Comparison of characteristics and burden of disease between patients with radiographic and non-radiographic axial Spondyloarthritis: a systematic literature review and meta-analysis.

Online supplementary material

Online Supplementary Table S1. Search strategy prepared for EMBASE, Medline and Cochrane:

EMBASE	
Topic	**Search string**
nr-axSpA	"non radiographic axial spondyloarthritis OR "non radiographic axial" OR "nonradiographic axial"
r-axSpA	spondylarthritis/exp OR ankylosing spondylitis/exp OR bechterew* OR bekhterev* OR sacroiliitis/exp
nr-axSpA vs. r-axSpA	1 AND 2 published in the last 10 years
Medline	
Topic	**Search string**
nr-axSpA	("non radiographic axial"[All Fields] OR (nonradiographic[All Fields] AND axial[All Fields]))
r-axSpA	(((((Bekhterev[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields])) OR ("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("bekhterev's"[All Fields] AND "disease"[All Fields]) OR "bekhterev's disease"[All Fields])) OR ((Bekhterev[All Fields] AND ("spondylitis"[MeSH Terms] OR "spondylitis"[All Fields])) OR (Bekhterev's[All Fields] AND ("spondylitis"[MeSH Terms] OR "spondylitis"[All Fields])))) OR (("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("bechterew"[All Fields] AND "disease"[All Fields]) OR "bechterew disease"[All Fields]) OR ("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("bechterew's"[All Fields] AND "disease"[All Fields]) OR "bechterew's disease"[All Fields]))) OR ("Spondylitis, Ankylosing"[Mesh] OR (("sacroiliitis"[MeSH Terms] OR "sacroiliitis"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR "Spondylarthritis"[Mesh] OR ("spondylarthritis"[MeSH Terms] OR "spondylarthritis"[All Fields] OR "spondyloarthritis"[All Fields]))))
nr-axSpA vs. r-axSpA	1 AND 2 AND published in the last 10 years
COCHRANE	
Topic	**Search string**

nr-axSpA	"non radiographic axial"
r-axSpA	"radiographic axial" OR "ankylosing spondylitis" OR sacroiliitis OR Bekhterev* OR Bechterew*
nr-axSpA vs. r-axSpA	1 AND 2 published in the last 10 years

Supplementary Table S2. Description of the outcomes evaluated.

Study identifiers	- Three first authors' names - Study title - Publication type - Publication year - Journal
Study type	- Randomized Controlled Trials (RCT) - Observational studies (cross-sectional, cohort, case control)
Participants	- Definition of r-axSpA and nr-axSpA - Number of patients per group and total
Intervention	- None - Treatment: TNFalpha inhibitors, NSAIDs, COXIBs, glucocorticoids (oral, intravenous or intraarticular), csDMARDs
Outcomes	
- **Clinical presentation**	**SOCIO-DEMOGRAPHIC VARIABLES** - Age (years) - Sex - Body Mass Index (BMI, kg/m^2) - Ethnicity - Smoker (ever vs. never) **SPONDYLOARTHRITIS FEATURES** - Age at symptom onset - Time to diagnosis (years) - HLA-B27 status - Inflammatory Back Pain - Good NSAIDs response - Family history of Spondyloarthritis - Peripheral manifestations (arthritis, heel enthesitis, any enthesitis, dactylitis) - Extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease) **IMAGING** - Positive sacroiliac MRI (sacroiliac joints or spine) according to the ASAS definition - Patients with erosions on MRI-SIJ - Patients with fatty lesions on MRI-SIJ - Quantification of bone marrow oedema (e.g. SPARCC, Berlin score) - mSASSS - Patients with at least one syndesmophyte
- **Burden of the disease**	**DISEASE ACTIVITY** - C-reactive protein (CRP) - Erythrocyte sedimentation rate (ESR)

	- BASDAI - ASDAS-CRP - VAS back pain - VAS pain - Patient Global Assessment - Physician Global Assessment **FUNCTION** - BASFI - HAQ-S **QUALITY OF LIFE** - SF-36 questionnaire Physical component (PCS) - SF-36 mental component (MCS) - ASQoL - HADS-anxiety - HADS-depression - EQ-5D **MOBILIY** - BASMI **WORK PRODUCTIVITY** - Days of sick leave - Work loss (absenteeism and presentism, including work disability)
- **Treatment**	- Number of patients under TNF-alpha inhibitors, NSAIDs, COXIBs, glucocorticoids (oral, intravenous or intraarticular), csDMARDs
- **Treatment effect**	- ASAS20 - ASAS40 - BASDAI50 - CRP - ASDAS - BASDAI - global VAS - pain VAS - ASAS partial remission - ASDAS major improvement - ASDAS inactive disease - MRI (sacroiliac joints or spine) or quantification of bone marrow oedema (e.g. SPARCC)

ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI: Bath Ankylosing Spondyitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; COXIBs: COX-2 inhibitors; csDMARDs: conventional synthetic Disease-modifying anti-rheumatic drugs; EQ-5D: EuroQuol-5D; HAQ-S: Health Assessment Questionnaire for Spondyloarthropathies; MRI: Magnetic Resonance Image; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs: non-steroidal anti-inflammatory drugs; SIJ: sacroiliac joints; SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system; VAS: Visual Analogue Scale.

Supplementary Table S3. Details of manuscripts selected for data extraction.

Randomized Controlled Trials							
Authors	**Study design**	**Follow-up**	**P (patients)**	**I (Intervention)**	**C (Comparator)**	**O (Outcome)**	**Risk of bias**
Song IH 2013	RCT	1 year	AS (n=20)	Etanercept 50mg/week vs. SSZ	Nr-axSpA (n=20)	-Clinical presentation -Burden of disease -Treatment effect	Unclear
Song IH 2014	RCT	3 years	AS (n=31)	Etanercept 50mg/week vs. SSZ	Nr-axSpA (n=30)	-Treatment effect	Unclear
Landewé R 2014	RCT	6 months (24 weeks)	AS (n=178)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=147)	-Clinical presentation -Burden of disease -Treatment -Treatment effect	Low risk
Sieper J 2015	RCT	6 months (24 weeks)	AS (n=178)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=147)	-Treatment effect	Low risk
Osterhaus JT 2014	RCT	1 year (48 weeks)	AS (n=178)	Certolizumab (200mg Q2W or 400 mg Q4W) vs. Placebo	Nr-axSpA (n=147)	-Burden of disease	Low risk
Sieper J 2015	RCT	2 years (96 weeks)	AS (n=178)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=147)	-Clinical presentation -Treatment effect	Low risk
Rudwaleit M 2016	RCT	2 years (96 weeks)	AS (n=178)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=147)	-Clinical presentation -Treatment effect	Low risk
van der Heijde D 2018	RCT	4 years (204 weeks)	AS (n=174)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=141)	-Clinical presentation -Treatment effect	Low risk

van der Heijde D 2017	RCT	4 years (204 weeks)	AS (n=97)	Certolizumab (200mg Q2W, or 400mg Q4W) vs. Placebo	Nr-axSpA (n=121)	-Treatment effect	Low risk
Sieper J 2016	RCT	28 weeks	AS (n=94)	IFX 5mg/kg iv + NPX 1000mg/day OR iv. Placebo + NPX 1000 mg/day	Nr-axSpA (n=56)	-Clinical presentation -Burden of disease -Treatment effect	Unclear
Observational studies							
Authors	**Study design**	**Follow-up**	**P (Patients)**	**I (Intervention)**	**C (Comparator)**	**O (Outcome)**	**Risk of bias**
Glintborg B 2017	Cohort	8 years	AS (n=622)	TNFb (all patients)	nr-axSpA (n=362)	-Clinical presentation -Burden of disease -Treatment	No risk
Poddubnyy D 2012	Cohort	2 years	AS (n=115)	None	Nr-axSpA (n=95)	-Clinical presentation -Burden of disease -Treatment	No risk
Poddubnyy D 2015	Cohort	2 years	AS (n=158)	None	Nr-axSpA (n=145)	-Clinical presentation -Burden of disease -Treatment	No risk
Jeong H 2015	Cohort	2-3 years	AS (n=459)	None	Nr-axSpA (n=155)	-Clinical presentation -Burden of disease	Unsure
Wallman JK 2015	Cohort	3 years	AS (n=238)	TNFb (all patients)	Nr-axSpA (n=86)	-Clinical presentation -Burden of disease -Treatment	Unsure
Poddubnyy D 2012	Cohort	2 years	AS (n=88)	NSAIDs (all patients)	Nr-axSpA (n=76)	-Clinical presentation -Burden of disease -Treatment	No risk

Baraliakos X 2017	Cohort	4 weeks	r-axSpA (n=50)	NSAIDs (all patients)	Nr-axSpA (n=50)	-Clinical presentation -Burden of disease	No risk
Dougados M 2016	Cohort	2 years	Nr-axSpA (n=326)	None	AS (n=123)	-Clinical presentation	No risk
Poddubnyy D 2011	Cohort	2 years	Nr-axSpA (n=115)	None	AS (n=95)	-Clinical presentation	No risk
Lubrano E 2015	Cohort	6 months	Nr-axSpA (n=62)	TNFb (all patients)	AS (n=259)	-Clinical presentation -Burden of disease -Treatment	No risk
Corli J 2015	Cohort	12 months	AS (n=263)	TNFb (all patients)	Nr-axSpA (n=98)	-Clinical presentation -Burden of disease -Treatment	Unsure
Ciurea A 2013	Cohort	12 months	AS (n=838)	TNFb	Nr-axSpA (n=232)	-Clinical presentation -Burden of disease -Treatment	No risk
Gavali M 2015	Cross-sectional	None	AS (n=55)	None	Nr-axSpA (n=41)	-Clinical presentation -Burden of disease	Unsure
Althoff CE 2013	Cross-sectional	None	AS (n=39)	None	Nr-axSpA (n=36)	-Clinical presentation -Burden of disease	No risk
Wallis D 2013	Cross-sectional	None	AS (n=639)	None	Nr-axSpA (n=73)	-Clinical presentation -Burden of disease -Treatment	Unsure
Mease PJ 2018	Cross-sectional	None	AS (n=310)	None	Nr-axSpA (n=97)	-Clinical presentation -Burden of disease -Treatment	Unsure
Poddubnyy D 2010	Cross-sectional	None	AS (n=153)	None	Nr-axSpA (n=116)	-Burden of disease	No risk
Malaviya AN 2018	Cross-sectional	None	AS (n=187)	None	Nr-axSpA (n=101)	-Clinical presentation -Burden of disease	Unsure

						-Treatment	
Prabhakar U 2018	Cross-sectional	None	AS (n=50)	None	Nr-axSpA (n=50)	-Clinical presentation -Burden of disease	Unsure
Zou Q 2016	Cross-sectional	None	AS (n=40)	None	Nr-axSpA (n=20)	-Clinical presentation -Burden of disease	Unsure
Weber U 2013	Cross-sectional	None	AS Cohort A: 10 Cohort B: 24	None	Nr-axSpA Cohort A:20 Cohort B:31	-Clinical presentation -Burden of the disease	No risk
Weber U 2015	Cross-sectional	None	AS Cohort A: 9 Cohort B: 24	None	Nr-axSpA Cohort A: 19 Cohort B: 31	-Clinical presentation	No risk
Bradbury LA 2018	Cross-sectional	None	AS (n=18)	TNFb	Nr-axSpA (n=20)	-Clinical presentation -Burden of disease	Unsure
Kilic E 2015	Cross-sectional	None	Nr-axSpA (n=132)	None	AS (n=155)	-Clinical presentation -Burden of disease	Unsure
Huang J 2017	Cross-sectional	None	AS (n=53)	None	Nr-axSpA (n=59)	-Clinical presentation	Unsure
Kiltz U 2012	Cross-sectional	None	Nr-axSpA (n=44)	None	AS (n=56)	-Clinical presentation -Burden of disease	No risk
Weber U 2015	Cross-sectional	None	Nr-axSpA Cohort A:20 Cohort B:30	None	AS Cohort A:10 Cohort B:24	-Clinical presentation	No risk
Erol K 2018	Cross-sectional	None	AS (n=352)	None	Nr-axSpA (n=193)	-Clinical presentation -Burden of disease -Treatment	Unsure
Bedaiwi M 2015	Cross-sectional	None	AS (n=615)	None	Nr-axSpA (n=66)	-Clinical presentation -Burden of disease -Treatment	No risk

Weber U 2014	Cross-sectional	None	Nr-axSpA Cohort A:20 Cohort B:31	None	AS Cohort A:10 Cohort B:24	-Clinical presentation	No risk
Deodhar A 2016	Cross-sectional	2 time points	AS (n=101)	None	Nr-axSpA (n=157)	-Clinical presentation -Burden of disease	No risk
Fan A 2017	Cross-sectional	None	Nr-axSpA (n=64)	None	AS (n=137)	-Burden of disease	Unsure
Castillo-Gallego C 2013	Cross-sectional	None	Nr-axSpA (n=24)	None	AS (n=19)	-Clinical presentation	No risk
Poddubnyy D 2013	Cross-sectional	None	AS (n=68)	TNFb (all patients)	Nr-axSpA (n=44)	-Clinical presentation	No risk
Akgul O 2013	Cross-sectional	None	Nr-axSpA (n=14)	None	AS (n=22)	-Clinical presentation -Burden of disease	No risk
Gok K 2018	Cross-sectional	None	Nr-axSpA (n=57)	None	AS (n=128)	-Clinical presentation -Burden of disease	No risk
Kang KY 2017	Cross-sectional	None	AS (n=45)	None	Nr-axSpA (n=36)	-Clinical presentation -Burden of disease -Treatment	No risk
Monti S 2018	Cross-sectional	None	AS (n=165)	TNFb (all patients)	Nr-axSpA (n=53)	-Clinical presentation -Burden of disease -Treatment	Unsure
Kilic G 2014	Cross-sectional	None	Nr-axSpA (n=142)	None	AS (n=174)	-Clinical presentation -Burden of disease	No risk
Wadeley A 2018	Cross-sectional	None	Nr-axSpA (n=61)	None	AS (n=598)	-Clinical presentation -Burden of disease	No risk
Kiltz U 2012	Cross-sectional	None	Nr-axSpA (n=44)	None	AS (n=56)	-Clinical presentation -Burden of disease	No risk

Rudwaleit M 2009	Cross-sectional	None	AS (n=119)	None	Nr-axSpA (n=226)	-Clinical presentation -Burden of disease -Treatment	No risk
Poddubnyy D 2012	Cross-sectional	None	AS (n=119)	None	Nr-axSpA (n=109)	-Clinical presentation -Burden of disease	No risk
Burgos-Vargas R 2016	Cross-sectional	None	Nr-axSpA (n=266)	None	AS (n=491)	-Clinical presentation -Burden of disease	No risk
Lubrano E 2018	Cross-sectional	12 months	AS (n=270)	TNFb (all patients)	Nr-axSpA (n=51)	-Clinical presentation	Unsure
van Hoeven L 2017	Cross-sectional	None	Nr-axSpA (n=71)	None	AS (n=24)	-Clinical presentation -Burden of disease	No risk
Bautista-Molano W 2018	Cross-sectional	None	AS (n=30)	None	Nr-axS-pA (n=14)	-Clinical presentation -Burden of disease	No risk
Fernandez-Espartero C 2014	Cross-sectional	None	AS (n=89)	None	Nr-axSpA (n=362)	-Clinical presentation -Burden of disease -Treatment	No risk
Hu Z 2016	Case-control	None	AS (n=297)	None	Nr-axSpA (n=126)	-Clinical presentation -Burden of the disease	No risk
Cantini F 2017	Case-control	12 months	AS (n=47)	None	Nr-axSpA (n=32)	-Clinical presentation	Unsure

AS: Ankylosing Spondylitis ; Nr-axSpA : non-radiographic axial Sondyloarthritis; RCT : Randomized Controlled Trials; r-axSpA: radiographic axial Spondyloarthritis; TNFb: TNF-alpha blockers.

Supplementary Table S4. Data for treatment effect from individual studies: ESTHER trial.

Etanercept vs. Sulfasalazine (ESTHER trial) 2 manuscripts						
Follow-up	**1 year n = 40**			**3 years n = 61**		
	r-axSpA	**nr-axSpA**	**p-value**	**r-axSpA**	**nr-axSpA**	**p-value**
ASAS partial remission	40%	60%	n.s.	26%	33%	NA
ASDAS major improvement	30%	25%	n.s.	26%	37%	NA
ASDAS				1.6 (1.0)	1.5 (1.0)	n.s.
BASDAI				2.7 (2.5)	2.4 (2.3)	n.s.

Supplementary Table S5. Data for treatment effect from individual studies: RAPID trial.

Certolizumab vs. Placebo (RAPID trial) 6 manuscripts									
Follow-up	**6 months n = 326**					**2 years n =218**		**4 years n = 218**	
Dose	**200mg Q2W**		**400mg Q4W**			**Any dose**		**Any dose**	
	r-axSpA	**nr-axSpA**	**r-axSpA**	**nr-axSpA**	**p-value**	**r-axSpA**	**nr-axSpA**	**r-axSpA**	**nr-axSpA**
ASAS40	47.7%	56.6%	58.9%	45.1%	n.s.	50.4%	50.5%	68.0%	68.3%
ASDAS major improvement						51.2%	47.4%		
ASDAS inactive disease						30.6%	38.1%	28.8%	35.0%

Supplementary Table S6. Data for treatment effect from individual studies: INFAST study.

Infliximab + Naproxen vs. Placebo + Naproxen (INFAST study)				
Follow-up	**28 weeks n = 150**			
	Infliximab + Naproxen		**Placebo + Naproxen**	
	r-axSpA	**nr-axSpA**	**r-axSpA**	**nr-axSpA**
ASAS partial remission	70.5%	50.0%	33.3%	37.5%
ASAS40	86.9%	60.6%	54.5%	56.3%
Median change SIJ MRI score	-3.0	-2.0	-3.0	-3.5
Median change Berlin MRI spine score	-1.0	0	-1.0	0

ASAS: Assessment in SpondyloArthritis International Society (ASAS); ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity

Index; nr-axSpA: non-radiographic axial Spondyloarthritis; Q2W: every 2 weeks; Q4W: every 4 weeks; r-axSpA: radiographic axial Spondyloarthritis

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