Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review for the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis

Online supplementary material

Table of Contents **Page**

1. LITERATURE SEARCH STRATEGY

1.1 Search terms

MEDLINE

1. exp Spondylitis/
2. (ankylos$ or spondyl$).tw.
3. SpA.tw.
4. (bekhterev$ or bechterew$).tw.
5. or/1-4
6. th.xs.
7. 5 and 6
8. ("review" or "review academic" or "review tutorial").pt.
9. (medline or medlars or embase or pubmed).tw,sh.
10. (scisearch or psychinfo or psycinfo).tw,sh.
11. (psychlit or psyclit).tw,sh.
12. cinahl.tw,sh.
13. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
14. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
15. (pooling or pooled or mantel haenszel).tw,sh.
16. (retraction of publication or retracted publication).pt.
17. (peto or dersimonian or der simonian or fixed effect).tw,sh.
18. or/9-17
19. 8 and 18
20. meta-analysis.pt.
21. meta-analysis.sh.
22. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
23. (systematic$ adj5 review$).tw,sh.
24. (systematic$ adj5 overview$).tw,sh.
25. (quantitativ$ adj5 review$).tw,sh.
26. (quantitativ$ adj5 overview$).tw,sh.
27. (quantitativ$ adj5 synthesis$).tw,sh.
28. (methodologic$ adj5 review$).tw,sh.
29. (methodologic$ adj5 overview$).tw,sh.
30. (integrative research review$ or research integration).tw.

31. or/20-30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomized.ab.
35. placebo.ab.
36. drug therapy.fs.
37. randomly.ab.
38. trial.ab.
39. groups.ab.
40. or/32-39
41. Epidemiologic studies/
42. exp case control studies/
43. exp cohort studies/
44. Case control.tw.
45. (cohort adj (study or studies)).tw.
46. Cohort analy$.tw.
47. (Follow up adj (study or studies)).tw.
48. observational study.pt.
49. (observational adj (study or studies)).tw.
50. Longitudinal.tw.
51. Retrospective.tw.
52. Cross sectional.tw.
53. Cross-sectional studies/
54. or/41-53
55. or/31,40,54
56. 7 and 55
57. exp animals/ not humans.sh.
58. 56 not 57
59. limit 58 to yr="2009 -Current"

Cochrane CENTRAL

#1 MeSH descriptor: [Spondylitis] explode all trees
#2 (ankylos* or spondyl*):ti,ab
#3 spa:ti,ab
#4 (bekhterev* or bechterew*):ti,ab

#5 #1 or #2 or #3 or #4

EMBASE

#1. 'spondylitis'/exp

#2. ankylos*:ab,ti OR spondyl*:ab,ti

#3. spa:ab,ti

#4. bekhterev*:ab,ti OR bechterew*:ab,ti

#5. #1 OR #2 OR #3 OR #4

#6. 'review'/de

#7. (literature NEAR/3 review*):ab,ti

#8. 'meta analysis'/de

#9. 'systematic review'/de

#10. #6 OR #7 OR #8 OR #9

#11. medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR pubmed:ab,ti OR cinahl:ab,ti OR amed:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR scisearch:ab,ti OR cochrane:ab,ti

#12. 'retracted article'/de

#13. #11 OR #12

#14. #19 OR #23 OR #33

#15. (systematic* NEAR/2 (review* OR overview)):ab,ti

#16. metaanal*:ab,ti OR metanaly*:ab,ti OR (meta NEAR/2 anal*):ab,ti

#17. #14 OR #15 OR #16

#18. random*:ab,ti

#19. #14 OR #15 OR #18

#20. random*:ab,ti

#21. clinical AND trial*

#22. 'health care quality'/exp

#23. #14 OR #15 OR #18

#24. 'cohort analysis'/de

#25. 'longitudinal study'/exp

#26. 'prospective study'/de

#27. 'follow up'/de

#28. cohort*:ab,ti

#29. 'case control study'/exp

#30. case*:ab,ti AND control*:ab,ti

#31. 'case study'/de

#32. case*:ab,ti AND series:ab,ti

#33. #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32

#34. #19 OR #23 OR #33

#35. #5 AND #34

#36. #35 AND AND [humans]/lim AND [embase]/lim

#37. #36 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND AND ('article'/it OR 'article in press'/it OR 'review'/it)

1.2 Review flow chart

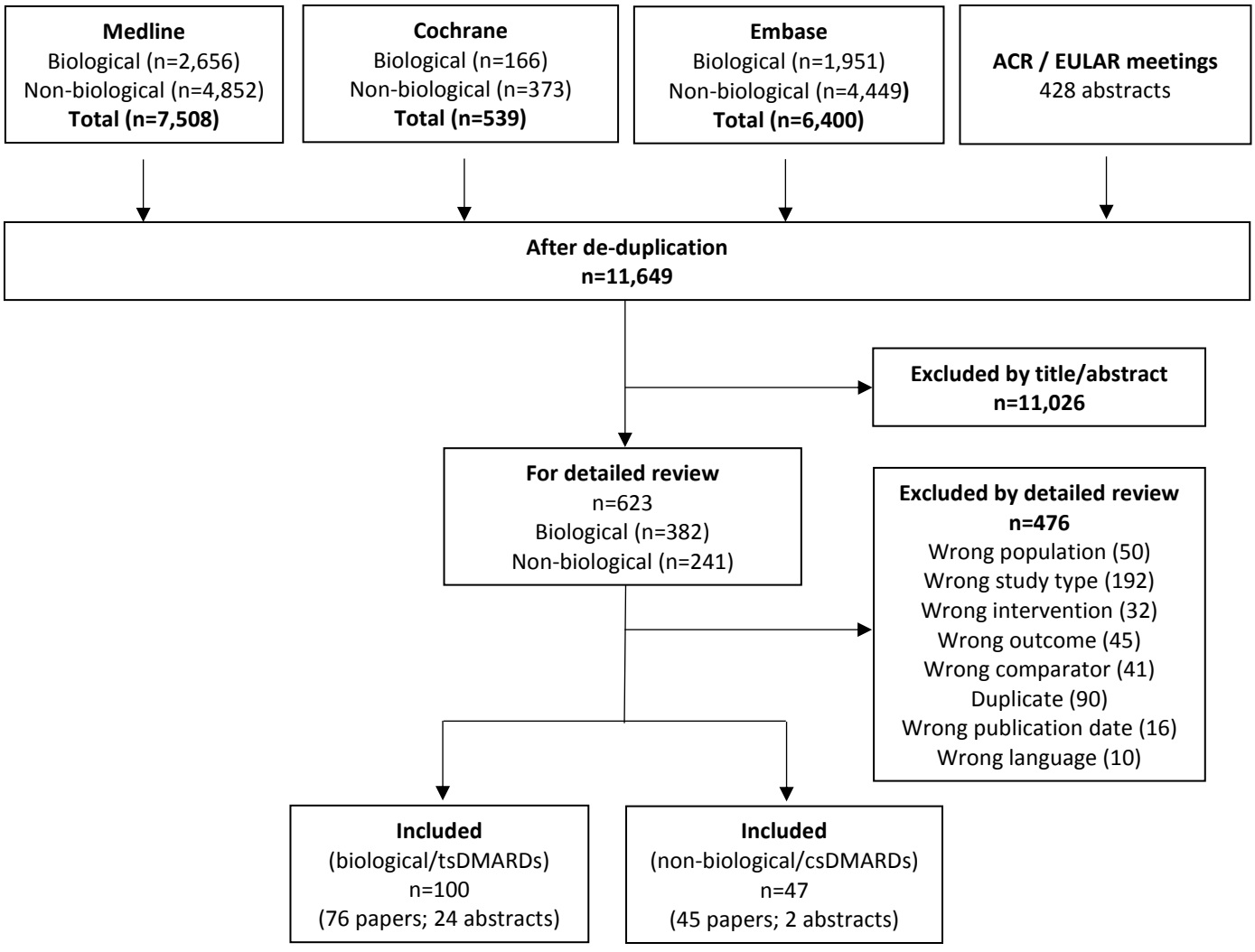

Figure S1. Flow-chart for the systematic literature review

2. SUMMARY OF PUBLICATIONS

Table S1. Results for non-biological search

Intervention	n	Study design					Publications	
		RCT	CCT	Cohort studies	case-control	Cochrane SLR	Full-text paper	Abstracts
Non-pharmacological Interventions	**29**	24	5				28	1
Non-biological Drugs	**15**	10	1	3		1	14	1
Surgical Interventions	**3**		2		1		3	
Total publications	**47**	**34**	**8**	**3**	**1**	**1**	**45**	**2**

Table S2. Non-pharmacological Interventions

Intervention	n	Study design		Publications	
		RCT	CCT	Full-text paper	Abstracts
Exercises	**23**	18	5	22	1
Education	**2**	2		2	
Other non-pharmacological Interventions	**4**	4		4	
Total publications	**29**	**24**	**5**	**28**	**1**

Table S3. Non-biological Drugs

Intervention	n	Study design				Publications	
		RCT	CCT	Cohort studies	Cochrane SLR	Full-text paper	Abstracts
NSAIDs	**8**	5		2	1	7	1
Glucocorticoids	**2**	1		1		2	
Other non-biological Drugs	**5**	4	1			5	
Total publications	**15**	**10**	**1**	**3**	**1**	**14**	**1**

Table S4. Surgical Interventions

Intervention	n	Study design		Publications	
		CCT	Nested case-control study	Full-text paper	Abstracts
Pedicle Subtraction Osteotomy	**1**	1		1	
Total Hip Replacement	**1**		1	1	
Pedicle Subtraction Osteotomy + Bone grafting	**1**	1		1	
Total publications	**3**	**2**	**1**	**3**	

3. DESCRIPTION OF PUBLICATIONS

3.1 Non-pharmacological Interventions

As only two (Jennings 2015[1], Strumse 2011[2]) of the non-pharmacological studies reported ASDAS response criteria (ASDAS clinically important improvement (Δ≥1.1), ASDAS major improvement (Δ≥2.0), ASDAS inactive disease (<1.3) and ASAS response criteria (ASAS20, ASAS40, ASAS 5/6, ASAS partial remission), the data for BASDAI, ASDAS, BASFI, BASMI and Pain global are presented in the following tables.

Jennings 2015[1] reported ASAS20 and Strumse 2011[2] presented both ASAS20 and ASAS40.

3.1.1 Efficacy

3.1.1.1 Exercises

Table S5. Study Protocol (Exercises)

Study ID	Intervention	n	Protocol	Frequency
Altan 2012 [3]	Pilates	30	Pilates exercise program of 1 h given by a certified trainer	3x/week
	Standard treatment	25	„usual care and continue participating in their usual physical activity“	NR
Aytekin 2012 [4]	Home-based exercise program	24	30 min/session	5x/week
	Home-based exercise program	32	30 min/session	<5x/week
Ciprian 2013 [5]	Spa therapy + rehabilitation + TNFi	15	1 session spa therapy: mud pack (40-45°) for 15 min (applied to the entire spine) + group rehabilitation for 1 h in a pool of thermal water (32-34°C) + TNFi treatment (etanercept/infliximab)	10 sessions over 2 weeks
	TNFi alone	15	Only TNFi treatment (etanercept or infliximab)	NR
Colina 2009 [6]	Spa therapy + Etanercept	30	Spa therapy: intensive rehabilitation program in thermal waters + Etanercept 25 mg s.c twice weekly	1x/day (spa therapy)
	Etanercept alone	30	Etanercept 25 mg s.c. twice weekly	NR
Dragoi 2016 [7]	Inspiratory muscle training + CE	23	Supervised inspiratory muscle training 3x/week (in total 24 sessions) + CE	NR
	Conventional exercises (CE)	24	CE: home program (5x/week, 40 minutes/session) + weekly group session (40 minutes/session) managed by a physical therapist	NR
Dundar 2014 [8]	Aquatic therapy	35	20 sessions under supervision of a physiotherapist; each session was conducted in groups of 8-9 patients and lasted 60 min in a swimming pool at 32-33 °C	5x/week

Study ID	Intervention	n	Protocol	Frequency
	Home-(land-)based therapy	34	Exercise program with muscle relaxation, flexibility, stretching and breathing exercises, straight posture	each exercise 1x/day with 15-20 repetition, lasting 60 min
Fernández García 2015 [9]	Aquatic + relaxation program	15	24 sessions of aquatic fitness + relaxation program	3x/week
	Control: no supervised therapies	15	No intervention	NR
Figen 2011 [10]	Inpatient rehabilitation model	29	15 sessions of the physical therapy and rehabilitation program	1x/day (spa therapy), 3 weeks
	Home exercise model	31	Exercises	2x/day with 20 repetitions/set, 3 weeks
Gallinaro ACR 2013 [11]	Stretching exercises	40	30 minutes of outdoor dynamic and static stretching exercises for the spine and limbs, using only a chair	2x/week
	Control		No exercises	NR
Gunendi 2010 [12]	Supervised exercise program	16	Aerobic, resistance, and stretching exercises	1 hour/day 5x/week
	Home exercise program	16	Strengthening + stretching exercises and a daily briskly walk for 30 min	NR
Hsieh 2014 [13]	ROM + strengthening + aerobic	9	Strengthening of the muscles of the major joints (spine, shoulder, elbow, wrist, hip, knee, ankle) + aerobic exercise (including fast walking, cycling, and swimming as suggested)	Strengthening 2x/week; aerobic 3x/week
	Range-of-motion exercises (ROM)	10	ROM: spine and major joints (shoulder, elbow, wrist, hip, knee, ankle), treated by a physical therapist, chest + breathing exercise	1x/day, 5 repetitions of each exercises
Jennings 2015 [1]	Aerobic (walking) + stretching exercises	35	Warm-up, walking, cool down, stretching exercises	3/week (1 session: 80 min)
	Stretching exercises	35	Stretching exercises for various muscle groups	3/week (30 min)
Karapolat 2009 [14]	Swimming + CE	13	CE + Swimming: warm-up, stretching, swimming at a moderate intensity (60-70% heart rate reserve - 12 beats/minute), cool down, stretching	Swimming: 30 min/day, 3x/week for 6 weeks
	Walking + CE	12	CE + Walking: at 60-70% of the pVO_2, at a level of 13-15 on the Borg scale and 60-70% heart rate reserve	Walking: 30 min/day, 3x/week for 6 weeks
	Conventional exercises (CE)	12	CE: flexibility (cervical, thoracic, lumbar spine), stretching (major muscle groups) and respiratory exercises and abdominal movement)	1x/day for 6 days
Kjeken 2013 [15]	Rehabilitation program	29	relevant medication + weekly exercise program designed by a physiotherapist; combination of exercises in the gym (2-3 sessions/week), water (3-5 sessions/week) or outdoor (3 sessions/week)	NR
	„treatment as usual“	34	"treatment as usual": e.g. relevant medications, consultations with a rheumatologist, community-based physiotherapy, self-management in terms of physical activity/exercises	NR
Masiero 2011 [16]	RG: Rehabilitation + Education program + TNFi	20	2 educational-behavioral + followed by 10 exercise training meetings + 12 twice weekly exercises sessions (60 min respectively), TNFi treatment	8 weeks
	EG: Education program + TNFi	20	2 educational-behavioral meetings, TNFi treatment	3 hour sessions every 2 weeks
	CG: TNFi, no rehabilitation	22	No program, only TNFi treatment	NR
Niedermann 2013 [17]	Nordic walking + flexibility	53	Flexibilty exercises + supervised Nordic walking (30 min) at moderate-intensity heart rate levels	2x/week
	Attention control + flexibility	53	Flexibilty exercises + attention control training: discussion groups on coping strategies and techniques of mindfulness-based stress reduction led by a psychologist	monthly about 2.5 hours

Study ID	Intervention	n	Protocol	Frequency
Rosu 2014 [18]	Pilates + McKenzie + Heckscher	48	Pilates (20 min) + Heckscher method (20 min) + McKenzie (10 min)	sessions of 50 min 3x/week
	Classic kinetic training	48	Classic kinetic program: warm-up (15 min) + main period (20 min) + cool-down (15 min)	sessions of 50 min 3x/week
Silva 2012 [19]	Global Postural Reeducation	22	Individual supervised GPR sessions	1 hour 1x/week
	Stretching + breathing exercises	16	Conventional segmental self-stretching sessions + breathing exercises	40 min 2x/week
So 2012 [20]	Incentive spirometer exercises (ISE) + CE + TNFi	23	ISE (6 different exercises on the incentive spirometer) + CE	1x/day (ISE and CE)
	Conventional Exercises (CE) + TNFi	23	CE: 20 exercises (on motion and flexibility of the spine) for 30 min	1x/day
Strumse 2011 [2]	Reha program in a Mediterranean country	65	Individualized physiotherapy with exercises, group exercises, passive therapy, relaxation, patient education	NR
	Reha program in Norway	42	Individualized physiotherapy with exercises, group exercises, passive therapy, relaxation, patient education	NR
Sveaas 2014 [21]	Endurance + strength training	10	Endurance (high intensity interval training) + strength training (major muscle groups)	40-60 min. 3x/week (2x/week under supervision in a fitness center)
	No exercises	24	No exercises during the study period	NR
Taspinar 2015 [22]	Hospital: calisthenic exercises + relaxation	18	Supervised by a physiatrist: calisthenic exercises 1 hour, 3 d/week + relaxation exercises 20 min 2 day/week	5 days/week
	Home: calisthenic exercises + relaxation	19	Performed alone at home: calisthenic exercises 1 hour, 3 d/week + relaxation exercises 20 min 2 day/week	5 days/week
Yigit 2013 [23]	Home exercises > 5x/week + TNFi	20	Muscle relaxation, flexibility exercises for the spine, range of motion exercises, stretching exercises	30 min 5x/week
	Home exercises < 5x/week + TNFi	20		30 min < 5x/week

Table S6. Study characteristics (Exercises)

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention (weeks)	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
Altan 2012 [3]	Pilates	30	mNY	Superiority trial, RCT	12	55	46.5 (11.2)	NR	mean 8.84 (range 2-22)	BASFI	(+)
	Standard treatment programs	25					43.6 (10.1)	NR			
Aytekin 2012 [4]	Home-based exercise program	24	mNY	CCT, NR*	12	74	34.35 (9.48)	NR	45.85 (68.84) months	NR	NR
	Home-based exercise program	32				84	35.75 (6.71)	NR	45.22 (42.51) months		

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention (weeks)	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
Ciprian 2013 [5]	Spa therapy + rehabilitation + TNFi	15	mNY	RCT, NR*	2	93	47.8 (10.0)	87	13.9 (8.6)	BASFI	NR
	TNFi alone	15				93	45.6 (11.8)	93	13.2 (8.8)		
Colina 2009 [6]	Spa therapy + Etanercept	30	mNY	CCT, NR*	1	NR	41.6 (6.9)	80	8.8 (4.2)	BASFI	(-)
	Etanercept alone	30				NR	40.7 (7.2)	78	8.4 (3.2)		
Dragoi 2016 [7]	Inspiratory muscle training + CE	23	mNY	RCT, NR*	8	100	47.7 (6.9)	NR	15.5 (6.0)	NR	NR
	Conventional exercises (CE)	24				100	49.4 (7.3)	NR	17.8 (9.0)		
Dundar 2014 [8]	Aquatic therapy	35	mNY	RCT, NR*	4	86	42.3 (11.3)	NR	13.7 (12.5)	NR	NR
	Home-(land-)based therapy	34				85	43.1 (11.7)	NR	14.1 (12.2)		
Fernández García 2015 [9]	Aquatic + relaxation program	15	ESSG	RCT, NR*	8	53	43.8 (9.1)	NR	6.7 (3.4)	several	(-)
	Control: no supervised therapies	15					50 (13.0)	NR	7.8 (4.8)		
Figen 2011 [10]	Inpatient rehabilitation model	29	mNY	RCT, NR*	3 weeks (1st FU 15 months)	82.7	42.5 (10.6)	NR	9.9 (7.7)	BASDAI, BASFI	Both (-)
	Home exercise model	31				64.5	37.0 (9.6)	NR	7.4 (7.7)		
Gallinaro ACR 2013 [11]	Stretching exercises	40	mNY	RCT, NR*	16	NR	47.1 (11.5)	NR	17.6 (10.0)	NR	NR
	Control					NR		NR			
Gunendi 2010 [12]	Supervised exercise program	16	mNY	CCT, NR*	3	81.3	45.6 (12.4)	NR	156.4 (146.4) months	NR	NR
	Home exercise program	16				68.8	43.4 (12.0)	NR	127.3 (103.3) months		
Hsieh 2014 [13]	ROM + strengthening + aerobic	9	mNY	Superiority trial, RCT	12	67	36.2 (11.7)	NR	11.1 (6.8)	BASFI	(+)
	Range-of-motion exercises (ROM)	10				70	42.1 (8.8)	NR	17.3 (10.7)		
Jennings 2015 [1]	Aerobic (walking) + stretching exercises	35	mNY	Superiority trial, RCT	12	74	42.9 (9.9)	NR	16.0 (8.9)	BASFI (-)	(-)
	Stretching exercises	35				66	40.2 (9.3)	NR	13.4 (7.8)		
Karapolat 2009 [14]	Swimming + CE	13	mNY	RCT, NR*	6	37	50.15 (12.40)	NR	20.62 (10.10)	NR	NR
	Walking + CE	12				29.6	46.92 (13.40)	NR	17.42 (12.43)		
	Conventional exercises (CE)	12				33.3	48.42 (9.47)	NR	18.63 (7.52)		
Kjeken 2013 [15]	Rehabilitation program	29	mNY	RCT, NR*	3 (assessment after 4 months)	78.3	49.4 (10.3)	NR	14.9 (9.6)	BASDAI, BASFI	BASDAI (+) BASFI (-)
	„treatment as usual“	34				53.1	48.6 (9.4)	NR	16.1 (12.0)		
Masiero 2011 [16]	**RG**: Rehabilitation + Education program + TNFi	20	mNY	RCT, NR*	8	75	47.5 (37.2-61.5)	NR	9.5 (4.0-14.0)	NR	NR

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention (weeks)	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
	EG: Education program + TNFi	20				80	44.0 (38.2-52.5)	NR	6.5 (4.0-10.0)		
	CG: TNFi, no rehabilitation	22				81.8	47.5 (40.7-52.5)	NR	9.0 (3.2-13.7)		
Niedermann 2013 [17]	Nordic walking + flexibility	53	mNY	RCT, NR*	12	64	50.1 (11.9)	NR	9 (0.5-45)	Physical work capacity on bicycle	(+)
	Attention control + flexibility	53				64	47.6 (12.4)	NR	8 (0.5-39)		
Rosu 2014 [18]	Pilates + McKenzie + Heckscher	48	mNY	RCT, NR*	48	81	25.33 (3.77)	NR	5.81 (3.02)	NR	NR
	Classic kinetic training	48				83	24.98 (3.83)	NR	5.35 (3.11)		
Silva 2012 [19]	Global Postural Reeducation	22	mNY	CCT, NR*	16	64	35.3 (12.2)	NR	10.1 (5.67)	NR	NR
	Stretching + breathing exercises	16				75	44.27 (10.55)	NR	7.07 (4.81)		
So 2012 [20]	Incentive spirometer exercises (ISE) + CE + TNFi	23	mNY	Superiority trial, RCT	16	95.7	34.6 (5.9)	NR	12.2 (6.4) (symptom duration)	NR	NR
	Conventional Exercises (CE) + TNFi	23				95.7	38.0 (9.1)	NR	12.9 (7.3) (symptom duration)		
Strumse 2011 [2]	Reha program in a Mediterranean country	65	mNY	RCT, NR*	4	58	48 (10; 28-70)*	88	NR	NR	NR
	Reha program in Norway	42				55	51 (8; 30-62)*	93	NR		
Sveaas 2014 [21]	Endurance + strength training	10	active axSpA (BASDAI ≥3.5)	RCT, NR*	12	20	46.6 (13.6)	NR	19.2 (19.8)	ASDAS	(-)
	No exercises	24				71	49.9 (11.1)	NR	28.6 (11.9)		
Taspinar 2015 [22]	Hospital: calisthenic exercises + relaxation	18	mNY	RCT, NR*	8	57	35.83 (8.08)	NR	7.16 (2.49)	NR	NR
	Home: calisthenic exercises + relaxation	19						NR			
Yigit 2013 [23]	Home exercises > 5x/week + TNFi	20	mNY	CCT, NR*	10	75	40.30 (8.05)	NR	9.55 (5.19)	NR	NR
	Home exercises < 5x/week + TNFi	20				85	36.45 (7.19)	NR	7.95 (4.59)		

* mean (SD; range); (+) positive trial; (-) negative trial; **values**: mean (SD); median (min-max)

Table S7. Disease activity outcomes – BASDAI, ASDAS (Exercises)

Study ID	Intervention	n	Time point (weeks)	BASDAI				ASDAS			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Altan 2012 [3]	Pilates	30	12	2.8 (1.7)	2.1 (2)	-0.7 (1.8)	0.003 (FU change)	NR	NR	NR	NR
	Standard treatment programs	25		2.6 (1.8)	3.1 (1.7)	0.5 (1.1)		NR	NR	NR	NR
Aytekin 2012 [4]	Home-based exercise program	24	12	4.44 (2.07)	3.77 (1.98)	NR	ns	NR	NR	NR	NR
	Home-based exercise program	32		3.98 (2.19)	4.07 (2.21)	NR		NR	NR	NR	NR
Ciprian 2013 [5]	Spa therapy + rehabilitation + TNFi	15	2	2.68 (1.22)	1.83 (1.04)	NR	NR	NR	NR	NR	NR
	TNFi alone	15		2.86 (1.76)	2.20 (1.31)	NR	NR	NR	NR	NR	NR
Colina 2009 [6]	Spa therapy + Etanercept	30	12	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept alone	30		NR	NR	NR	NR	NR	NR	NR	NR
Dragoi 2016 [7]	Inspiratory muscle training + CE	23	8	3.9 (1.2)	NR	NR	NR	NR	NR	NR	NR
	Conventional exercises (CE)	24		3.7 (0.9)	NR	NR	NR	NR	NR	NR	NR
Dundar 2014 [8]	Aquatic therapy	35	4	3.9 (1.9)	2.6 (1.5)	NR	NR	NR	NR	NR	NR
	Home-(land-) based therapy	34		4.0 (2.3)	2.8 (2.1)	NR	NR	NR	NR	NR	NR
Fernández García 2015 [9]	Aquatic + relaxation program	15	8	4.45 (1.98)¥	4.03 (1.29)¥	NR	0.048	NR	NR	NR	NR
	Control: no supervised therapies	15		5.88 (2.36)¥	2.81 (1.15)¥	NR		NR	NR	NR	NR
Figen 2011 [10]	Inpatient rehabilitation model	29	60	4.8 (2.5)	4.0 (3.6)	NR	NR	NR	NR	NR	NR
	Home exercise model	31		3.9 (2.3)	2.5 (2.4)	NR	NR	NR	NR	NR	NR
Gallinaro ACR 2013 [11]	Stretching exercises	40	16	NR	NR	NR	NR	NR	NR	NR	NR
	Control			NR	NR	NR	NR	NR	NR	NR	NR
Gunendi 2010 [12]	Supervised exercise program	16	3	2.1 (1.7)	1.2 (1.3)	0.9 (0.2; 1.5)	NR	NR	NR	NR	NR
	Home exercise program	16		2.6 (2.2)	3.1 (2.6)	-0.5 (-1.4; 0.5)	NR	NR	NR	NR	NR
Hsieh 2014 [13]	ROM + strengthening + aerobic	9	12	4.2 (1.9)	3.7 (1.8)	NR	0.414	NR	NR	NR	NR
	Range-of-motion exercises (ROM)	10		4.5 (2.1)	4.5 (3.0)	NR		NR	NR	NR	NR
Jennings 2015 [1]	Aerobic (walking) + stretching exercises	35	12	3.46 (2.39)	2.75 (2.12)	NR	NR	2.44 (1.07)	1.98 (0.93)	NR	NR
	Stretching exercises	35		3.62 (2.06)	2.79 (1.99)	NR	NR	2.24 (0.91)	2.00 (0.94)	NR	NR

Study ID	Intervention	n	Time point (weeks)	BASDAI				ASDAS			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Karapolat 2009 [14]	Swimming + CE	13	6	2.73 (1.93)	1.90 (1.61)	NR	NR	NR	NR	NR	NR
	Walking + CE	12		2.49 (1.68)	2.68 (2.19)	NR	NR	NR	NR	NR	NR
	Conventional exercises (CE)	12		2.65 (2.13)	2.03 (1.86)	NR	NR	NR	NR	NR	NR
Kjeken 2013 [15]	Rehabilitation program	29	16	57.8 (54.7; 60.8)	43.2 (37.3; 49.2)	NR	NR	NR	NR	NR	NR
	„treatment as usual“	34		56.9 (53.4; 60.4)	57.5 (51.3; 63.6)	NR	NR	NR	NR	NR	NR
Masiero 2011§ [16]	**RG**: Rehabilitation + Education program + TNFi	20	8	3.6 (2.2-3.0)	2.4 (1.0-3.5)	NR	0.045 (RG vs EG)	NR	NR	NR	NR
	EG: Education program + TNFi	20		3.0 (2.0-6.3)	2.7 (1.5-3.4)	NR	0.444 (EG vs CG)	NR	NR	NR	NR
	CG: TNFi alone, no rehabilitation	22		3.2 (1.7-4.3)	2.7 (1.7-4.9)	NR	0.05 (RG vs CG)	NR	NR	NR	NR
Niedermann 2013 [17]	Nordic walking + flexibility	53	12	3.3 (1.9)	2.84 (0.24)	NR	0.31	2.2 (0.8)	2.43 (0.17)	NR	0.38
	Attention control + flexibility	53		3.6 (2.1)	3.15 (0.23)	NR		2.3 (1.0)	2.23 (0.18)	NR	
Rosu 2014 [18]	Pilates + McKenzie + Heckscher	48	48	5.41 (1.95)	2.10 (0.82)	NR	0.001	NR	NR	NR	NR
	Classic kinetic training	48		5.29 (1.96)	4.13 (1.66)	NR		NR	NR	NR	NR
Silva 2012 [19]	Global Postural Reeducation	22	16	6.6 (0.52)	3.1 (0.17)	NR	0.73	NR	NR	NR	NR
	Stretching + breathing exercises	16		7.0 (0.31)	4.9 (0.19)	NR		NR	NR	NR	NR
So 2012 [20]	Incentive spirometer exercises (ISE) + CE + TNFi	23	16	2.37 (1.09)	1.97 (1.54)	NR	NS	NR	NR	NR	NR
	Conventional Exercises (CE) + TNFi	23		2.75 (1.15)	2.58 (1.65)	NR		NR	NR	NR	NR
Strumse 2011 [2]	Reha program in a Mediterranean country	65	4	5.0 (1.7)	NR	-3.3 (1.9)	<0.001	NR	NR	NR	NR
	Reha program in Norway	42		4.8 (1.3)	NR	-1.6 (1.3)		NR	NR	NR	NR
Sveaas 2014 [21]	Endurance + strength training	10	12	5.3 (1.4)	3.3 (2.0)	NR	NR	2.3 (0.6)	1.8 (0.9)	NR	NR
	No exercises	24		5.3 (1.3)	5.2 (2.0)	NR	NR	2.7 (0.8)	2.6 (0.8)	NR	NR
Taspinar 2015 [22]	Hospital: calisthenic exercises + relaxation	18	8	4.15 (1.79)	3.66 (1.84)	0.49 (1.03)	>0.05 (FU change)	NR	NR	NR	NR
	Home: calisthenic exercises + relaxation	19		5.02 (2.43)	4.66 (2.02)	0.36 (1.08)		NR	NR	NR	NR
Yigit 2013 [23]	Home exercises > 5x/week + TNFi	20	10	3.85 (2.45)	2.61 (1.83)	1.24 (1.00)	<0.001 (FU change)	NR	NR	NR	NR
	Home exercises < 5x/week + TNFi	20		3.81 (2.38)	3.77 (2.33)	0.04 (0.29)		NR	NR	NR	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control; § Masiero 2011: median (25th-75th percentile); ¥ mean (95% CI)

Table S8. Mobility, Function and Pain – BASFI, BASMI, Pain global (Exercises)

Study ID	Intervention	n	Time point (weeks)	BASFI				BASMI				Pain global			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Altan 2012 [3]	Pilates	30	12	2.4 (1.6)	1.7 (1.6)	-0.7 (1.5)	0.059 (FU change)	8.8 (1.8)	8.4 (1.9)	-0.4 (0.7)	0.304 (FU change)	NR	NR	NR	NR
	Standard treatment programs	25		2.2 (1.6)	2.3 (1.7)	0.1 (0.9)		8.9 (1.7)	8.7 (1.8)	-0.2 (0.8)		NR	NR	NR	NR
Aytekin 2012 [4]	Home-based exercise program	24	12	2.54 (2.26)	2.05 (2.14)	NR	NS	NR	NR	NR	NR	5.1 (2.1)	4.1 (2.0)	NR	0.786
	Home-based exercise program	32		2.90 (2.30)	2.99 (2.26)	NR		NR	NR	NR	NR	3.9 (2.3)	3.9 (2.0)	NR	
Ciprian 2013 [5]	Spa therapy + rehabilitation + TNFi	15	2	2.68 (1.38)	1.48 (1.21)	NR	NR	5.11 (3.03)	3.56 (2.91)	NR	NR	23.11 (16.27)	20.22 (11.56)	NR	NR
	TNFi alone	15		2.71 (1.48)	NR	NR	NR	4.15 (1.40)	3.92 (1.19)	NR	NR	26.31 (16.39)	21.15 (14.45)	NR	NR
Colina 2009 [6]	Spa therapy + Etanercept	30	12	5.6 (2.2)	1.9	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept alone	30		5.3 (2.5)	1.2	NR		NR	NR	NR	NR	NR	NR	NR	NR
Dragoi 2016 [7]	Inspiratory muscle training + CE	23	8	2.9 (1.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Conventional exercises (CE)	24		2.7 (1.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dundar 2014 [8]	Aquatic therapy	35	4	3.5 (2.9)	2.5 (2.2)	NR	NR	5.3 (2.7)	4.0 (2.4)	NR	NR	5.1 (2.6)	2.6 (2.5)	NR	NR
	Home-(land-) based therapy	34		3.6 (2.8)	2.5 (2.2)	NR	NR	5.2 (3.1)	3.9 (2.8)	NR	NR	4.9 (2.8)	3.3 (2.3)	NR	NR
Fernández García 2015 [9]	Aquatic + relaxation program	15	8	5.33 (1.69)¥	5.77 (1.96)¥	NR	0.015	NR	NR	NR	NR	NR	NR	NR	NR
	Control: no supervised therapies	15		5.68 (2.04)¥	3.81 (1.84)¥	NR		NR	NR	NR	NR	NR	NR	NR	NR
Figen 2011 [10]	Inpatient rehabilitation model	29	60	5.0 (2.9)	4.2 (3.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Home exercise model	31		3.4 (2.7)	2.7 (3.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gallinaro ACR 2013 [11]	Stretching exercises	40	16	NR	NR	NR	NR	4.7 (2.1)	NR	NR	NR	NR	NR	NR	NR
	Control			NR	NR	NR	NR		NR	NR	NR	NR	NR	NR	NR
Gunendi 2010 [12]	Supervised exercise program	16	3	2.8 (1.8)	1.7 (1.4)	1.1 (0.4; 1.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Home exercise program	16		2.4 (1.7)	2.9 (2.1)	-0.5 (-1.4; 0.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study ID	Intervention	n	Time point (weeks)	BASFI				BASMI				Pain global			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Hsieh 2014 [13]	ROM + strengthening + aerobic	9	12	3.7 (3.3)	1.9 (2.3)	NR	0.041	NR	NR	NR	NR	NR	NR	NR	NR
	Range-of-motion exercises (ROM)	10		3.5 (2.9)	3.5 (3.1)	NR		NR	NR	NR	NR	NR	NR	NR	NR
Jennings 2015 [1]	Aerobic (walking) + stretching exercises	35	12	4.28 (2.78)	3.37 (2.49)	NR	NR	5.15 (1.95)	4.93 (1.94)	NR	NR	NR	NR	NR	NR
	Stretching exercises	35		4.27 (2.32)	3.34 (2.07)	NR	NR	4.79 (2.22)	4.65 (2.14)	NR	NR	NR	NR	NR	NR
Karapolat 2009 [14]	Swimming + CE	13	6	2.34 (1.70)	1.97 (1.24)	NR	NR	5.15 (2.27)	4.18 (2.99)	NR	NR	NR	NR	NR	NR
	Walking + CE	12		2.25 (1.81)	2.25 (2.30)	NR	NR	4.54 (2.58)	4.54 (2.07)	NR	NR	NR	NR	NR	NR
	Conventional exercises (CE)	12		2.70 (2.52)	3.13 (2.65)	NR	NR	3.83 (3.75)	3.75 (2.67)	NR	NR	NR	NR	NR	NR
Kjeken 2013 [15]	Rehabilitation program	29	16	38.6 (33.5; 43.6)	33.6 (28.7; 38.6)	NR	NR	3.0 (2.3; 3.6)	2.8 (2.4; 3.3) [12 months]	NR	NR	NR	NR	NR	NR
	„treatment as usual“	34		42.4 (36.8; 48.0)	39.6 (34.6; 44.7)	NR	NR	2.6 (2.1; 3.1)	2.8 (2.4; 3.2) [12 months]	NR	NR	NR	NR	NR	NR
Masiero 2011§ [16]	**RG**: Rehabilitation + Education program + TNFi	20	8	2.5 (1.8-4.9)	1.6 (1.0-2.9)	NR	0.226 (RG vs EG)	4.4 (3.4-6.1)	3.7 (2.6-4.7)	NR	0.055 (RG vs EG)	NR	NR	NR	NR
	EG: Education program + TNFi	20		2.7 (1.2-3.5)	1.3 (0.6-4.0)	NR	0.222 (EG vs CG)	3.6 (2.6-5.1)	3.6 (2.6-4.7)	NR	0.844 (EG vs CG)	NR	NR	NR	NR
	CG: TNFi alone, no rehabilitation	22		2.8 (1.2-4.0)	3.0 (1.3-3.8)	NR	0.025 (RG vs CG)	3.8 (2.8-5.4)	3.7 (3.1-5.4)	NR	0.021 (RG vs CG)	NR	NR	NR	NR
Niedermann 2013 [17]	Nordic walking + flexibility	53	12	2.4 (1.9)	2.53 (0.21)	NR	0.63	2.9 (2.1)	2.53 (0.21)	NR	0.46	NR	NR	NR	NR
	Attention control + flexibility	53		2.4 (2.1)	2.40 (0.20)	NR		2.8 (1.9)	2.66 (0.28)	NR		NR	NR	NR	NR
Rosu 2014 [18]	Pilates + McKenzie + Heckscher	48	48	3.56 (1.83)	1.50 (1.11)	NR	0.001	3.73 (0.45)	1.19 (0.84)	NR	0.001	36.46 (10.42)	13.54 (7.85)	NR	0.001
	Classic kinetic training	48		3.42 (1.94)	2.76 (1.56)	NR		3.3 (0.45)	3.02 (0.44)	NR		34.79 (12.03)	21.04 (8.81)	NR	
Silva 2012 [19]	Global Postural Reeducation	22	16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Stretching + breathing exercises	16		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
So 2012 [20]	Incentive spirometer exercises (ISE) + CE + TNFi	23	16	0.98 (1.23)	0.75 (1.17)	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR
	Conventional Exercises (CE) + TNFi	23		1.72 (1.73)	1.26 (1.56)	NR		NR	NR	NR	NR	NR	NR	NR	NR
Strumse 2011 [2]	Reha program in a Mediterranean country	65	4	4.3 (2.0)	-2.6 (1.7)	NR	<0.001	NR	NR	NR	NR	NR	NR	NR	NR

Study ID	Intervention	n	Time point (weeks)	BASFI				BASMI				Pain global			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
	Reha program in Norway	42		4.3 (1.5)	-1.2 (1.2)	NR		NR	NR	NR	NR	NR	NR	NR	NR
Sveaas 2014 [21]	Endurance + strength training	10	12	2.6 (2.2)	1.5 (1.5)	NR	NR	2.3 (1.5)	2.0 (1.6)	NR	NR	NR	NR	NR	NR
	No exercises	24		3.1 (1.6)	3.1 (1.4)	NR	NR	3.0 (1.8)	2.9 (1.8)	NR	NR	NR	NR	NR	NR
Taspinar 2015 [22]	Hospital: calisthenic exercises + relaxation	18	8	3.16 (2.43)	2.63 (2.07)	0.53 (1.23)	>0.05 (FU change)	2.38 (1.19)	1.83 (1.04)	0.55 (0.78)	0.007 (FU change)	NR	NR	NR	NR
	Home: calisthenic exercises + relaxation	19		3.64 (2.87)	3.78 (2.67)	0.14 (1.50)		2.42 (1.50)	2.52 (1.34)	0.10 (0.56)		NR	NR	NR	NR
Yigit 2013 [23]	Home exercises > 5x/week + TNFi	20	10	3.22 (2.96)	2.27 (2.10)	0.96 (1.06)	<0.001 (FU change)	5.05 (2.74)	4.15 (2.62)	0.90 (1.07)	<0.001 (FU change)	NR	NR	NR	NR
	Home exercises < 5x/week + TNFi	20		3.86 (2.36)	4.00 (2.41)	-0.14 (1.07)		5.55 (2.50)	5.70 (2.52)	-0.15 (0.37)		NR	NR	NR	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control; § Masiero 2011: median (25th-75th percentile); ¥ mean (95% CI)

Table S9. Cochrane risk of bias assessment (Exercises)

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Altan 2012 [3]	U	U	H	H	L	L	L	H	Randomisation using random number table by researcher independently from study, no blinding of patients or outcome assessor
Aytekin 2012 [4]	H	H	H	H	L	U	L	H	No randomisation, no blinding of patients or outcome assessor; primary endpoint and time point not specified, unclear whether superiority or non-inferiority trial
Ciprian 2013** [5]	H	U	H	H	L	U	L	H	Randomisation by investigator, no blinding, small patient groups, no formal intergroup comparison; unclear whether superiority or non-inferiority trial, unclear whether negative or positive trial, time point for primary endpoint was not defined

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Colina 2009** [6]	H	H	H	H	L	H	L	H	No randomisation, no blinding, selctive reporting high; unclear whether superiority or non-inferiority trial, time point for primary endpoint was not specified
Dragoi 2016 [7]	H	L	H	U	L	L	L	H	Randomisation by investigator; no blinding of patients; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
Dundar 2014 [8]	L	L	H	U	L	L	L	U	No blinding of patients → blinding of outcome assessor can be broken, primary endpoint and time point not specified, unclear whether superiority or non-inferiority trial
Férnandez García 2015 [9]	H	H	H	H	L	H	L	H	Randomisation by an assistant, no blinding of patients or outcome assessors
Figen 2011 [10]	H	U	H	U	H	L	L	H	Randomisation by physiatrists; no blinding of patients; high drop-out rate
Gallinaro 2013* [11]	U	U	H	U	L	U	U	U	Abstract; less information; random sequence generation unclear; blinding unclear; primary endpoint and time point not specified, unclear whether superiority or non-inferiority trial
Gunendi 2010 [12]	H	H	H	H	L	U	L	H	No randomisation, no blinding; primary endpoint and time point not specified, unclear whether superiority or non-inferiority trial
Hsieh 2014 [13]	U	U	H	U	U	L	L	H	Random sequence generation unclear; allocation concealment unclear; no blinding of patients
Jennings 2015 [1]	L	L	H	U	L	L	L	H	No blinding of patients → blinding of outcome assessor can be broken; time point for primary endpoint was not defined
Karapolat 2009 [14]	U	L	H	U	L	U	L	H	Random sequence generation unclear; no blinding of patients; blinding of outcome assessors unclear; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
Kjeken 2013 [15]	L	L	H	U	L	L	L	U	No blinding of patients → blinding of outcome assessor can be broken; relatively high drop-out rate (during 12 months follow-up); unclear whether superiority or non-inferiority trial
Masiero 2011** [16]	L	U	H	U	L	U	L	H	Allocation concealment unclear, no blinding of patients or outcome assessors; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Niedermann 2013 [17]	L	L	H	U	L	L	L	U	No blinding of patients → blinding of outcome assessor can be broken; unclear whether superiority or non-inferiority trial
Rosu 2014 [18]	U	U	H	H	L	U	L	H	Blinding unclear, no drop-outs over 48 weeks, open label; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
Silva 2012 [19]	H	H	H	H	L	U	L	H	No randomisation, no blinding of patients or outcome assessors; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
So 2012** [20]	L	U	H	H	L	U	L	H	Randomised open-label case control study; no blinding; primary endpoint and time point not specified
Strumse 2011 [2]	H	U	H	H	L	U	L	H	Randomisation by a statistician, no blinding of patients or outcome assessors; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
Sveaas 2014 [21]	L	L	H	U	L	L	L	U	No blinding of patients → blinding of outcome assessor can be broken; unclear whether superiority or non-inferiority trial
Taspinar 2015 [22]	L	U	H	U	L	U	U	H	Allocation concealment unclear, no blinding of patients, blinding of outcome assessors unclear; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial
Yigit 2013** [23]	H	H	H	H	L	L	L	H	No randomisation; no blinding; primary endpoint and time point not specified; unclear whether superiority or non-inferiority trial

H= high risk; L = low risk; U = unclear risk.

*Abstract ** in combination with TNFi therapy

3.1.1.2 Education

Table S10. Study Protocol (Education)

Study ID	Intervention	n	Protocol	Frequency
Kaya 2013 [24]	Educational sessions	27	Educational sessions in small groups (10 patients respictively) from peer educators	1h/week
	Control	29	Educational booklet only, no other intervention	NR
Rodriguez-Lozano 2013 [25]	Education + home exercise program	381	30 min with a rheumatologist (information about physiopathology, disease process, …) + 30 min with a rheumatology nurse (information about general disease management, …) + 60 min exercises with a physiotherapist (first theoretically, then practically)	NR
	Standard care	375	Usual pharmacological and not-pharmacological treatments; no further educational program	NR

Table S11. Study characteristics (Education)

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention (weeks)	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
Kaya 2013 [24]	Educational sessions	27	mNY	RCT, NR*	4	78	43.1 (9.1)	NR	9 (1-31)	SF-36, ASQoL	Both (-)
	Control	29				86	40.9 (9.3)	NR	5 (1-25)		
Rodriguez-Lozano 2013 [25]	Education + home exercise program	381	mNY	RCT, NR*	24	71	45 (12)	NR	17 (10)	BASDAI, BASFI	Both (+)
	Standard care	375				73	46 (11)	NR	18 (11)		

(+) positive trial; (-) negative trial; **values**: mean (SD); median (min-max), *no information whether superiority or non-inferiority trial

Table S12. Disease activity outcomes – BASDAI, ASDAS (Education)

Study ID	Intervention	n	Time point (weeks)	BASDAI				ASDAS			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Kaya 2013 [24]	Education sessions	27	4	3.4 (0.2-9.2)	NR	NR	NR	NR	NR	NR	NR
	Control	29		2.2 (0.4-6.7)	NR	NR	NR	NR	NR	NR	NR
Rodriguez-Lozano 2013 [25]	Education + home exercise program	381	24	3.5 (2.3)	NR	-0.65 (-0.82; -0.47)	NR	NR	NR	NR	NR
	Standard care	375		3.7 (2.3)	NR	-0.37 (-0.55; -0.19)	NR	NR	NR	NR	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control

Table S13. Mobility, Function and Pain – BASFI, BASMI, Pain global (Education)

Study ID	Intervention	n	Time point (weeks)	BASFI				BASMI				Pain global			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Kaya 2013 [24]	Education sessions	27	4	3.9 (0.3-8.5)	NR	NR	NR	4 (0-10)	NR	NR	NR	NR	NR	NR	NR
	Control	29		2.1 (0.1-7.4)	NR	NR	NR	3 (0-10)	NR	NR	NR	NR	NR	NR	NR
Rodriguez-Lozano 2013 [25]	Education + Home exercise program	381	24	3.6 (2.5)	NR	-0.54 (-0.68; -0.40)	NR	NR	NR	NR	NR	3.5 (2.8)	NR	-0.76 (-0.99; -0.53)	NR
	Standard care	375		3.7 (2.6)	NR	-0.21 (-0.36; -0.007)	NR	NR	NR	NR	NR	3.7 (3.0)	NR	-0.44 (-0.68; -0.20)	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control

Table S14. Cochrane risk of bias assessment (Education)

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Kaya 2013 [24]	L	U	H	H	U	U	L	H	No blinding of patients or outcome assessors; unclear whether superiority or non-inferiority trial; time point for primary endpoint not defined
Rodriguez-Lozano 2013 [25]	L	L	H	U	L	L	L	U	No blinding of patients → blinding of outcome assessor can be broken; unclear whether superiority or non-inferiority trial

H= high risk; L = low risk; U = unclear risk.

3.1.1.3 Other non-pharmacological Interventions

Table S15. Study Protocol (Other non-pharmacological Interventions)

Study ID	Intervention	n	Protocol	Frequency
Annegret 2013 [26]	Radon Spa therapy	20	12 regional-specific radon baths of 36-38 °C and 20 min duration	Every 2-3 days
	Taper water baths	19	Same conditions as treatment group	NR
Aydin 2013 [27]	Low Laser Therapy	19	Laser: 1.2 Joule radiant energy, 30 mWatt power	10 sessions (ca. 20 min respectively)
	Placebo Laser	18	Placebo laser with inactive probe	NR
Stasinopoulos 2016 [28]	Low Laser Therapy + stretching	24	Active Laser: 2x/week (week 1-4); 1x/week (week 5-8) + stretching 2x/week for 16 weeks	NR
	Placebo Laser + stretching	24	Placebo Laser: 2x/week (week 1-4); 1x/week (week 5-8) + stretching 2x/week for 16 weeks	NR
Turan 2014 [29]	Magnetotherapy + exercises	35	Magnetotherapy (2 hertz, 80 Gauss, 20 min), heat pack, short wave, range of motion exercises	15 sessions (1 session/day)
	Placebo Magnetotherapy + exercises	31	Placebo, heat pack, short wave, range of motion exercises	

Table S16. Study characteristics (Other non-pharmacological Interventions)

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention (weeks)	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
Annegret 2013 [26]	Radon Spa therapy	20	mNY	Superiority trial, RCT	4	96	60.5 (17.1)	NR	NR	Pain (VAS 0-10)	(+)
	Taper water baths	19				97	59.6 (12.9)	NR	NR		
Aydin 2013 [27]	Low Laser Therapy	19	mNY	RCT, NR*	2	79	38.9 (10.7)	NR	6.6 (6.1)	NR	NR
	Placebo Laser	18				55	41.3 (13.4)	NR	8.7 (7.1)		
Stasinopoulos 2016 [28]	Low Laser Therapy + stretching	24	mNY	RCT, NR*	8	58.3	46.4 (7.5)	NR	8.9 (2.6)	NR	NR
	Placebo Laser + stretching	24				62.5	47.0 (8.9)	NR	8.0 (2.8)		
Turan 2014 [29]	Magnetotherapy + exercises	35	mNY	RCT, NR*	2	71	42.7 (9.1)	NR	160.6 (117.2) months	Harris hip assessment index	(-)
	Placebo Magnetotherapy + exercises	31				65	40.6 (9.8)	NR	168.9 (88.2) months		

(+) positive trial; (-) negative trial; **values**: mean (SD); *no information whether superiority or non-inferiority trial

Table S17. Disease activity outcomes – BASDAI, ASDAS (Other non-pharmacological Interventions)

Study ID	Intervention	n	Time point (weeks)	BASDAI				ASDAS			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Annegret 2013 [26]	Radon Spa therapy	20	4	NR	NR	NR	NR	NR	NR	NR	NR
	Taper water baths	19		NR	NR	NR	NR	NR	NR	NR	NR
Aydin 2013 [27]	Low Laser Therapy	19	2	5.4 (3.4-7.1)	2.8 (0.6-4.5)	NR	>0.05	NR	NR	NR	NR
	Placebo Laser	18		4.8 (1.9-5.5)	3.0 (1.6-5.0)	NR		NR	NR	NR	NR
Stasinopoulos 2016 [28]	Low Laser Therapy + stretching	24	8	28.2 (13.3)	21.3 (9.3)	NR	NR	NR	NR	NR	NR
	Placebo Laser + stretching	24		25.9 (12.0)	26.6 (10.0)	NR	NR	NR	NR	NR	NR
Turan 2014# [29]	Magnetotherapy + exercises	35	4	3.8 (2.05-5.6)	2.1 (1.0-3.4)	NR	0.19	NR	NR	NR	NR
	Placebo Magnetotherapy + exercises	31		3.7 (1.8-6.3)	3.2 (1.3-4.2)	NR		NR	NR	NR	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control; # Turan 2014: baseline: median (range); FU: median (25th-75th percentile)

Table S18. Mobility, Function and Pain – BASFI, BASMI, Pain global (Other non-pharmacological Interventions)

Study ID	Intervention	n	Time point (weeks)	BASFI				BASMI				Pain global			
				baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU	baseline	FU status	FU change	p-value* at FU
Annegret 2013 [26]	Radon Spa therapy	20	4	3.6 (2.0)	NR	-0.24 (1.49)	NR	NR	NR	NR	NR	5.35 (1.66)	NR	NR	NR
	Taper water baths	19		3.9 (2.3)	NR	-0.11 (0.86)	NR	NR	NR	NR	NR	5.50 (2.18	NR	NR	NR
Aydin 2013 [27]	Low Laser Therapy	19	2	3.1 (1.9-5.8)	1.6 (0.9-4.5)	NR	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo Laser	18		2.9 (1.6-5.8)	2.6 (1.5-5.2)	NR		NR	NR	NR	NR	NR	NR	NR	NR
Stasinopoulos 2016 [28]	Low Laser Therapy + stretching	24	8	51.5 (16.7)	37.4 (13.7)	NR	NR	NR	NR	NR	NR	70.0 (14.9)	33.1 (8.6)	NR	NR
	Placebo Laser + stretching	24		48.6 (17.5)	50.6 (15)			NR	NR	NR	NR	67.5 (15.8)	65.6 (14.3)	NR	NR
Turan 2014# [29]	Magnetotherapy + exercises	35	4	4.3 (1-6)	1.7 (0.4-4)	NR	0.466	4 (2-6)	3 (2-5)	NR	0.622	NR	NR	NR	NR
	Placebo Magnetotherapy + exercises	31		4.3 (1-6.4)	3 (0.3-5.7)	NR		4 (2-6)	3 (1-6)	NR		NR	NR	NR	NR

values: mean (SD); mean (-95%CI; + 95% CI); median (min-max); *treatment vs. control; # Turan 2014: baseline: median (range); FU: median (25th-75th percentile)

Table S19. Cochrane risk of bias assessment (Other non-pharmacological Interventions)

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Annegret 2013 [26]	L	U	L	L	L	L	L	L	
Aydin 2013 [27]	U	U	L	L	L	U	L	U	Randomisation unclear; no primary endpoint and time point defined
Stasinopoulos 2016 [28]	L	L	L	L	U	U	L	U	Primary endpoint and time point not specified, unclear whether superiority or non-inferiority trial
Turan 2014 [29]	L	U	L	L	L	L	L	L	

H= high risk; L = low risk; U = unclear risk.

3.1.2 Safety

Only Dundar 2014[8], Figen 2011[10], Karapolat 2009[14], Sveaas 2014[21], Aydin 2013[27] and Stasinopoulos 2016[28] reported data on adverse events. In none of these studies an adverse event occurred. All remaining studies did not give any information whether an adverse event occurred or not.

3.2 Non-biological Drugs

Cochrane Review: Kroon 2014 [30] - Non-steroidal anti-inflammatory drugs in axial spondyloarthritis: A cochrane review

3.2.1 Randomized Controlled Trials and Clinical Controlled Trials

Table S20. Study characteristics (Non-biological Drugs)

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
NSAIDs											
Balazcs ACR 2015 [31]	Naproxen 1000 mg/d	143	mNY	Non-inferiority trial, RCT	6 weeks	70.9	45.2	NR	NR	Δ Spinal Pain Intensity (VAS 0-100)	(+)
	Etoricoxib 60 mg/d	660						NR	NR		
	Etoricoxib 90 mg/d	144						NR	NR		
Huang 2014 [32]	Celecoxib 200 mg/d	117	mNY	Non-inferiority trial, RCT	6 weeks	88	29.5 (8.9)	NR	NR	Δ PatGA of Pain Intensity (VAS 0-100)	(+)
	Diclofenac 75 mg/d	115				84	28.8 (9.1)	NR	NR		
Zheng 2014 [33]	Palisade sacroiliac joint radiofrequency neurotomy	82	mNY	RCT, NR*	12 weeks	72	41.3 (38.3; 44.2)	76.8	8.4 (6.7; 10.0)	Global Pain Intensity (VAS 0-100)	(+)
	Celecoxib 400 mg/d	73				74	43.3 (40.5; 46.1)	79.5	7.9 (6.4; 9.3)		
Sieper 2015 [34]	Diclofenac continuous 150 mg/d	62	mNY	RCT, NR*	2 years	71	40.7 (9.6)	88.7	12.8 (11.3)	Δ mSASSS	(-)
	Diclofenac on-demand	60				66.7	45 (10.4)	91.7	17.0 (12.6)		
Kroon 2012 [35]	Celecoxib continuous 200 mg/d	76	mNY	RCT, NR* (Post hoc analyse of Wanders 2005)	2 years	66	38 (10.7)	88	13.0 (10.2)	Δ mSASSS	(+)
	Celecoxib on-demand	74				70	40.1 (10.5)	88	10.2 (9.3)		
Glucocorticoids											
Haibel 2014 [36]	Placebo	13	mNY	RCT, NR*	2 weeks	77	43 (16)	91	16 (16)	BASDAI 50	(-)
	Prednisolone 20 mg/d	11				82	35 (8.3)	73	13 (7.5)		
	Prednisolone 50 mg/d	12				92	42 (8.5)	73	14 (9.2)		

Study ID	Intervention	n	Definition of SpA	Study design	Duration of intervention	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)	Primary endpoint	Primary endpoint met?
Other non-biological Drugs											
Chang 2013 [37]	Tramadol 37.5mg/Acetaminophen 325mg + Aceclofenac 100mg (2x/d)	30	mNY	RCT, NR*	12 weeks	80	38 (17)	NR	NR	ASAS20	(+)
	Placebo + Aceclofenac 100mg (2x/d)	30				79.3	33 (13)	NR	NR		
Sarkar 2012 [38]	Pamidronate 60mg i.v. monthly	66	Amor	CCT, NR*	6 months	35	35.85 (6.04)	NR	3.85 (1.18)	ASAS20	(NR)
	Placebo	21				48	35.33 (6.34)	NR	3.71 (0.96)		
Jenks 2010 [39]	Probiotics (3 types) (ca. 0.8g 2x/d)	32	ESSG	RCT, NR*	12 weeks	59	45.5 (15)	94	9.8 (13)	BASFI	(-)
	Placebo	31				68	41.1 (10)	87	7.9 (7)		
Liu 2014 [40]	Xinfeng Capsule (1.5g 3x/d)	60	ASAS 2009	RCT, NR*	3 months	83	28 (10)	NR	10 (8)	NR	NR
	Sulfasalazine (1g 2x/d)	60						NR			
Wang 2013 [41]	Jitongning Capsule (0.5g 3x/d)	58	mNY	RCT, NR*	12 months	80	27.50 (8.20)	93	5.01 (3.56)	ASAS20	(-)
	Sulfasalazine (1g 2x/d)	53				80	29.50 (6.85)	95	4.83 (3.25)		

values: mean (SD); (+), positive trial; (-), negative trial; *no information whether superiority or non-inferiority trial

Sieper 2015: Diclofenac continuous (150 mg/day, at least 75 mg/day) vs. on-demand

Kroon 2012: Celecoxib continuous (200 mg/day, increase to 400 mg/day was allowed) vs. on-demand

Table S21. Disease activity outcomes – BASDAI, ASDAS, ASAS response criteria (Non-biological Drugs)

Study ID	Intervention	n	Time-point	BASDAI			BASDAI 50		ASDAS			ASAS 20		ASAS 40		ASAS partial remission	
				FU status	FU change	p-value*	%	p-value*	FU status	FU change	p-value*	%	p-value*	%	p-value*	%	p-value*
NSAIDs																	
Balazcs ACR 2015 [31]	Naproxen 1000 mg/d	143	6 weeks	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Etoricoxib 60 mg/d	660		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Etoricoxib 90 mg/d	144		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2014 [32]	Celecoxib 200 mg/d	117	6 weeks	NR	-1.1	NR	NR	NR	NR	NR	NR	40.7	NR	NR	NR	NR	NR
	Diclofenac 75 mg/d	115		NR	-1.4	NR	NR	NR	NR	NR	NR	42.6	NR	NR	NR	NR	NR
Zheng 2014 [33]	Palisade sacroiliac joint radiofrequency neurotomy	82	12 weeks	NR	NR	NR	NR	NR	NR	-0.1	NR	47.6	0.214	NR	NR	NR	NR
	Celecoxib 400 mg/d	73		NR	NR	NR	NR	NR	NR	-0.3	NR	57.5		NR	NR	NR	NR
Sieper 2015 [34]	Diclofenac continuous 150 mg/d	62	2 years	2.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Diclofenac on-demand	60		3.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kroon 2012 [35]	Celecoxib continuous 200 mg/d	76	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Celecoxib on-demand	74		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Glucocorticoids																	
Haibel 2014 [36]	Placebo	13	2 weeks	NR	-0.66	Ref	8	Ref	NR	-0.34	Ref	23	Ref	15	Ref	0	Ref
	Prednisolone 20 mg/d oral	11		NR	-1.19	0.41	27	0.3	NR	-1.16	0.036	39	0.08	27	0.63	18	0.2
	Prednisolone 50 mg/d oral	12		NR	-2.39	0.033	23	0.16	NR	-1.56	0.01	58	0.19	33	0.38	17	0.22
Other non-biological Drugs																	
Chang 2013 [37]	Tramadol 37.5mg/Acetaminophen 325mg + Aceclofenac 100mg (2x/d)	30	3 months	NR	-2.2	0.35	NR	NR	NR	NR	NR	53.3	0.047	NR	NR	NR	NR
	Placebo + Aceclofenac 100mg (2x/d)	30		NR	-1.5		NR	NR	NR	NR	NR	31.0		NR	NR	NR	NR
Sarkar 2012 [38]	Pamidronate 60mg i.v. monthly	66	12 months	3.99	NR	NR	63.64	NR	NR	NR	NR	72.73	NR	NR	NR	NR	NR
	Placebo	21		8.20	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jenks 2010 [39]	Probiotics (ca. 0.8g 2x/d)	32	12 weeks	3.2	NR	NS	NR	NR	NR	NR	NR	18.8	0.338	NR	NR	NR	NR
	Placebo	31		3.9	NR		NR	NR	NR	NR	NR	25.8		NR	NR	NR	NR

Study ID	Intervention	n	Time-point	BASDAI			BASDAI 50		ASDAS			ASAS 20		ASAS 40		ASAS partial remission	
				FU status	FU change	p-value*	%	p-value*	FU status	FU change	p-value*	%	p-value*	%	p-value*	%	p-value*
Liu 2014 [40]	Xinfeng Capsule (1.5g 3x/d)	60	3 months	2.54	NR	<0.05	91.7	<0.01	NR	NR	NR	93.3	<0.01	NR	NR	NR	NR
	Sulfasalazine (1g 2x/d)	60		2.92	NR		66.7		NR	NR	NR	71.7		NR	NR	NR	NR
Wang 2013 [41]	Jitongning Capsule (0.5g 3x/d)	58	12 months	2.03	NR	NR	NR	NR	NR	NR	NR	72.4	NS	NR	NR	NR	NR
	Sulfasalazine (1g 2x/d)	53		2.19	NR	NR	NR	NR	NR	NR	NR	67.9		NR	NR	NR	NR

*treatment vs. control

ASDAS response criteria: ASDAS clinically important improvement (Δ≥1.1), ASDAS major improvement (Δ≥2.0), ASDAS inactive disease (<1.3) were not reported by any trial on non-biological drugs.

ASAS response criteria: ASAS 5/6 was not reported by any of the study on non-biological drugs.

Table S22. Function, mobility and other outcomes (Non-biological Drugs)

Study ID	Intervention	n	Time-point	BASFI			BASMI			Pain global			mSASSS		
				FU status	FU change	p-value*	FU status	FU change	p-value*	FU status	FU change	p-value*	FU status	FU change	p-value*
NSAIDs															
Balazcs ACR 2015 [31]	Naproxen 1000 mg/d	143	6 weeks	NR	NR	NR	NR	NR	NR	NR	-29.0	NR	NR	NR	NR
	Etoricoxib 60 mg/d	660		NR	NR	NR	NR	NR	NR	NR	-31.23	NR	NR	NR	NR
	Etoricoxib 90 mg/d	144		NR	NR	NR	NR	NR	NR	NR	-30.59	NR	NR	NR	NR
Huang 2014 [32]	Celecoxib 200 mg/d	117	6 weeks	NR	-0.5	NR	NR	NR	NR	NR	-23.7	NR	NR	NR	NR
	Diclofenac 75 mg/d	115		NR	-0.8	NR	NR	NR	NR	NR	-26.7	NR	NR	NR	NR
Zheng 2014 [33]	Palisade sacroiliac joint radiofrequency neurotomy	82	12 weeks	NR	-2.5	NR	NR	-1.7	NR	NR	-4.7	NR	NR	NR	NR

Study ID	Intervention	n	Time-point	BASFI			BASMI			Pain global			mSASSS		
				FU status	FU change	p-value*	FU status	FU change	p-value*	FU status	FU change	p-value*	FU status	FU change	p-value*
	Celecoxib 400 mg/d	73		NR	-1.1	NR	NR	-0.4	NR	NR	-2.5	NR	NR	NR	NR
Sieper 2015 [34]	Diclofenac continuous 150 mg/d	62	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR	12.2	1.28	0.39 (FU change)
	Diclofenac on-demand	60		NR	NR	NR	NR	NR	NR	NR	NR	NR	17.2	1.79	
Kroon 2012 [35]	Celecoxib continuous 200 mg/d	76	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Celecoxib on-demand	74		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Glucocorticoids															
Haibel 2014 [36]	Placebo	13	2 weeks	NR	-0.74	Ref	NR	0.13	Ref	NR	-1.22	Ref	NR	NR	NR
	Prednisolone 20 mg/d oral	11		NR	-0.94	0.83	NR	-0.32	0.36	NR	-1.83	0.51	NR	NR	NR
	Prednisolone 50 mg/d oral	12		NR	-1.76	0.2	NR	-0.93	0.02	NR	-3.52	0.062	NR	NR	NR
Other non-biological Drugs															
Chang 2013 [37]	Tramadol 37.5mg/Acetaminophen 325mg + Aceclofenac 100mg (2x/d)	30	12 weeks	NR	NR	NR	NR	NR	NR	NR	-45.6	0.087	NR	NR	NR
	Placebo + Aceclofenac 100mg (2x/d)	30		NR	NR	NR	NR	NR	NR	NR	-25.7		NR	NR	NR
Sarkar 2012 [38]	Pamidronate 60mg i.v. monthly	66	6 months	3.82	NR	NR	3.08	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	21		7.91	NR	NR	7.81	NR	NR	NR	NR	NR	NR	NR	NR
Jenks 2010 [39]	Probiotics (ca. 0.8g 2x/d)	32	12 weeks	2.9	NR	NS	2.3	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	31		3.1	NR		2.4	NR	NR	NR	NR	NR	NR	NR	NR
Liu 2014 [40]	Xinfeng Capsule (1.5g 3x/d)	60	3 months	2.24	NR	<0.01	NR	NR	NR	2.16	NR	<0.01	NR	NR	NR
	Sulfasalazine (1g 2x/d)	60		3.25	NR		NR	NR	NR	3.14	NR		NR	NR	NR
Wang 2013 [41]	Jitongning Capsule (0.5g 3x/d)	58	12 months	0.76	NR	NR	0.81	NR	NR	1.42	NR	NR	NR	NR	NR
	Sulfasalazine (1g 2x/d)	53		0.91	NR	NR	1.30	NR	NR	2.50	NR	NR	NR	NR	NR

*treatment vs. control

Table S23. Main safety outcomes (Non-biological Drugs)

Study ID	Intervention	n	Time-point	Any Adverse events (AEs)			Serious AEs	Withdrawals due to AEs		Cardiovascular AEs		Gastrointestinal AEs		Infections		Renal AEs	
				n	%	p-value*	n	n	%	n	%	n	%	n	%	n	%
NSAIDs																	
Balazcs ACR 2015 [31]	Naproxen 1000 mg/d	143	6 weeks	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Etoricoxib 60 mg/d	660		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Etoricoxib 90 mg/d	144		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2014 [32]	Celecoxib 200 mg/d	117	6 weeks	5	4.2	NR	NR	2	1.7	0	NR	2	1.7	0	NR	NR	NR
	Diclofenac 75 mg/d	115		8	6.7	NR	NR	3	2.5	1	0.8	4	3.3	1	0.8	NR	NR
Zheng 2014 [33]	Palisade sacroiliac joint radiofrequency neurotomy	82	12 weeks	14	NR	NR	0	1	NR	NR	NR	2	2.4	3	3.7	NR	NR
	Celecoxib 400 mg/d	73		40	NR	NR	0	1	NR	NR	NR	12	**16.4**	0	NR	NR	NR
Sieper 2015 [34]	Diclofenac continuous 150 mg/d	62	2 years	19	NR	NR	19	NR	NR	3	NR	1	NR	NR	NR	1	NR
	Diclofenac on-demand	60		21	NR	NR	21	NR	NR	2	NR	7	NR	NR	NR	2	NR
Kroon 2012 [35]	Celecoxib continuous 200 mg/d	76	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Celecoxib on-demand	74		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Glucocorticoids																	
Haibel 2014 [36]	Placebo	13	2 weeks	6	46	NR	1	1	NR	NR	NR	NR	NR	NR	NR	1	NR
	Prednisolone 20 mg/d oral	11		4	36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Prednisolone 50 mg/d oral	12		5	42	NR	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other non-biological Drugs																	
Chang 2013 [37]	Tramadol 37.5mg/Acetaminophen 325mg + Aceclofenac 100mg (2x/d)	30	12 weeks	43	64.2	<0.001	NR	1	NR	NR	NR	7	10.4	1	1.5	NR	NR
	Placebo + Aceclofenac 100mg (2x/d)	30		24	35.8		NR	3	NR	NR	NR	3	4.5	1	1.5	NR	NR
Sarkar 2012 [38]	Pamidronate 60mg i.v. monthly	66	6 months	11	16.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	21		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jenks	Probiotics (ca. 0.8g 2x/d)	32	12 weeks	14	43.8	NR	0	NR	NR	NR	NR	NR	NR	1	NR	NR	NR

Study ID	Intervention	n	Time-point	Any Adverse events (AEs)			Serious AEs	Withdrawals due to AEs		Cardiovascular AEs		Gastrointestinal AEs		Infections		Renal AEs	
				n	%	p-value*	n	n	%	n	%	n	%	n	%	n	%
2010 [39]	Placebo	31		12	38.7	NR	0	NR	NR	NR	NR	NR	NR	0	NR	NR	NR
Liu 2014 [40]	Xinfeng Capsule (1.5g 3x/d)	60	3 months	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Sulfasalazine (1g 2x/d)	60		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang 2013 [41]	Jitongning Capsule (0.5g 3x/d)	58	12 months	6	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Sulfasalazine (1g 2x/d)	53		6	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR

bold = significant

No study reported a withdrawal due to death.

Table S24. Cochrane risk of bias assessment (Non-biological Drugs)

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
NSAIDs									
Balazcs ACR 2015* [31]	U	U	L	L	U	U	U	U	Abstract; less information; difficult to assess every item; 2-part, double-blind, active comparator-controlled non-inferiority study
Huang 2014 [32]	L	U	L	L	L	U	U	U	Part I: randomized, double-blind, active comparator (well designed); Part II: open-label extenstion (unclear, how the switch from 2 into 4 groups was performed after part I)
Zheng 2014 [33]	L	H	H	H	L	L	U	H	No information whether superiority or non-inferiority trial; open-label RCT, randomisation performed by an operating room nurse (probably involved in patient care)

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall	Comments on the assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*			
Sieper 2015 [34]	L	L	H	L	L	L	L	L	Blinding of the patients is not possible due to the length of the intervention, however most important in this study, the radiograph assessment was blinded
Kroon 2012 [35]	L	L	H	L	L	L	L	L	Blinding of the patients is not possible due to the length of the intervention, however most important in this study, the radiograph assessment was blinded
Glucocorticoids									
Haibel 2014 [36]	L	L	L	L	L	L	L	L	
Other non-biological Drugs									
Chang 2013 [37]	U	U	U	U	H	U	U	H	Blinding of patients and outcome assessors unclear; high drop-out rate
Sarkar 2012 [38]	H	U	U	U	U	H	H	H	non-randomized, no blinding for patients and outcome assessors, no comparison, selective reporting (e.g. ASAS 20 and BASDAI 50 only for pamidronate group); no intergroup comparison
Jenks 2010 [39]	L	L	L	L	L	L	L	L	
Liu 2014 [40]	U	U	U	U	U	H	H	H	Not clearly defined whether superiority or non-inferiority trial; primary endpoint and time point were not specified
Wang 2013 [41]	L	U	U	U	L	H	H	H	No information whether superiority or non-inferiority trial; time point for primary endpoint was not defined; blinding of patients and outcome assessors unclear, selective reporting

H= high risk; L = low risk; U = unclear risk.

3.2.2 Observational studies

The observational studies were included to assess the safety of different non-biological drugs. Studies were only eligible when when a comparator was available or population-based incidence rates were reported and at least 50 participants per group were included.

Table S25. Study characteristics – observational studies (Non-biological Drugs)

Study ID	Group / Intervention		n	Follow-up	Definition of SpA	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)
NSAIDs									
Kristensen 2015 [42]	r-axSpA/ other SpA	Etoricoxib	1,655	2006-2009	r-axSpA/other SpA (ICD codes)	48.2	83.8% <60 years	NR	NR
		Celecoxib	858			48.8	78.8% <60 years	NR	NR
		Traditional NSAIDs	15,580			51.6	79.9% <60 years	NR	NR
		Non-User	4,260			53.2	68.0% <60 years	NR	NR
Essers 2016 [43]	General population (control)		25,299	1987-2015	mNY	70.7	83% <60 years	NR	NR
	r-axSpA	Any NSAID	1,233			70.5	83% <60 years	NR	NR
		Naproxen	291					NR	NR
		COX-II inhibitors	287					NR	NR
		Traditional NSAID	692					NR	NR
Glucocorticoids									
Zhang 2015 [44]	Prednisone 10mg/methylprednisolone 8mg + NSAIDs (acemetacin 90mg/indomethacin 50mg/meloxicam 7.5mg)		555	variable (at least 6 months)	mNY	86.5	28 (9)	88.5	6.7 (5.9)
	NSAIDs (acemetacin 90mg/ indomethacin 50mg/meloxicam 7.5mg)		275			88	28 (10)	88.4	6.2 (6.1)

Table S26. Main safety outcomes – observational studies (Non-biological Drugs)

Study ID	Group / Intervention		n	Atherosclerotic events*	Ischaemic Heart Disease	GI-events	Serious infections
				aRR (95% CI)	aHR (95% CI)	aRR (95% CI)	aHR (95% CI)
NSAIDS							
Kristensen 2015 [42]	r-axSpA/other SpA	Etoricoxib	1,655	0.8 (0.4; 1.7)	NR	1.3 (0.6; 2.7)	NR
		Celecoxib	858	0.8 (0.3; 1.7)	NR	0.8 (0.3; 2.2)	NR
		Traditional NSAIDs	15,580	Ref	NR	Ref	NR
		Non-User	4,260	1.0 (0.7; 1.5)	NR	**0.5 (0.3; 0.7)**	NR
	r-axSpA	Etoricoxib	803	0.9 (0.4; 2.0)	NR	1.7 (0.8; 4.0)	NR
		Celecoxib	458	0.6 (0.2; 1.5)	NR	0.8 (0.2; 3.0)	NR
		Traditional NSAIDs	7,720	Ref	NR	Ref	NR
		Non-User	1,960	0.9 (0.7; 1.1)	NR	0.6 (0.4; 1.1)	NR
	r-axSpA/other SpA	Diclofenac	7,390	Ref	NR	Ref	NR
		Ibuprofen	3,200	0.9 (0.5; 1.5)	NR	0.6 (0.2; 1.4)	NR
		Indomethacin	907	1.3 (0.7; 2.3)	NR	1.2 (0.5; 2.8)	NR
		Ketoprofen	5,010	0.7 (0.4; 1.1)	NR	1.1 (0.6; 1.8)	NR
		Naproxen	3,250	0.9 (0.6; 1.4)	NR	0.9 (0.4; 1.7)	NR
		Non-User	4,260	0.9 (0.6; 1.2)	NR	**0.5 (0.3; 0.9)**	NR
Essers 2016 [43]	General Population (control)		25,299	NR	Ref §	NR	NR
	r-axSpA	Any NSAID	1,233	NR	**1.36 (1.00; 1.85)**	NR	NR
		Naproxen	291	NR	0.26 (0.04; 1.84)	NR	NR
		COX-II inhibitors	287	NR	**3.03 (1.61; 5.69)**	NR	NR
		Traditional NSAID	692	NR	1.32 (0.93; 1.89)	NR	NR
	Men r-axSpA	Any NSAID	893	NR	1.35 (0.95; 1.92)	NR	NR
		Naproxen	206	NR	0.29 (0.04; 2.05)	NR	NR
		COX-II inhibitors	202	NR	**3.11 (1.54; 6.29)**	NR	NR
		Traditional NSAID	514	NR	1.27 (0.85; 1.90)	NR	NR
	Female r-axSpA	Any NSAID	340	NR	1.68 (0.84; 0.33)	NR	NR
		Naproxen	85	NR	NR	NR	NR
		COX-II inhibitors	85	NR	**1.98 (1.34; 2.92)**	NR	NR
		Traditional NSAID	178	NR	1.55 (0.71; 3.37)	NR	NR
Glucocorticoids							
Zhang 2015 [44]	GC # + NSAIDs		555	NR	NR	NR	NR
	NSAIDs		275	NR	NR	NR	NR

bold = significant (p < 0.05); *atherosclerotic events = cardiac and cardiovascular; § R-axSpA-patients were compared with all controls, irrespective of their NSAIDs-use. The controls are the reference group. # Duration of GC-therapy: 1.7 (1.6) years

Table S27. Risk of bias assessment (Hayden tool for observational studies) (Non-biological Drugs)

Study ID	Study Participation	Study Attrition	Prognostic Factor Measurement	Study Confounding	Analysis	Overall	Comments on the assessment
NSAIDs							
Kristensen 2015 [42]	M	L	L	M	M	M	Register-based cohort; Outcome measurements were not validated; several confounders were mentioned, however they did not include the dose, level or duration of exposures
Essers 2016 [43]	M	L	M	M	M	M	Claims dataset; Outcome measurements not validated (IHD was defined as all types of IHD (included e.g. AMI, coronary artery bypass surgery, percutaneous intervention); information about the over-the-counter use of NSAID was lacking, which could lead to a missclassification of NSAID exposure; Limitation of definition „incident“ patients with AS (either because of a delay in diagnosis or because the first diagnostic code did not correspond with the actual date of diagnosis)
Glucocorticoids							
Zhang 2015 [44]	L	L	L	H	H	H	Claims dataset; Selective reporting -> only a few outcomes (blood lipids, bone mineral density, blood glucose, BMI) were shown and depending on the duration of GC exposure (<0,5 years, 0,5.-2 years, >2 years); Adjustment for confounding factors was limited due to the retrospective nature of the study; at baseline several data already missed; no validated outcomes used

H= high risk; L = low risk; M = moderate risk.

3.3 Surgical Interventions

Table S28. Study characteristics (Surgery)

Study ID	Group / Intervention			n	Follow-up	Definition of SpA	Males (%)	Age (years)	HLA-B27+ (%)	Disease duration (years)
Debarge 2011 [45]	r-axSpA	all	PSO §	28	variable (minimum 2 years)	r-axSpA not further defined with **fixed kyphotic deformity**	68	41.7 (8.3) [22-64]	NR	NR
		low pelvic incidence¥ (≤50°)	PSO §	7			NR	NR	NR	NR
		high pelvic incidence¥ (≥50°)	PSO §	21			NR	NR	NR	NR
	control	healthy young volunteers	no PSO	154			NR	NR	NR	NR
Goodman 2014 [46]	r-axSpA	Total Hip Replacement #		30	2 years	Clinical diagnosis of r-axSpA + mNY	80	52.7 (16.2)	NR	NR
	OA			132			45	53.2 (14.6)	NR	NR
	r-axSpA *primary*			28			NR	62.0 [45.0-70.0]	NR	NR
	r-axSpA *revision*			7			NR	52.0 [43.0-69.0]	NR	NR
Lee 2010 [47]	r-axSpA	PSO + Bone grafting*		10	mean 22 months	R-axSpA not further defined with **fixed kyphotic deformity**	70	41.3 (30-67)	NR	NR
	DSD			26			46	43.1 (35-50)	NR	NR

mean (min-max); mean (SD); median [min-max]; mean (SD) [range]

¥ Pelvic incidence: angle between a line drawn from center of the hip axis to the center of the superior endplate of S1 and perpendicular to the endplate

§ Pedicle subtraction osteotomy (PSO): one-level osteotomy in all patients; Angulations osteotomies ranged between 30-40°; height: L3 (12 patients), L4 (16 patients)

r-axSpA: THR (primary unilateral: 21 patients; primary bilateral: 2 patients; revision unilateral: 7 patients); **sacroiliitis (mNY):** in 28 patients available; grade availibility of follow-up data: 63%; **OA**: availibility of follow-up data: 100%

****First step***: **r-axSpA**: pedicle subtraction osteotomy (1 patient: Smith-Petersen osteotomy), followed by posterolateral fusion, and decompression and posterolateral fusion; **DSD**: pedicle subtraction osteotomy, followed by posterolateral fusion, and decompression and posterolateral fusion; ***Second step:*** **r-axSpA**: two-level bone grafting: autogenous bone grafts or bone substitutes overall 9 (hydroxyapatite + calcium phosphate 6 patients; demineralized bone matrix 2 patients; allograft 1 patient); **DSD**: two-level only autogenous iliac bone grafting after decompression and spinal fusion (diagnosis: spinal stenosis 15 patients; spondylolisthesis 8 patients; herniated lumbar disc 3 patients)

Table S29. Main outcomes (Surgery)

Study ID	Group / Intervention			n	Radiographic assessment						Short-form health survey-12						Lenke´s classification bone union #	
					Pelvic Tilt (°)			C7 tilt (°)			Physical component scale			Mental Component Scale				
					pre-op	post-op	p-value¥	pre-op	post-op	p-value¥	baseline	2 years status score	p-value*	baseline	2 years status score	p-value*	Time point post-op	p-value*
Debarge 2011 [45]	r-axSpA	all	PSO	28	38.5 (10.9) [15-64]	31.7 (9.2) [13-50]	0.003	72.6 (14.7) [23-98]	83.1 (7.3) [60-95]	0.0025	NR	NR	NR	NR	NR	NR	NR	NR
		low pelvic incidence (≤50°)	PSO	7	32.7 (8.4) [22-47]	26.1 (7.8) [15-38]	0.003	72.3 (6.7) [66-88]	86.4 (5.7) [77-95]	0.0025	NR	NR	NR	NR	NR	NR	NR	NR
		high pelvic incidence (≥50°)	PSO	21	40.4 (10.8) [15-64]	33.6 (8.8) [13-50]	0.003	71.0 (15.9) [23-98]	82 (7.4) [60-92]	0.0025	NR	NR	NR	NR	NR	NR	NR	NR
	control	healthy young volunteers	no PSO	154	11.1 (5.8) [8-34]	NR	NR	95.4 (1.4) [90-97]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Goodman 2014 [46]	r-axSpA	Total Hip Replacement		30	NR	NR	NR	NR	NR	NR	29.6 (8.7)	41.2 (11.1)	<0.001	43.2 (11.7)	51.0 (9.1)	0.14	NR	NR
	OA			132	NR	NR	NR	NR	NR	NR	36.0 (8.1)	50.1 (10.1)		49.7 (11.6)	53.9 (9.9)		NR	NR
	r-axSpA *primary*			28	NR	NR	NR	NR	NR	NR	NR	47.9 (13.4-58.0) §	0.09	NR	56.4 (20.1-67.1)§	0.34	NR	NR
	r-axSpA *revision*			7	NR	NR	NR	NR	NR	NR	NR	30.5 (11.5-58.5) §		NR	49.6 (30.1-70.1) §		NR	NR
Lee 2010 [47]	r-axSpA	PSO + Bone grafting*		10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.5 months (3-5)	0.023
	DSD			26	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	5.6 months (4-12)	

mean (SD) [range]; mean (SD); mean (min-max); *r-axSpA vs. control; § median (min-max); ¥ pre-operative vs. post-operative; # to assess the overall union; type A: solid bilateral union; type B: unilateral large fusion mass with contralateral small fusion mass; Pelvic tilt: horizontal distance of C7 plumb from the posterosuperior corner of L5/S1 disc and the sacro-horizontal angle

None of the surgical studies reported data on other disease activity (BASDAI, ASDAS), functional (BASFI) or mobility parameters (BASMI). Therefore some data of each study is shown separately (i.e. for outcomes not a priori defined for this SLR).

Data on safety was not provided by any of the surgical studies.

Table S30. Risk of bias assessment (Hayden tool for observational studies) (Surgery)

Study ID	Study Participation	Study Attrition	Prognostic Factor Measurement	Study Confounding	Analysis	Overall	Comments on the assessment
Debarge 2011 [45]	H	H	H	H	H	H	Radiographic study; no confounders mentioned; small group size (only 26 AS-patients); comparator: radiographic angles of healthy controls
Lee 2010 [47]	H	H	H	H	H	H	No confounders mentioned; small group size (only 10 AS-patients); comparator: patients with degenerative spinal disease

H= high risk; L = low risk; M = moderate risk.

Table S31. Risk of bias assessment (Newcastle-Ottawa Scale Score for case-control studies) (Surgery)

Study ID	Selection (max. 4 stars)	Comparability (max. 2 stars)	Exposure (max. 3 stars)	Overall	Comments on the assessment
Goodman 2014 [46]	2 stars	0 star	1 star	H	Comparator: patients with osteoathritis (hospital controls); unclear, whether interviewer was blinded to case/control status; no information about non-response rate for every group respectively

Overall: 1-3 stars = High risk; 4-6 stars = Moderate risk; 7-9 stars = Low risk

4. LIST OF PUBLICATIONS

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5. STUDIES EXCLUDED DUE TO LANGUAGE RESTRICTION (NO FULL-TEXT OBTAINED)

Table S32 Studies excluded due to language restriction (no full-text obtained)

Study	Title	Journal	Language
Gaidukova 2014	[Etoricoxib in the treatment of active sacroiliitis in patients with axial spondyloarthritis, including ankylosing spondylitis]	Ter Arkh. 86(12):42-7	Russian (full-text)
Gaydukova 2014	Efficacy and safety of different schemes of etoricoxib administration in patients with axial spondyloarthritis-results of a 12-week, prospective, open-label study	Eular 2014	Russian (full-text)
Gunay 2011	The impact of the exercise therapy on the quality of life and the respiratory functions in patients with ankylosing spondylitis, Ankilozan spondilitli hastalarda egzersiz tedavisinin solunum fonksiyonlarina ve yaflam kalitesine etkisi. [Turkish, English]	Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi	Turkish
Jo 2012	Acupuncture's Efficacy and Safety in Axial Spondyloarthritis within 4 Weeks Session: a Randomized, Double-blind, Sham-controlled Trial	Not mentioned	Korean
Yildiz 2013	Effectiveness of physical therapy agents in patients with ankilosing spondilitis, Ankilozan Spondilit Hastalarinda Fizik Tedavi Ajanlarinin Etkinliti. [Turkish, English]	Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi	Turkish

6. LIST OF ABBREVIATIONS

AE	Adverse events
aHR	adjusted Hazard ratio
AMI	Acute Myocardial Infarction
aOR	adjusted Odds ratio
AS	Ankylosing Spondylitis = R-axSpA
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
axSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Metrology Index
BMI	Body Mass Index
CCT	Controlled Clinical Trial
CI	Confidence interval
CRP	C-reactive protein
csDMARDs	conventional-synthetic DMARDs
DAE	Dermatological adverse event
DMARDs	Disease-modifying antirheumatic drugs
DSD	Degenerative spinal disease
ESSG	European Spondyloarthropathy Study Group
FU	follow-up
GC	Glucocorticoids
GI	Gastrointestinal
HLA-B27	Human Leukocyte Antigen
HR	Hazard Ratio
HSS	Hospital for Special Surgery
ICD	International Classification of Disease
IHD	Ischaemic heart disease
i.v.	intravenous
mNY	modified New York-criteria
MPR	Medication Possession Rate
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
mths	months
NR	Not-reported
NS	Non-significant
NSAIDs	Non-steroidal anti-inflammatory drugs
py	patient-years
OA	Osteoarthritis
OR	Odds Ratio
PatGA	Patient Global Assessment
PSO	Pedicle Subtraction Osteotomy

R-axSpA	Radiographic axial spondyloarthritis
RCT	Randomized Controlled Trial
SD	Standard Deviation
SF-36	Short Form 36
SLR	Systematic Literature Review
SpA	Spondyloarthritis
THR	Total Hip Replacement
TNFi	Tumor necrosis factor inhibitor
tsDMARDs	targeted-synthetic DMARDs
VAS	visual analog scale
Δ	change from baseline to FU