- Long-term supervised exercise therapy improves physical functioning in people with axSpA experiencing severe functional limitations.
- Long-term supervised exercise therapy should be considered for people with axSpA and severe functional limitations.

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Introduction

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease, characterized by inflammation of the spine and sacroiliac joints. Over time, inflammation can lead to structural spinal damage including ankylosis, which can lead to decreased spinal mobility and poor functioning. Primary symptoms of axSpA include (back)pain, pronounced stiffness, sleep problems and fatigue [1, 2]. Peripheral joints, in particular the shoulder and hip joints, may also be affected, whereas extra-musculoskeletal manifestations may occur in the eye, skin or gut [1].

International clinical guidelines for the management of axSpA include both pharmacological and non-pharmacological treatment modalities [3–5]. Pharmacological treatment of people with axSpA includes non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic, target synthetic or biological disease modifying anti-rheumatic drugs (csDMARDs, tsDMARDs, bDMARDS) and/or local glucocorticosteroids. The cornerstones of non-pharmacological treatment are patient education and exercise therapy [3–5]. The recommendations on exercise therapy are based on evidence showing that exercise (e.g. aerobic, muscle strengthening and functional exercises) is an effective intervention improving pain, disease activity, functional ability and axial mobility in people with axSpA [6–11]. Exercise therapy seems to be safe, however, no clear evidence is available as harm outcomes of exercise therapy are poorly reported
[7, 11, 12]. Moreover, no studies were performed on the impact of exercise on the long-term radiographic progression, whereas preclinical research suggests that exercise could contribute to new bone formation [13].

When considering the evidence supporting exercise in axSpA it is critical to acknowledge that, clinical trials assessing the effectiveness of exercise therapy typically tend to exclude people with axSpA who exhibit persistent disease activity, inconsistent medication use, multiple joint replacements and/or comorbidities. Even with the current optimal pharmacological treatment, a significant proportion of the axSpA population experiences inadequate symptom control [14]. A Dutch expert group estimated in 2016 that around 5% to the total population of people with a diagnosis of axSpA experience severe functional ability (i.e. limitations in basic daily activities related to selfcare, transfers and/or mobility indoors or outdoors), possibly jeopardizing their functional independence [15]. Notably, no research specific to this subpopulation could be identified, resulting in a lack of evidence regarding the benefits and harms of exercise therapy for people with axSpA and severe functional limitations.

Due to an unfavourable course of the disease, people with axSpA and severe functional limitations may gain substantial benefits from exercise therapy, provided that it is tailored to the complexity of their individual impairments and functional limitations. Recent guidelines on the management of axSpA underscore the importance of tailored approaches to personalized care [3–5, 10]. Considering the potential variety and evolvement of needs over time due to varying underlying health problems, this particular subgroup requires a long-lasting, specific, personalized approach. Earlier research has shown that a tailored exercise intervention for people with rheumatoid arthritis and severe functional limitations [16], for elderly people with mobility problems [17, 18] and people with knee osteoarthritis and multimorbidity [19] were feasible and effective with respect to physical functioning and pain. However, the efficacy of such a comprehensive, personalized approach in people with axSpA and severe functional limitations remains to be established.

In summary, there is a knowledge gap on the benefits and harms of active exercise therapy in people with axSpA with severe functional limitations. The aim of the study was to evaluate the effectiveness of a long-term, personalized, supervised exercise therapy program on functional ability compared to usual care in a population of people with axSpA and severe functional limitations in daily activities and/or participation.

Methods

Study design

The Longstanding EXercise therapy in axial SPondyloArthritis (L-EXSPA) study was conducted in parallel with a similar study in people with rheumatoid arthritis. The protocol of both studies was published earlier [20]. The L-EXSPA study concerns a 52-week, randomized, assessor-blinded, parallel-group study, with follow-up assessments at 104 or 156 weeks. The study complies with the Declaration of Helsinki and was approved by the Medical Ethical Review Board Leiden-Den Haag-Delft (METC-LDD, NL70093.058.19) and was registered in the Netherlands Trial Register, in the International Clinical Trials Registry Platform (ICTRP, NL8238). This paper presents the primary 52-week results.

Participants

Eligible individuals were adults (aged ≥18 years) with a clinical diagnosis of axSpA as confirmed by their rheumatologist. These individuals experienced self-perceived severe limitations in basic daily activities related to self-care (such as dressing and washing), transfers (including getting in and out of bed, rising from a chair or using the toilet), and/or mobility indoors or outdoors. The limitations were directly or indirectly linked to their axSpA, e.g. being caused by persisting or progressive disease activity despite optimal medical treatment and/or severe ankylosis and/or deformities and/or severe comorbidities (e.g. pulmonary or cardiovascular disease, obesity). Additionally, it was determined that their functional limitations were unlikely to improve or be resolved with a brief exercise therapy intervention. Individuals who had undergone physical therapy in the past three months, or those who were in need for admission to a hospital or rehabilitation centre, were excluded from the study. If a potential participant was undergoing physical therapy but met the other eligibility criteria, he/she could still participate if physical therapy was stopped for a minimum of 3 months.

Randomization

Participants were randomly allocated (1:1) to receive either long-term, personalized exercise therapy or usual care for 52 weeks using randomization software Castor Electronic Data Capture [(EDC), Amsterdam, The Netherlands, 2019]. Randomization was stratified by sex (female/male) and health care insurance coverage of physical therapy (<12 or ≥12 sessions physical therapy) and executed in blocks of varying sizes of 4, 6 or 8. The two researchers responsible for the randomization (WFP, SvW) communicated the allocation to the participants and managed the recruitment and training of intervention physical therapists.

Recruitment and selection procedures

During the recruitment period of 28 months (planned 19 months, plus 9 months elongation due to COVID-19 pandemic) information on the study was disseminated widely. For people with axSpA dissemination occurred through websites, digital newsletters, flyers and (digital)posters; for rheumatologists and clinical nurse specialists via e-mails, and presentations. The Dutch Arthritis Society (ReumaNederland) and local/regional patient organizations supported the dissemination. Information letters were sent to invite possibly eligible people with axSpA in three centres (Reade, Amsterdam; Sint Maartenskliniek, Nijmegen; Leiden Univeristy Medical Center, Leiden). Interested people registered for the study online or via their treating clinician. Eligibility screening, except for the clinical diagnosis of axSpA, was conducted by one of two researchers via telephone interview and subsequently all screening results (presence of functional limitations in specific basic daily activities; the potential relationship of functional limitations with their rheumatic condition or associated comorbidities; likeliness of effect of a short-term intervention, based on the duration of the limitations and previous use of exercise therapy or failure of such an intervention; planned multidisciplinary team intervention or admission to hospital or rehabilitation centre) were discussed with two other members of the research team (experienced physical therapists). In case of doubt consultations were sought with other members of the research team, and, when necessary, communication was established with the patient and/or their treating rheumatologist. Finally, the treating rheumatologist was asked to confirm the diagnosis of axSpA. People meeting all eligibility criteria and providing written informed consent were enrolled.

Intervention and usual care condition

The description of the intervention, a personalized, supervised active exercise therapy lasting 52 weeks, delivered according a standardized protocol, is described in Supplementary Table S1, available at *Rheumatology* online. In summary, the intervention involved an initial assessment, collaborative goal-setting with the patient regarding functional ability, and supervised active exercise therapy with regular monitoring, evaluation and adaptation as needed. The treatment encompassed various exercises (aerobic, muscle strengthening, flexibility/joint range of motion and functional/neuromotor exercises), patient education and promotion of physical activity. A wearable activity tracker was provided to motivate participants to stay active by monitoring their physical activity levels. Physical therapists tailored the intervention to each patient's limitations and health status, following guidelines for exercise dosage [9, 21, 22]. A recommended fixed frequency of two sessions per week for the initial 12 weeks was advised, followed by a decrease to once weekly, totalling 64 sessions, with 14 additional optional sessions based on participants' needs. Physical therapists underwent mandatory training through live training sessions or an e-learning app and were instructed not to treat those in the usual care condition.

Participants in the usual care group received care determined by their clinician(s) and themselves, including regular physical therapy through physician or self-referral, without specific encouragement or discouragement. After 52 weeks, both participants in the intervention and usual care groups had access to the intervention until the end of the study.

Outcome measures

The detailed description of the baseline characteristics and primary and secondary outcome measures are described in Supplementary Table S2, available at *Rheumatology* online. In addition, the treating rheumatologist was asked to provide the following clinical information: year of axSpA diagnosis; radiographic/non-radiographic axSpA; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at time of inclusion. The selection of outcome measures was primarily based on their ability to reflect functional ability on the level of the ICF component 'Activities and Participation' [23]. The primary endpoint was the change in the highest-ranked Patient-Specific Complaints Numeric Rating Scale (PSC1) score [24, 25] at 52 weeks. The PSC consists of the participant's three most limited activities, ranked from 1 to 3, with level of difficulty of each activity scored on a Numeric Rating Score (NRS, anchors 0: easy to 10: impossible to do). Secondary endpoints included measures of physical functioning and quality of life: PSC activities rated as second and third (PSC2 and PSC3), the Patient Reported Outcome Measurement Information System Physical Function-10 (PROMIS PF-10) [26, 27], Bath Ankylosing Spondylitis Functional Index (BASFI) [28, 29] and the 6-min walk test (6-MWT) [30], the Short Form-36 (SF-36) Physical and Mental Component Summary Score (PCS and MCS) [31, 32].

The occurrence of Serious Adverse Events (SAEs) or Adverse Events (AEs) was prospectively recorded in the intervention group by the treating physical therapists. For the purpose of this study, SAEs were defined as events that resulted in death or were life threatening, required hospitalization or resulted in significant or permanent (aggravation of) disability or incapacity and were directly related to the exercise therapy treatment. AEs were defined as unfavourable events directly related to exercise therapy treatment but that were not severe, such as a temporary interruption of the therapy for nausea or a fall without serious injuries. At 52 weeks, participants in the intervention group who had used the intervention and participants in the usual care group who had used physical therapy were asked to complete four questions on two common AEs related to exercise or physical therapy treatment: occurrence of muscle soreness (yes/no), occurrence of fatigue (yes/no) and, if yes, a rating of severity on a scale from 0 to 10 (0 = no—10 = severe muscle soreness/fatigue).

Data collection and blinding

Data on the PSC and the 6MWT were collected at baseline and at 52 weeks, all other outcomes were collected at baseline, 26 and 52 weeks (Supplementary Table S3, available at *Rheumatology* online). Data were collected by electronic questionnaires using the data monitoring system OnlinePROMs® (2020, Interactive Studios BV, Den Bosch, The Netherlands) and through face–face encounters. All data were gathered by two assessors (MT and MvW), who were blinded to the treatment allocation. Participants were instructed to refrain from revealing their allocation to assessors to avoid unblinding. At 52-weeks, researchers documented their inference regarding the participant's group assignment (yes/no).

Statistical analyses

A planned sample of 172 participants was estimated to provide >90% power for testing the superiority of the long-term, personalized exercise intervention versus usual care for the primary endpoint of the PSC at week 52. The assumed

difference was based on a population effect size of 0.5, being an accepted threshold for discrimination for changes in patient reported outcomes in chronic diseases [33]. Power estimations were calculated using a two-sided significance level of 0.05. Taking into account a 20% drop-out rate, 215 people with axSpA and severe functional limitations needed to be included.

Effectiveness analyses were performed according to the intention-to-treat principle, with the allocation only being revealed after completing all analyses. Only measurements performed within a time frame of 6 weeks around the initially planned time points were used in analyses. The mean changes between baseline and 52 weeks in PSC1, PSC2, PSC3 and the 6MWT between the intervention and usual care groups were compared using unpaired Student's *t* test. For the other outcomes, linear mixed models were employed as three time points were available for these outcomes and differences between the groups at these time points were estimated.

In addition, the effect size of the difference in change of the primary and secondary outcome measures between the two groups was determined using Cohen's Effect Size d = (Mean difference intervention group—Mean difference usual care group)/pooled standard deviation (S.D.), the latter calculated with the formula: $\text{S.D.} = \sqrt{[(\text{S.D.}1^2 + \text{S.D.}2^2)/2]}$.

We omitted the intended secondary per-protocol analysis because in the intervention group, the number of attended treatment sessions was likely to be related to a high degree of achieving individual goals. Furthermore, in the usual care group, a variety of factors such as participants' health status or insurance, could influence the use of conventional physical therapy, making it difficult to define per-protocol treatment.

Results

Patient recruitment, randomization and baseline characteristics

A total of 426 individuals were screened for eligibility, of whom 217 met the eligibility criteria and were willing to participate. They were randomly allocated to long-term personalized exercise therapy or usual care. After randomization, one patient in each group immediately withdrew from the study; to reach the intended number of 215 participants two additional participants were randomized. In the usual care group, one patient appeared to have no clinical axSpA diagnosis and was excluded secondarily. This resulted in 110 participants in the intervention group and 104 participants in the usual care group (Fig. 1). Between baseline and 52 weeks, 12 participants were lost to follow-up. One participant in the usual care group deceased, while others were lost to follow-up due to serious deterioration of health conditions other than axSpA, lack of interest, private circumstances or lost contact. At 52 weeks, 3 of the 202 assessments were conducted outside the predefined 6-week time frame. Thus, 101 (92%) participants of the intervention group and 98 (94%) of the usual care group were included in the primary analysis.

The distribution of demographic and disease characteristics was balanced between the intervention and usual care groups (Table 1). Approximately two third of the participants had a BASDAI score >4. Participants experienced high levels of functional limitations as reflected by the BASFI, mean (S.D.) scores were 6.0 (2.1) and 5.9 (1.8) for the intervention and the usual care group, respectively.

Intervention and effectiveness

A total of 102 (93%) participants started the intervention with 117 physical therapists trained for its delivery; in 15 participants two physical therapists were involved. The mean number of treatment sessions was 41 (S.D. 15.1) in these 102 participants. Seven of the 102 participants started their treatment more than 3 months after their inclusion date. Due to a logistical error, two participants (2%) in the usual care group were given access to the intervention before they finished the assessment at 52 weeks (one week too early). Furthermore, in the 52-week study period, 70 (67%) participants in the usual care group had physical therapy other than the designated study intervention.

The blinding was unsuccessful in 16 of the 202 (8%) participants who completed the 52-week assessment. For 126 of the remaining 186 participants (68%) the assessors were able to guess the treatment allocation correctly at 52 weeks.

Primary outcome measure

At week 52, the improvement in PSC1 was statistically significantly greater in the intervention group than in the usual care group (mean difference −1.8 [95%CI −2.4 to −1.2]), the accompanying effect size was 0.8 (Table 1).

Secondary outcome measures

The results of the secondary outcome measures are shown in Table 2. Change scores of the PSC2 [mean difference −1.3 (−1.9 to −0.6)], PSC3 [−1.5 mean difference (−2.2 to −0.8)] and 6MWT [mean difference 30 meter (13–48)] showed statistically significant differences at 52 weeks in favour of the intervention group. Effects size were 0.5 for PSC2, 0.7 for PSC3 and 0.5 for the 6MWT.

The results for the other secondary outcomes assessed at baseline, 26 and 52 weeks are shown in Table 3. There was a statistically significantly improvement favouring the intervention group for the PROMIS PF-10, BASFI and the SF-36 PCS, while there were no differences regarding the changes of the SF-36 MCS. The accompanying effect sizes were 0.6 for the PROMIS PF-10, 0.5 for BASFI, 0.4 for SF-36 PCS and 0.1 for the SF-36 MCS.

Harms

Throughout the 52-week study period, no (S)AEs related to the intervention occurred. In the usual care group, one patient died because of cancer. At 52 weeks, 87% (89 out of 102) of the intervention group participants and 70% (31 out of 44) of the usual care group participants who underwent physical therapy completed questions about muscle soreness and fatigue. Among those who received physical therapy, 76% ($n = 68/89$) of the participants in the intervention group and 70% ($n = 31/44$) of the usual care group reported muscle soreness, while 80% ($n = 71/89$) and 64% ($n = 28/44$), respectively, reported fatigue. The mean severity ratings for muscle soreness were 3.8 (S.D. 2.1) and 4.5 (S.D. 2.4), and 4.6 (S.D. 2.4) and 4.6 (S.D. 2.9) for fatigue in the intervention and usual care groups, respectively.

Discussion

This study assessed the effectiveness of long-term, personalized, supervised exercise programme in people with axSpA and severe functional limitations compared with usual care. The intervention group showed significantly greater

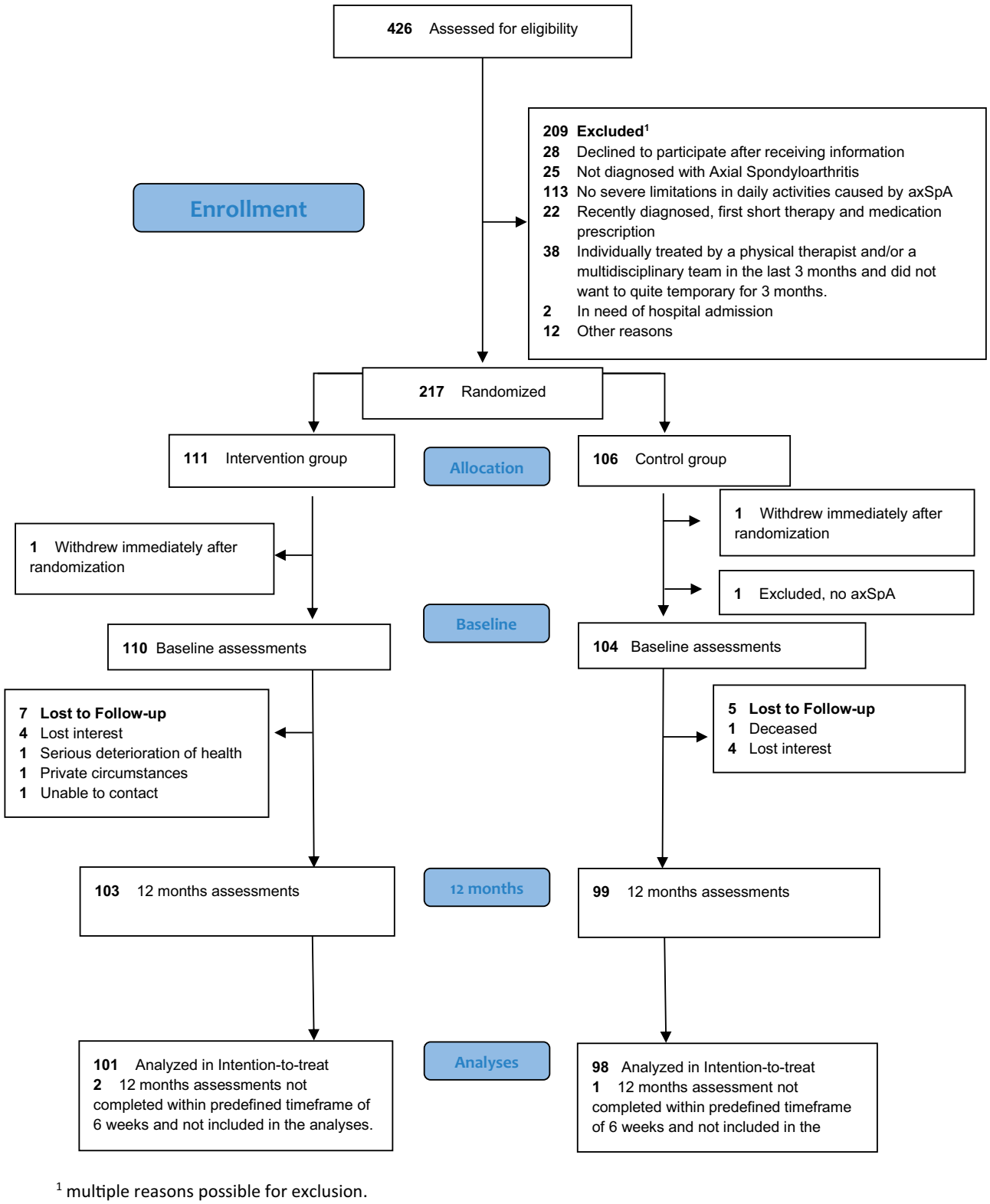

Figure 1. Flowchart

improvements than the usual care group in primary and secondary outcome measures of functional ability and quality of life, with the exception of the SF-36 MCS.

A novelty of our study is our intentional selection of participants with severe functional limitations. This highly-selected population has been omitted from prior research on exercise therapy for axSpA [6, 7, 34], which makes this study a valuable addition to existing evidence. The demographic composition of our study cohort skews towards an older age group with a higher proportion of female participants than other studies into the effectiveness of exercise therapy. Moreover, more than half of the participants enrolled presented with

Table 1. Baseline demographics and disease characteristics of participants with axSpA and severe functional limitations in the intervention and usual care group

	Intervention group ($N = 110$)	Usual care group ($N = 104$)
Female, *N* (%)	56 (50.9)	49 (47.1)
Age in years, mean (S.D.)	51.9 (11.7)	52.4 (12.1)
Age in categories		
18–40 years, *N* (%)	19 (17.3)	19 (18.3)
41–65 years, *N* (%)	76 (69.1)	70 (67.3)
≥66 years, *N* (%)	15 (13.6)	15 (14.4)
BMI (kg/m^2), mean (S.D.)	28.0 (5.1) ($n = 107$)	28.1 (5.5) ($n = 104$)
Single-person household, *N* (%)	26 (23.9) ($n = 109$)	22 (21.2) ($n = 104$)
Higher Education, *N* (%)	47 (43.1) ($n = 109$)	31 (29.8) ($n = 104$)
Work status		
≤66 years old, *N* (%)	97 (88.2)	90 (86.5)
Paid job, N (%)	*33 (34.0)*	*34 (37.8)*
No job, health problems, N (%)	*22 (22.7)*	*16 (17.8)*
No job, other reasons, N (%)	*42 (43.3)*	*40 (44.4)*
Health insurance with additional coverage, *N* (%)	94 (87.0) ($n = 108$)	83 (81.4) ($n = 102$)
Self-reported duration of axial complaints (years), mean (S.D.)	23.5 (12.9) ($n = 107$)	24.6 (14.9) ($n = 102$)
Years since diagnosis (years), Mean (S.D.)	14.1 (11.3) ($n = 97$)	16.1 (14.8) ($n = 91$)
Radiographic spondyloarthritis, *N* (%)	74 (80) ($n = 93$)	79 (87) ($n = 91$)
BASDAI, Mean (S.D.)	4.9 (2.1) ($n = 64$)	5.0 (1.6) ($n = 70$)
BASDAI >4, *N* (%)	44 (69) ($n = 64$)	46 (66) ($n = 70$)
BASFI, Mean (S.D.)	6.0 (2.1) ($n = 105$)	5.9 (1.8) ($n = 99$)
PA 150 min per week of moderate-intensity PA, *N* (%)	84 (77.8) ($n = 108$)	80 (78.4) ($n = 102$)
PA two times a week muscle- and bone-strengthening, *N* (%)	39 (36.1) ($n = 108$)	29 (28.4) ($n = 102$)
Current medication use[a], *N* (%)	$n = 106$	$n = 102$
Any DMARD	68 (64)	66 (65)
bDMARD	63 (59)	65 (64)
tsDMARD	1 (1)	3 (3)
csDMARD	10 (9)	8 (8)
NSAIDs	55 (52)	47 (46)
Glucocorticoids *Oral*	15 (14)	11 (11)
No axSpA treatment related medication	6 (6)	7 (7)
Smoking status: Ever smoked, *N* (%)	64 (59) ($n = 108$)	67 (66) ($n = 102$)
Number of comorbidities, *N* (%)	($n = 106$)	($n = 101$)
0	4 (3.8)	11 (10.9)
1–2	23 (21.7)	24 (23.8)
3–4	33 (31.1)	28 (27.7)
≥5	46 (43.4)	38 (37.6)
Joint replacement surgeries ≥1, *N* (%)	11 (10)	15 (14)

Higher education: associate degree program, higher education Bachelor program; 4-year education at universities of applied sciences, Master degree program at universities of applied sciences and at research universities and doctoral degree program at research universities.

[a] Multiple answers possible.

BMI: Body Mass Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index;PA: physical activity; bDMARDS: biological DMARDS; tsDMARD: targeted synthetic DMARDS; csDMARD: conventional synthetic DMARDS.

three or more comorbidities. Female sex, comorbidities and age are factors known to be associated with functional disability and a high disease burden [14, 35, 36]. Furthermore, women are more likely to participate in research than men [37, 38]. We deliberately selected participants facing severe functional limitations as a result of an unfavourable progressive disease course, which likely accounts for the notable prevalence of individuals with radiographic axSpA. This characteristic composition of our study population is also distinctly reflected in the baseline scores on the BASFI, averaging around 6, which contrasts with the mean BASFI observed in recent randomized controlled trials exploring the effectiveness of exercise therapy, which typically range between 2 and 3.5 [39–42]. These findings underscore the lack of research on the effectiveness of exercise therapy in this patient category.

Overall, our intervention program yielded effects sizes ranging from 0.4 to 0.8 on outcomes measures related to physical functioning. The effect on physical functioning assessed in our study (BASFI β difference −0.78, 95%CI: −1.21 to −0.34) is smaller than those reported in a recent meta-analysis on the effectiveness of an exercise program combining aerobic, flexibility and muscle strength exercises based on seven RCTs (BASFI −1.19, 95%CI: −1.61 to −0.76) [43], but larger than those reported in a recent Cochrane review including five RCTs comparing exercise therapy with usual care (BASFI −0.4, 95%CI: −0.6 to −0.2) [7]. These numbers illustrate that, if guided by a trained physical therapist applying a personalized approach, people with severe functional limitations due to an unfavourable course or comorbidities, can be just as responsive to training as people with axSpA without severe limitations.

Our findings align with previous studies in rheumatic disorders or elderly people demonstrating the advantages of a personalized approach to exercise therapy [16–18]. Notably, we only included people with severe limitations that were directly or indirectly linked to their axSpA, despite optimal medical treatment. This suggests that sustained guidance from physical therapy significantly contributes to the health status of optimally treated people with axSpA and severe functional limitations. Consequently, we advocate integrating a long-term, personalized, supervised exercise program into

Table 2. Differences between groups on the primary and secondary outcome PSC NRS and 6-MWT at 52 weeks: intention to treat analyses

	Intervention group			Control group			Intervention *vs* usual care group
	Baseline mean (S.D.)	52 weeks mean (S.D.)	Mean change (95% CI)	Baseline mean (S.D.)	52 weeks mean (S.D.)	Mean change (95% CI)	Mean difference in change scores between groups (95% CI)
N	101	101	101	98	98	98	199
Primary outcome							
PSC NRS 1[a] **(0–10)**	7.6 (1.1)	4.6 (2.5)	−3.0 [−3.4, −2.5]	7.7 (1.1)	6.5 (2.2)	−1.2 [−1.6, −0.7]	−1.8 [−2.4. −1.2]
Secondary outcome							
PSC NRS 2[b] **(0–10)**	7.4 (1.1)	4.9 (2.5)	−2.5 [−3.0, −2.1]	7.4 (1.2)	6.1 (2.1)	−1.3 [−1.7, −0.8]	−1.3 [−1.9, −0.6]
PSC NRS 3[b] **(0–10)**	7.4 (1.2)	4.8 (2.6)	−2.6 [−3.2, −2.1]	7.2 (1.3)	6.1 (2.3)	−1.1 [−1.6, −0.7]	−1.5 [−2.2, −0.8]
6-MWT[b] **(meters)**	401 (102) ($n = 88$)	436 (108) ($n = 88$)	35 [22, 48]	403 (87) ($n = 93$)	407 (95) ($n = 93$)	4 [−7, 16]	30 [13, 48] ($n = 181$)

[a] Primary outcome measure.
[b] Secondary outcome measures.
PSC: Patient-Specific Complaints; NRS: numeric rating scale; *N*: number of patients; 6-MWT: Six Min Walk Test.

Table 3. Differences between groups on the secondary outcomes PROMIS PF-10, BASFI, SF-36 PCS and SF-36 MCS over time: intention to treat analyses

Outcome measure	Timepoints	Intervention group		Control group		Estimated mean differences between groups	
		N	Mean (S.D.)	*N*	Mean (S.D.)	*β*	95%CI
PROMIS PF-10	Baseline	105	35.2 (4.65)	99	36.5 (4.64)		
(13.5–61.9)	26 weeks	99	37.3 (5.68)	92	36.4 (5.45)	2.03	[0.98, 3.09]
	52 weeks	96	37.9 (6.05)	97	36.4 (5.29)	2.58	[1.39, 3.76]
BASFI (0–10)[a]	Baseline	105	6.0 (2.09)	99	5.9 (1.84)		
	26 weeks	97	5.2 (2.34)	92	5.9 (2.11)	−0.70	[−1.14, −0,27]
	52 weeks	96	5.1 (2.35)	97	5.8 (1.88)	−0.78	[−1.21, −0,34]
SF-36 PCS (0–100)	Baseline	105	28.2 (8.18)	99	29.4 (7.22)		
	26 weeks	97	31.6 (9.71)	92	29.4 (7.71)	3.11	[1.09, 5.13]
	52 weeks	95	32.0 (9.08)	97	29.6 (8.85)	3.21	[1.04, 5.38]
SF-36 MCS (0–100)	Baseline	105	44.6 (10.56)	99	45.7 (11.42)		
	26 weeks	97	46.3 (10.38)	92	46.0 (11.18)	1.04	[−1.50, 3.58]
	52 weeks	95	46.4 (10.15)	97	46.3 (10.93)	0.88	[−1.73, 3.49]

[a] Lower score indicates better outcome.
N: number of patients; PROMIS PF-10: Patient Reported Outcome Measurement Information System Physical Function 10-Item Short Form; SF-36 PCS: 36-item Short Form Health Survey Physical Component Summary Score; SF-36 MCS: 36-item Short Form Health Survey Mental Component Summary Score.

clinical practice for all people with axSpA and severe functional limitations. Furthermore, this approach is likely to offer benefits in the treatment of other, albeit less common, rheumatic diseases with potential complex consequences. However, our findings are in particular generalizable to other countries than the Netherlands with a similar healthcare system for people with inflammatory rheumatic disorders. Successful implementation of our intervention in clinical practice requires careful design of implementation strategies after examination of the context [44].

This study exhibits notable strengths, characterized by its randomized design, blinded raters, sufficient power and a low drop-out rate. Moreover, the treatment followed a well-defined protocol, and the intervention's physical therapists underwent comprehensive training. However, the study is not without limitations. The reliance on self-reported data for the collection of axSpA treatment-related medication may have compromised accuracy, potentially influencing group differences. Baseline medication data might not be entirely precise, as the relatively high self-reported use of oral glucocorticoids could be attributed to treating comorbid conditions and extra-musculoskeletal manifestations. Furthermore, we did not gather information on medication changes during the 52-week study period, so it is unknown to what extent possible differences between the intervention and usual care groups could have affected our results. However, only participants who received optimal medical treatment at baseline were included. The selection of outcome measures primarily focussed on their ability to reflect functional ability on the level of the ICF component 'Activities and Participation' [23]. Measures reflecting underlying impairments (e.g. pain, fatigue, spinal mobility) were considered less suitable due to anticipated individual variation. Additionally, for logistic reasons we did not assess the effects of our exercise program on physical activity and disease activity levels. Consequently, our findings do not permit inferences about the possible mediation role of those variables on measures of functional ability. However, exercise programs are known to have a substantial effect on disease activity [6]. Finally, we did not gather information on the presence of widespread pain, nor on the presence of peripheral involvement or extra-articular manifestations at baseline. Considering the substantial size of our research sample, the likelihood of significant imbalances between groups is minimal. However, it is unknown to what

extent this data had a possible impact on the content of the intervention and usual care groups and to what extent this could have affected the results of the trial.

In conclusion, to our knowledge this is the first study on the effectiveness of a supervised exercise program for people with axSpA and severe functional limitations. We demonstrated that long-term, personalized, supervised exercise therapy was more effective with respect to functional ability and quality of life than usual care over 52 weeks of treatment. Further research is needed to explore the long-term outcomes, and assess its cost-effectiveness and applicability of this approach in the management of other rheumatic diseases with potential complex consequences.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contribution statement

All authors made substantial contributions to the conception and design of the study. W.P. and S.v.W. performed the randomization, recruitment and training of physical therapists and administrative procedures. M.v.W., M.T., E.M., D.v.S., F.v.G., J.S., A.v.T. had a substantial role in the acquisition of data. The analyses and the interpretation of the data were conducted by M.v.W., T.V.V., S.v.W., M.T., C.E. and M.G. All authors were involved in drafting the work or revising it critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for their aspects of the work.

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References

1. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011; 377:2127–37.
2. Kiltz U, Essers I, Hiligsmann M *et al.* Which aspects of health are most important for patients with spondyloarthritis? A best worst scaling based on the ASAS health index. Rheumatology (Oxford) 2016;55:1771–6.
3. National Institute for Health and Care Excellence (NICE). Spondyloarthritis. 2018. https://www.nice.org.uk/guidance/qs170/resources/spondyloarthritis-pdf-75545654188741 (27 October 2023, date last accessed).
4. Ramiro S, Nikiphorou E, Sepriano A *et al.* ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82:19–34.
5. Ward MM, Deodhar A, Gensler LS *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Care Res (Hoboken) 2019;71:1285–99.
6. Ortolan A, Webers C, Sepriano A *et al.* 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 2023;82:142–52.
7. Regnaux J-P, Davergne T, Palazzo C *et al.* Exercise programmes for ankylosing spondylitis. Cochrane Database Syst Rev 2019; 10:CD011321.
8. O'Dwyer T, O'Shea F, Wilson F. Exercise therapy for spondyloarthritis: a systematic review. Rheumatol Int 2014;34:887–902.
9. Rausch Osthoff A-K, Juhl CB, Knittle K *et al.* 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 2018;4:e000713.
10. Rausch Osthoff A-K, Niedermann K, Braun J *et al.* 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77:1251–60.
11. Gwinnutt JM, Wieczorek M, Cavalli G *et al.* Effects of physical exercise and body weight on disease-specific outcomes of people with

rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. RMD Open 2022;8:e002168.
12. Teuwen MMH, Vlieland TPMV, van Weely SFE *et al.* Quality of reporting and nature of harms in clinical trials on supervised exercise in patients with rheumatoid arthritis or axial spondyloarthritis. Rheumatol Int 2024;44:25–39.
13. Perrotta FM, Lories R, Lubrano E. To move or not to move: the paradoxical effect of physical exercise in axial spondyloarthritis. RMD Open 2021;7:e001480.
14. Redeker I, Siegmund B, Ghoreschi K *et al.* The impact of extramusculoskeletal manifestations on disease activity, functional status, and treatment patterns in patients with axial spondyloarthritis: results from a nationwide population-based study. Ther Adv Musculoskelet Dis 2020;12:1759720X20972610.
15. van Albada-Kuipers GA, Dekker J, van den Ende CHM *et al.* Aangepaste definitie fysiotherapie bij RA en SA. 2016. https://reumanederland.nl/wp-content/uploads/2020/09/140401-Verzoek-aan-Zorginstituut-Nederland-fysiotherapie.pdf (27 October 2023, date last accessed).
16. Teuwen MMH, van Weely SFE, Vliet Vlieland TPM *et al.* Effectiveness of longstanding exercise therapy compared with usual care for people with rheumatoid arthritis and severe functional limitations: a randomised controlled trial. Ann Rheum Dis 2024;83:437–45.
17. de Vries NM, Staal JB, van der Wees PJ *et al.* Patient-centred physical therapy is (cost-) effective in increasing physical activity and reducing frailty in older adults with mobility problems: a randomized controlled trial with 6 months follow-up. J Cachexia Sarcopenia Muscle 2016;7:422–35.
18. de Vries NM, van Ravensberg CD, Hobbelen JSM *et al.* The Coach2Move approach: development and acceptability of an individually tailored physical therapy strategy to increase activity levels in older adults with mobility problems. J Geriatr Phys Ther 2015;38:169–82.
19. de Rooij M, van der Leeden M, Cheung J *et al.* Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: a randomized controlled trial. Arthritis Care Res (Hoboken) 2017;69:807–16.
20. van Wissen MAT, Teuwen MMH, van den Ende CHM *et al.* Effectiveness and cost-effectiveness of longstanding exercise therapy versus usual care in patients with axial spondyloarthritis or rheumatoid arthritis and severe limitations: the protocols of two parallel randomized controlled trials. Physiother Res Int 2022;27:e1933.
21. Garber CE, Blissmer B, Deschenes MR *et al.*; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59.
22. Hoogeboom TJ, Kousemaker MC, van Meeteren NL *et al.* i-CONTENT tool for assessing therapeutic quality of exercise programs employed in randomised clinical trials. Br J Sports Med 2021;55:1153–60.
23. WHO. International classification of disability, functioning and health: ICF. Geneva: WHO, 2001. https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health (27 October 2023, date last accessed).
24. Stevens A, Koke A, van der Weijden T, Beurskens A. Ready for goal setting? Process evaluation of a patient-specific goal-setting method in physiotherapy. BMC Health Serv Res 2017;17:618.
25. Beurskens AJ, de Vet HC, Köke AJ *et al.* A patient-specific approach for measuring functional status in low back pain. J Manipulative Physiol Ther 1999;22:144–8.
26. Terwee CB, Roorda LD, de Vet HCW *et al.* Dutch-Flemish translation of 17 item banks from the patient-reported outcomes measurement information system (PROMIS). Qual Life Res 2014;23:1733–41.
27. Gershon RC, Rothrock N, Hanrahan R, Bass M, Cella D. The use of PROMIS and assessment center to deliver patient-reported outcome measures in clinical research. J Appl Meas 2010;11:304–14.
28. Van Tubergen A, Debats I, Ryser L *et al.* Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 2002;47:242–8.
29. Calin A, Jones SD, Garrett SL, Kennedy LG. Bath ankylosing spondylitis functional index. Br J Rheumatol 1995;34:793–4.
30. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed) 1982;284:1607–8.
31. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
32. Aaronson NK, Muller M, Cohen PD *et al.* Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055–68.
33. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–92.
34. Regel A, Sepriano A, Baraliakos X *et al.* Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open 2017;3:e000397.
35. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018;20:35.
36. Garrido-Cumbrera M, Poddubnyy D, Gossec L *et al.*; EMAS Working Group. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). Clin Rheumatol 2021;40:2753–61.
37. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17:643–53.
38. Strait A, Castillo F, Choden S *et al.* Demographic characteristics of participants in rheumatoid arthritis randomized clinical trials: a systematic review. JAMA Netw Open 2019;2:e1914745.
39. Acar Y, Ilcin N, Gurpinar B, Can G. The effects of clinical pilates training on disease-specific indices, core stability, and balance in patients with ankylosing spondylitis. J Bodyw Mov Ther 2023;33:69–75.
40. Gandomi F, Soufivand P, Ezati M *et al.* The effect of aqua stretching exercises and pilates on pain, function and spine posture in patients with ankylosing spondylitis: a randomized controlled trial. BMC Sports Sci Med Rehabil 2022;14:183.
41. Oksuz S, Unal E. Comparison of the effects of aerobic training alone versus aerobic training combined with clinical Pilates exercises on the functional and psychosocial status of patients with ankylosing spondylitis: a randomized controlled trial. Physiother Theory Pract 2023;39:61–71.
42. Sveaas SH, Bilberg A, Berg IJ *et al.* 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;54:292–7.
43. Boudjani R, Challal S, Semerano L, Sigaux J. Impact of different types of exercise programs on ankylosing spondylitis: a systematic review and meta-analysis. Disabil Rehabil 2023;45:3989–4000.
44. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. BMJ 2013;347:f6753.

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