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# The impact of concomitant Sjogren's disease on rheumatoid arthritis disease activity

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1	The impact of concomitant Sjogren's disease on rheumatoid arthritis
2	disease activity: a systematic review and meta-analysis
3	
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24	Running title: Sjogren's impacting RA disease activity

25 Abstract

### 26 **Objectives:**

27 Rheumatoid arthritis (RA) and Sjögren's Syndrome (SjS) frequently co-exist but the 28 consequence for RA disease activity of having concomitant SjS (RA/SjS) is not well 29 established. We conducted a systematic review and meta-analysis to investigate the 30 impact of SjS on disease outcomes in individuals with RA.

31 Methods:

We searched Web of Science (Core Collection, FSTA, Medline), PubMed and Cochrane databases, without language restriction. Studies reporting RA disease activity scores, joint counts, visual analogue scales (VAS), disability and joint damage, and comparing RA and RA/SjS were selected. Outcomes reported in at least 3 studies in which the diagnosis of SjS fulfilled classification criteria underwent meta-analysis, using a random effects model where heterogeneity was detected.

38 **Results:** 

39 The literature search identified 2991 articles and abstracts; 23 underwent full-text review 40 and 16 were included. The studies included a total of 29722 patients (8614 with RA/SjS 41 and 21108 with RA). Using studies eligible for meta-analysis (744 patients with RA/SjS 42 and 4450 with RA), we found higher DAS-28 ESR scores (mean difference 0.50, 95% CI -0.008-1.006; p = 0.05), higher swollen joint count scores (mean difference 1.05, 95% CI 43 44 0.42-1.67; p = 0.001), and greater functional disability as measured by HAQ (mean 45 difference 0.19, 95% CI 0.05-0.34; p=0.009) in RA/SjS compared to RA alone. Other 46 outcome measures (tender joint count, fatigue VAS) showed a numerical trend towards 47 higher scores in RA/SjS but were not statistically significant.

48 **Conclusion:** 

49	RA/SjS patients appear to have higher disease activity and more functional disability than
50	patients with RA alone. The aetiology and clinical implications of this are unclear and
51	warrant further investigation.
52	
53	Keywords:
54	Sjögren's syndrome;
55	arthritis, rheumatoid;
56	outcome assessment, Health care;
57	patient reported outcome measures;
58	disability evaluation;
59	fatigue;
60	arthropathy, erosive
61	
62	Key messages:
63	• Patients with RA/SjS may have higher disease activity than RA alone.
64	• The pathobiology and clinical implications of this require further investigation
65	
66	
67	Introduction
68	Rheumatoid arthritis (RA) is the most common rheumatic immune-mediated
69	inflammatory disease (IMID). Poorly controlled disease activity is associated with
70	disability and joint damage. Numerous disease-modifying treatments exist that are
71	introduced in a trial-and-error approach with few pointers to indicate which patient may

72 respond best to which treatment. Sjögren's syndrome (SjS) is another IMID that is

73 characterised by focal lymphocytic infiltration of the exocrine glands, dryness, fatigue 74 and extraglandular manifestations including non-erosive arthritis (1,2). Estimates suggest 75 between 3.6-31% of individuals with RA also have SjS, with the differing values 76 influenced by divergent classification criteria, methodology, geographics and disease 77 duration (3–6). Rather than considering SjS as 'secondary' to RA, it is possible that SjS 78 concomitant with RA (RA/SiS) might define a disease subset with differing 79 pathophysiology and treatment response (7). The preferential SLE outcomes with 80 epratuzumab for a SLE/SiS subset in the post-hoc analysis of the EMBODY trials 81 illustrates this possibility (8). The pathogenesis of SjS is strongly associated with type I 82 interferon and B cell hyperactivity and lack of response to anti-TNF (9,10). Type 1 83 interferon is also associated with poor outcomes in RA (11) but whether the co-existence 84 of RA and SjS is associated with worse RA outcomes is not clear. Several studies have 85 assessed the impact of concomitant SjS on RA disease activity, but these studies are often 86 small, inconclusive or have divergent conclusions. Furthermore, SjS is associated with 87 higher ESR, due to hypergammaglobulinaemia, and high symptom burden, including limb pain and fatigue. Elevated ESR and symptom burden due to SjS might impact the 88 89 measurement of composite scores of RA disease activity.

Despite the prevalence of RA/SjS, data remains scarce on its interaction with RA disease
 activity and patient outcomes. Identifying the characteristics and impact of RA/SjS may
 help clinicians improve assessment and treatment in this population.

We conducted a systematic review and meta-analysis to understand if disease activity
scores, joint damage and disability differed according to the presence or absence of SjS.
If composite disease activity scores differed, we aimed to understand which components
were responsible for the observed differences.

98 Methods

#### 99 Search strategy and study selection

100 Our systematic review was performed following an a priori described protocol according

101 to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

102 Guideline (12). This review protocol was registered with PROSPERO (registration

number CRD 42022377490) (13). We searched Web of Science (Core Collection, FSTA,

Medline), PubMed, Cochrane databases up to September 2022 to find studies comparing the RA clinical outcomes of RA alone with RA/SjS. There were no restrictions on age, sex or duration of the study. There were no geographic or language limitations. Two authors (TT and TC) independently selected studies based on titles and abstracts. Afterward, full-text articles were acquired for those studies assumed to satisfy the inclusion criteria. The papers were independently evaluated by the 2 assessment-authors.

110 A third assessment-author (BF) was consulted if agreement was not reached.

We included the following search terms: 'rheumatoid arthritis', 'Sjögren', 'secondary', 'overlap', 'disease activity', 'erosions', 'disability', 'DAS (Disease activity score) 28', 'SDAI (Simplified Disease Activity Index)' and 'CDAI (Clinical Disease Activity Index)'. We excluded single case reports. Studies where either the 2002 American-European Consensus Group (AECG), 2012 provisional American College of Rheumatology (ACR) or 2016 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for SjS could not be applied were excluded from meta-analysis.

118

### 119 Data extraction and quality evaluation

120 All data were independently extracted by two authors (TT and TC). Information on the

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study such as author, year of publication, study design, study place, sample size, diagnosis
of RA and SjS and classification criteria used, age and gender of patients were collected.
We evaluated the quality of evidence of studies with the Newcastle-Ottawa Scale (NOS)
(14,15). The maximum NOS score is 9 points and studies achieving 0-3, 4-6 or 7-9 points
were considered low, medium, and high quality, respectively.

126

### 127 *Outcome evaluation*

128 The primary outcome was a composite measure of RA disease activity: DAS28-ESR

129 (Erythrocyte sedimentation rate), DAS28-CRP (C-reactive protein), SDAI or CDAI.

130 Secondary outcomes were Swollen Joint Count (SJC), Tender Joint Count (TJC), Health

131 Assessment Questionnaire-Disability Index (HAQ-DI) or modified Health Assessment

132 Questionnaire (mHAQ), Visual Analogue Scale (VAS), joint damage indices and number

133 of patients with damaged joints.

134

### 135 Statistical analysis

136 We performed a meta-analysis on observational or case control studies using a random 137 effects model. Clinical parameters with less than 3 studies were considered inappropriate 138 for statistical analysis. Heterogeneity of selected studies were assessed using the I2 139 statistic; I2 value of <25% indicates low heterogeneity, 25%-75% as moderate 140 heterogeneity and >75% as considerable heterogeneity (16). In addition, we assessed heterogeneity of studies with the Tau-squared method (17) and using Cochran's Q-141 142 statistics with a significance level of p<0.10. Publication bias was assessed with funnel 143 plots (18). We did not perform meta-regression analysis because the number of obtainable 144 studies for each analysis was less than 10. For continuous data, mean difference (MD) and 95% CI were calculated with mean value and standard deviation (SD) of RA and RA/SjS patients. When data were not presented as means and standard deviations, we estimated with the median, first quartile, third quartile, and sample size (19–21). If data were skewed, we performed subgroup analyses of studies with skewed data and no skewed data for examination of the effect of skewed data on results. Statistical analyses were performed with R commander (manova; R Ver 2.7-1) (22). All statistical tests adapted a two-sided p-value of 0.05 for significance except for the Q-statistics.

152

#### 153 **Results**

154 Study Selection

We identified 3723 references through the literature search of which we removed 36 duplicates (n=36) and 696 ineligible (n =696) articles prior to screening. A further 2991 titles and abstracts were excluded after primary screening. After reviewing the remaining 23 full text articles, we excluded 5 studies without enough data and 2 studies with overlapping samples from the same database. Finally, 16 full-text papers met all eligibility criteria (Figure 1).

161

### 162 *Characteristics of the included studies*

Table 1 shows the characteristics of the 16 included observational papers (5 cohort studies,
5 case-control studies and 6 cross-sectional studies) with a total of 21108 RA patients and
8614 RA/SjS patients. All papers were published between 1999 and 2022, with 6 studies
in Europe, 2 studies in North America, 3 studies in South America, 5 papers in East Asia,
1 paper in South Asia. The method of SjS diagnosis was described in all the studies except
Uhlig et al. (23). However, this paper contained a group with low tear and saliva flow that

we considered would likely meet 2002 AECG classification for SjS. Harrold et al described a registry-based study where SjS was a physician-reported diagnosis and the study did not capture whether SjS classification criteria were fulfilled; this study was therefore excluded from meta-analysis.

The mean age of RA and RA/SjS patients were 58.5 and 61.1 years. The proportions of 173 174 female patients were 68.1% and 81.6%, in the RA and RA/SjS groups respectively. 175 Disease duration did not differ between groups except in three studies(5,24,25). Several 176 studies identified a higher proportion of patients in the RA/SiS group as being rheumatoid 177 factor or anti-citrullinated protein antibody positive when compared with RA alone. 178 However, no study stratified their analysis by autoantibody status. Where available, data 179 on comorbidities and RA treatments are included in Supplementary Tables 1 and 2. Using 180 NOS we determined that 8 papers were of high quality (7–9 points) and 8 papers medium 181 quality (4-6 points).

182

183 *Composite measures of disease activity* 

There was only one paper containing data for CDAI and no papers containing data for
SDAI. Therefore, we only performed meta-analysis for DAS28-ESR and DAS28-CRP.

187 Meta-analysis of DAS28-ESR included 7 studies (23,26–31), with a total of 1920 RA and 188 320 RA/SjS patients. For one paper (27), the mean DAS28-ESR and SD were calculated 189 using the provided data. The calculated data-distribution was not significantly skewed. 190 We adopted a random effects model due to the high heterogeneity of studies (I2 = 78.3%, 191  $\tau 2 = 0.38$ , P < 0.01; Figure 2A). The difference between the two patient groups showed a 192 strong trend to higher DAS28-ESR scores in RA/SjS with borderline statistical 193 significance (MD: 0.50; 95% CI [-0.008; 1.006] P = 0.05; Figure 2A).

194

195 For meta-analysis of DAS28-CRP we included 6 studies (3,24,26,28,32,33) comprising 196 2166 RA and 330 RA/SjS patients. We adopted a random effects model due to the high 197 heterogeneity between studies (I2 = 90 %,  $\tau$ 2 = 0.32, P < 0.01; Figure 2B). There was no 198 significant difference despite a numerical trend to higher scores in the RA/SiS group 199 (MD: 0.37; 95% CI [-0.13; 0.87] P = 0.15; Figure 2B). For two papers (32,33), the mean 200 and SD of DAS28-CRP were calculated using the provided data. These two papers 201 showed a skewed distribution of calculated data. Therefore, we performed a subgroup 202 analysis of studies with and without skewed data (Supplementary Figure 1). There was 203 no significant difference between studies with skewed data and papers without skewed 204 data (Q = 0.04, p = 0.84).

Consistent with these observed trends, Harrold et al. showed that their RA/SjS group had
higher CDAI values (n=7870, Mean 13.4, SD 12.8) than the RA alone group (n= 16658,
Mean 11.3, SD 11.9) (5).

208

209

210 Joint Counts

For meta-analysis of SJC we utilized 8 studies (3,23,29-31,34-36) comprising 1637 RA and 342 RA/SjS patients. We observed no significant heterogeneity of studies (I2 = 12%,  $\tau 2 = 0.014$ , P = 0.33; Figure 3A). There was a statistically significant higher SJC in RA/SjS compared with RA alone (MD: 1.05; 95% CI [0.42; 1.67], P = 0.001; Figure 3A). We included 8 studies (3,23,29-31,34-36) in the meta-analysis of TJC with a total of 1637 RA and 342 RA with SjS patients. There was significant heterogeneity between studies (I2 = 60%,  $\tau$ 2 = 2.6923, P = 0.01; Figure 3B). We found no significant difference between RA patients and RA/SjS patients, despite a numerical trend to higher counts in the RA/SjS group (MD: 0.88; 95% CI [-0.58; 2.35], P = 0.24; Figure 3B.

220

221

222 Function

223 We found 4 papers with function data suitable for meta-analysis; 3 studies with HAQ-224 DI(26)(29)(34) and 1 study with mHAQ(23). Altogether, they included 693 RA and 126 RA/SiS patients. There was no significant heterogeneity of studies (I2 = 21.9%,  $\tau 2 <$ 225 226 0.0001, P = 0.2791; Figure 4). Function was worse in the RA/SjS group compared with 227 RA alone (MD: 0.19; 95% CI [0.05; 0.34], P=0.009; Figure 4). We also performed 228 subgroup analysis using papers with HAQ-DI data and studies with mHAQ data 229 (Supplemental Fig 2). We observed no significant differences between studies with HAQ-230 DI and papers with mHAQ (Q=0.01, p=0.9306; Supplementary Figure 2).

Our literature search identified a further paper by Harrold et al presenting data from a very large registry study in the USA(5). We did not include this in our meta-analysis as the diagnosis of SjS was a physician answered question without evidence of fulfilment of SjS classification criteria. Nevertheless, consistent with the data above, this study found RA/SjS patients had a higher mHAQ (0.4, SD 0.5; n=7659) compared to RA alone (0.3, SD 0.4; n=16466).

237

238 VAS

Studies with groups meeting SjS classification criteria and reporting VAS data included
2 papers with patient-reported pain VAS (3,23), 3 studies with patient-reported fatigue

- VAS (23,29,34), 2 papers with patient global assessment VAS (patient's global assessment)(23,29), and only 1 study with physician global assessment VAS(23).
- 243
- Uhlig et al (23) reported that the RA/SjS patients had worse pain VAS scores (Mean=43.1,
- 245 SD=22.0, n=46) than RA alone (Mean=32.9, SD=22.0, n=377). Haga et al (3). supported
- these findings, with their RA/SjS group having worse scores (Mean=39.00, SD=28.68,

n=11) than those with RA alone (Mean= 29.13, SD= 23.81, n=296).

- Uhlig et al (23) also reported that the RA/SjS group (Mean= 2.91, SD= 0.98, n= 46) had
- worse scores for patient global assessment (range 1–5) than the RA group (Mean= 2.55,
- 250 SD= 0.87, n=377). On the contrary, Lins et al (29). reported that the RA/SjS group had a
- better score using a different patient global assessment (range 0-100 mm) (Mean= 46.7,

252 SD= 32.9, n= 39) than RA group (Mean=53.2, SD= 31.7, n= 191).

253

Meta-analysis of fatigue VAS included 638 RA and 112 RA/SjS (23,29,34). There was no significant heterogeneity of papers (I2 = 42.6%,  $\tau 2$  = 29.53, P = 0.18; Supplementary Figure 3). We found no significant difference between RA patients and RA/SjS patients (MD: 3.73; 95% CI [-5.42; 12.88], P = 0.42; Supplementary Figure 3).VAS data from the Harrold et al. registry study were excluded from the meta-analysis because they did not use classification criteria of SjS (5,37), but similarly reported that the RA/SjS group had higher pain scores and patient global assessment.

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262

263 *Joint damage* 

264 There were only 2 studies which included Sharp/van der Heijde scores as a measure of

radiographic joint damage (24,32) and only one paper with a damaged joint count as aclinical measure (23).

267 With the Sharp/van der Heijde method, Laroche et al. demonstrated that the RA/SjS 268 group had more radiographic joint damage (n=39, median=15.4) compared with RA alone 269 (n=39, median=13.9). However there was no statistical significance (p=0.79) (32). Brown 270 et al. also described the same tendency; RA/SjS (n=85, median=47.5) having more 271 radiographic joint damage than RA alone (n=744, median=17.0) (24). Using a less 272 sensitive clinical measure, Uhlig et al. reported no difference in deformed joint count (0-18) between RA alone (n=377, Mean=1.8, SD=3.5) and RA/SiS (n=46, Mean=1.8) 273 274 SD=3.4) (23).

275 Three papers reported the percentage of patients with at least one damaged joint. 276 (25,35,38). Yang et al used radiographic assessments, but was non-informative as all 277 patients in both groups had at least one damaged joint (35). The other two papers assessed 278 joint deformity clinically. He J et al. reported that RA/SjS patients (n=74, 60.8%) were 279 more likely to have a clinically deformed joint than patients with RA alone (n=435, 45.3%) (25). Meanwhile, Santosh et al. demonstrated a numerically higher percentage of 280 281 patients with  $\geq 1$  damaged joint in the RA/SjS group (36%) compared to RA alone (32%), 282 although this did not reach statistical significance (p=0.292) (38).

283

### 284 Discussion

The coexistence of more than one autoimmune disease is common (39) but the impact of one autoimmune disease on the disease activity or outcomes of a second is rarely examined. Various small studies have suggested that RA disease activity may be higher in patients with concomitant SjS. Based on available data, our meta-analysis confirms 289 that patients with RA/SjS have higher DAS28-ESR scores (p=0.05). It is well-recognised 290 that patients with SjS often have raised ESR, at least in part due to higher immunoglobulin 291 levels, however CRP is typically normal except in the presence of certain extra-glandular 292 features that may include inflammatory arthritis. Patients with SjS are also well-293 recognised to have a high symptom burden, including limb pain and fatigue, that 294 negatively impacts health-related quality of life. It is therefore possible that these factors, 295 ESR and symptoms, may be the drivers behind the observed higher DAS28-ESR scores. 296 It is therefore of interest that we also found that patients with RA/SjS had a higher swollen 297 joint count than those with RA alone. Further, although the DAS28-CRP meta-analysis 298 did not reach statistical significance, it showed a similar numerical trend. Other papers 299 we identified showed higher symptom burden, higher disability as measured by 300 mHAQ/HAQ and higher joint erosion scores.

The papers identified in our systematic review do not identify any biological mechanisms underlying the observations of higher disease activity in RA/SjS and this will need to be a subject of further research. However, a biological mechanism is not implausible as, for example, SjS is strongly associated with a high type 1 interferon signature (40) that in RA is a poor prognostic factor (11).

There are potential implications related to our findings. Uncontrolled disease activity in RA is associated with joint damage, disability, and higher risk for subsequent joint replacement. Although there are numerous therapies used to control disease activity in RA, these are typically introduced in the order of their historical introduction into medicine, with no reliable predictors of response to specific therapies and primary nonresponse rates of at least 30%; both factors leading to cycling through treatments. Whether the presence of concomitant SjS should influence the selection of therapy in RA 313 is yet to be determined but is worthy of further research. Firstly, if there are 314 pathobiological differences in RA processes between RA/SjS and RA alone, there may be 315 a differential response to certain immunomodulators depending on the presence or 316 absence of SjS. Secondly, in RA/SjS there are two autoimmune processes that may have 317 a discordant or concordant response to any potential therapy, for example, anti-TNF has 318 not been demonstrated to be efficacious in primary SiS (9,10). Thirdly, SiS-related 319 pathobiology may influence drug-response through other means. For example, Chen et al 320 utilised an autoantigen microarray in adalimumab treated RA patients and identified that 321 the presence of anti-Ro60 antibodies were associated with formation of anti-drug 322 antibodies and poor EULAR response (41), although this finding needs further validation 323 in larger cohorts. The presence of anti-Ro antibodies also predicts a poorer response to 324 abatacept (42), although again this needs validation in larger cohorts.

325 Our study has significant limitations meaning that we need to be cautious about our 326 conclusions. The included studies showed statistically significant heterogeneity, although 327 we compensated for this by selecting a conservative random effects model, as opposed to 328 a fixed effects model, to evaluate statistical significance. Studies were mainly cross-329 sectional, and it was not possible to correct for factors that may have differed between 330 groups such as disease duration, sex, co-morbidities, and therapy. We were unable to identify if our observations applied equally to RF or ACPA positive and negative patients, 331 332 or if seropositivity was a confounding factor given the imbalance observed in some 333 studies, as none of the analyses were stratified by autoantibody status. No SjS-specific 334 outcome measures were available and SjS disease activity might also impact functional 335 scores such as the HAO.

336 There are also particular challenges in researching RA/SjS. Studies which have

337 carefully documented the presence of SjS using recognised classification criteria are 338 typically small well-characterised cohorts which may therefore lack statistical power to explore differences in some outcomes or to adjust for confounders, co-morbidities, 339 340 disease duration and treatment. An alternative approach is to utilise large registry studies 341 which may have the requisite statistical power to assess disease activity and treatment 342 response in a fully adjusted analysis, but where the diagnosis of SjS may not be based 343 upon classification criteria. Whilst a physician diagnosis may be conservative and based upon objective evidence of SjS, as well as reflecting 'real-world' clinical practice, it is 344 345 very possible that the method for diagnosing SjS may vary between sites. The diagnosis 346 of SjS without a full evaluation of tests typically included in classification criteria is 347 subject to potential error as dryness symptoms are common and may be due to other 348 causes such as meibomian gland deficiency, age or drug side effects. Thus, physician 349 diagnosis may under or over diagnose SjS relative to classification criteria. The 350 challenges of correct classification will only be amplified further with studies attempting 351 to utilise larger primary care databases.

352

### 353 Conclusion

We have identified that RA disease activity is higher in RA/SjS patients. Whilst we need to be cautious in our interpretation, we believe our findings are important for raising awareness and stimulating further research to characterise the underlying biological mechanisms and clinical implications.

358

359

360 Contributors Literature search: TT, TC and BF. Figures creation: TT. Study design: TT and BF. Data

361 collection: TT, TC and BF. Data analysis: TT. Data interpretation: TT, TC and BF. Drafting of

362 manuscript: TT, TC, FK, SB, HI, SM and BF. Full responsibility for the integrity of the work as a

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- has undertaken consultancy in the past 3 years for Abbvie, BMS, Galapagos, Iqvia, J&J, Kiniksa and
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- 377 supplementary data.

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533 Table 1: Characteristics of included studies

References	Study	Nation	Center	Number of	Mean Duration	Rheumatoid factor +ve	ACPA +ve	NOS
	Design			participants	in years	[N/T (%); RA, RA/SjS]	[N/T (%); RA, RA/SjS]	
				(RA, RA/SjS)	(RA, RA/SjS)			
Harrold	Cohort	USA	Multi	16658, 7870	19.5, 13.6	6338/9492 (66.8%),	4076/7451 (54.7%),	8
2020					p=N/A	2983/4296 (69.4%)	1999/3420 (58.5%)	
						p=0.002#	p=0.0003#	
Moerman	Cohort	Netherlands	Single	58, 6	10.0, 15.0	48/58 (83%), 6/6 (100%)	48/58 (83%), 5/6 (83%)	7
2020					p=0.18	p=0.48	p=0.58	
Brown	Cohort	USA	Single	744, 85	13.3, 16.9	460/744 (61.8%), N/A (76.8%)	454/744 (61.0%), N/A (73.8%)	7
2015					p=0.01	p=0.008	p=0.03	
Zhang	Cohort	China	Single	970, 129	2.0, 2.0	733/970 (75.6%),	841/970 (86.7%), 117/129 (90.7%)	7
2020					p=N/A	116/129 (89.9%)	p=0.20#	
						p=0.0003#		
Uhlig	Cohort	Norway	Multi	377, 46	11.8, 12.8	182/377 (48.2%), N/A (62.2%)	N/A	6
1999					p=0.42	p=0.08		
Lins	Case	Brazil	Single	191, 45	9.3, 10.6	N/A	N/A	8
2016	Control				p=0.22			
Oliveira	Case	Brazil	Single	46, 20	N/A, N/A	29/46 (63.0%), 15/20 (75.0%)	39/46 (84.8%), 18/20 (90.0%)	6
2015	Control				p=N/A	p=0.15	p= 0.71	
Не	Case	China	Single	435, 74	9.5, 14.6	155/435 (35.6%), N/A (54.3%)*	313/435 (71.9%), N/A (77.8%)	6
2013	Control				p <0.001	p=0.24	p=0.41	

Yang	Case	China	Single	210, 105	N/A, 4.0	168/210 (79.0%), 93/105 (88.6%)	173/210 (82.3%), 72/94 (76.6%)	5
2018	Control				p=N/A	p=0.06	p=0.10	
Laroche	Case	France	Single	39, 39	16.1, 16.9	N/A	N/A	6
2022	Control				p=0.89			
Romanowska	Cross	Poland	Single	59, 60	N/A, N/A	30/59 (51%), 46/56 (82%)	46/59 (78%), 28/31 (90%)	7
2016	Sectional				p=N/A	p=0.0004#	p=0.15#	
Santosh	Cross	India	Single	199, 11	6.7, 9.2	162/188 (86%), 10/11 (91%)	N/A	7
2017	Sectional				p=0.13	p=1.0		
Kim	Cross	Korea	Single	755, 72	8.0, 7.5	520/748 (69.5%), 61/72 (84.7%)	606/730 (83.0%), 66/72 (91.7%)	7
2020	Sectional				p=0.45	p=0.007	p=0.06	
2020 Haga	Sectional Cross	Denmark	Single	296, 11	p=0.45 10.6, 10.9	p=0.007 N/A	p=0.06 N/A	6
2020 Haga 2012	Sectional Cross Sectional	Denmark	Single	296, 11	p=0.45 10.6, 10.9 p=NS	p=0.007 N/A	p=0.06 N/A	6
2020 Haga 2012 Villani	Sectional Cross Sectional Cross	Denmark Italy	Single	296, 11 12, 12	p=0.45 10.6, 10.9 p=NS 13.5, 13.7	p=0.007 N/A 11/12 (92%), 9/12 (75%)	p=0.06 N/A N/A	6
2020 Haga 2012 Villani 2013	Sectional Cross Sectional Cross Sectional	Denmark Italy	Single	296, 11 12, 12	p=0.45 10.6, 10.9 p=NS 13.5, 13.7 p=N/A	p=0.007 N/A 11/12 (92%), 9/12 (75%) p=0.27#	p=0.06 N/A N/A	6
2020 Haga 2012 Villani 2013 Melo	Sectional Cross Sectional Cross Sectional Cross	Denmark Italy Brazil	Single Single Single	296, 11 12, 12 70, 29	p=0.45 10.6, 10.9 p=NS 13.5, 13.7 p=N/A 9.1, 10.9	p=0.007 N/A 11/12 (92%), 9/12 (75%) p=0.27# N/A	p=0.06 N/A N/A N/A	6 5 5

534 ACPA: Anti-Citrullinated Protein/Peptide Antibody, Duration: RA disease duration, N: Number of Seropositive Patients, N/A: No Data

535 Available, NOS: Newcastle–Ottawa Scale, NS: Not Significant, +ve: Positive, RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, T: Total

536 Number of Patients with Data Available. \* Based on IgG. #Calculated by Chi-square test when p value not presented in cited papers.

### 537 Figure Legends

- 538 Figure 1: Flow diagram of study selection
- 539 Figure 2: Forest plots from the meta-analysis of DAS28-ESR (A) and DAS28-CRP (B)
- 540 composite disease outcome scores
- 541 Figure 3: Forest plots from the meta-analysis of swollen (A) and tender (B) joint counts
- 542 Figure 4: Forest plot from the meta-analysis of function (HAQ-DI and mHAQ)

#### Figure1: Flow diagram of the eligible studies selection

Identification of studies via databases and registers



	Expe	rimental	Co	ontrol				Weight	Weight
Study	Total	Mean SD	Total	Mean SD	Mean Difference	MD	95% -CI	(common)	(random)
					1.10				
Moerman 2020	6	5.10 1.40	58	2.70 1.10		2.40	[1.24; 3.56]	1.3%	9.2%
Kim 2020	72	2.76 0.68	755	2.56 0.81	+	0.20	[0.03; 0.37]	60.6%	17.2%
Romanowska 2016	60	5.20 1.30	59	4.70 1.50		0.50	[0.00; 1.00]	6.7%	15.0%
Lins 2016	42	4.50 1.70	190	4.30 1.60		0.20	[-0.36; 0.76]	5.4%	14.4%
Oliveira 2015	20	4.14 1.54	46	4.74 1.37		-0.60	[-1.38; 0.18]	2.8%	12.4%
He 2013	74	6.44 1.38	435	5.96 1.54		0.48	[0.13; 0.83]	14.1%	16.2%
Uhlig 1999	46	5.08 1.41	377	4.20 1.42	<del>  = -</del>	0.88	[0.45; 1.31]	9.1%	15.6%
Common effect model	320		1920		\$	0.33	[ 0.20; 0.46]	100.0%	-
Random effects mode					$\diamond$	0.50	[-0.01; 1.01]	-	100.0%
Heterogeneity: $I^2 = 78\%$ , 1	t <sup>2</sup> = 0.381	11, p < 0.01							
Test for overa	ll effe	ect: z=1.	93, p	=0.0536	-3 -2 -1 0 1 2 3				

### Figure2A: Forest plots of the meta-analysis on DAS28-ESR

### Figure2B: Forest plots of the meta-analysis on DAS28-CRP

	Expe	erimental	Co	ontro	01				Weight	Weight
Study	Total	Mean SD	Total	Mean	SD	Mean Difference	MD	95% -CI	(common)	(random)
Laroche 2022	39	2 68 0 69	39	170	0 23	13 =	0.98	[075 <sup>.</sup> 121]	39.3%	19.5%
Moerman 2020	6	4.10 1.50	58	2.40	0.80		- 1.70	[0.48; 2.92]	1.4%	9.3%
Zhang 2020	129	3.79 1.46	970	3.88	1.49	+	-0.09	[-0.36; 0.18]	28.8%	19.2%
Romanowska 2016	60	4.70 1.20	59	4.60	1.40	- 1	0.10	[-0.37; 0.57]	9.6%	17.3%
Brown 2015	85	4.32 1.80	744	3.88	1.60	+	0.44	[0.04; 0.84]	13.2%	18.0%
Haga 2012	11	2.74 0.85	296	3.10	1.22		-0.36	[-0.88; 0.16]	7.7%	16.7%
Common effect model	330		2166			\$	0.42	[ 0.28; 0.57]	100.0%	-
Random effects model	ļ					$\diamond$	0.37	[-0.13; 0.87]	-	100.0%
Heterogeneity: $I^2 = 90\%$ , $\tau$	2 = 0.322	22, p < 0.01								
Test for overall	effect	: z=1.44,	p=0.1	1503		-2 -1 0 1 2				

DAS28-ESR (Disease Activity Score 28 - Erythrocyte Sedimentation Rate), DAS28-CRP (Disease Activity Score 28 - C-reactive protein), SD (Standard Deviation), MD (Mean Difference), MD (Mean Difference), 95%-CI (95%-confidence interval)

Study	Expe Total	e <i>rime</i> Mean	ental SD	C Total	o <i>ntrol</i> Mean s	D	Mean D	ifference	MD	95% -CI	Weight (common)	Weight (random)
Melo 2021 Yang 2018	29 105	3.40 17.80	4.00 10.20	70 210	2.30 4. 15.80 7.3	10 30	-		1.10 2.00	[-0.64; 2.84] [-0.19; 4.19]	12.6% 8.0%	12.7% 8.1%
Lins 2016	45	2.60	3.70	191	1.90 3.9	90	-		0.70	[-0.51; 1.91]	26.0%	25.7%
Oliveira 2015	20	2.42	4.41	46	3.05 3.3	30			-0.63	[-2.79; 1.53]	8.3%	8.3%
Villani 2013	12	13.00	2.90	12	11.70 3.	10		- Harrison	1.30	[-1.10; 3.70]	6.7%	6.7%
He 2013	74	15.86	7.79	435	12.90 8.4	48		-	2.96	[1.01; 4.91]	10.1%	10.2%
Haga 2012	11	0.73	2.41	296	0.28 0.9	94			0.45	[-0.98; 1.88]	18.8%	18.7%
Uhlig 1999	46	8.50	6.70	377	7.00 5.	70	-		1.50	[-0.52; 3.52]	9.4%	9.5%
Common effect model Random effects mode Heterogeneity: $l^2 = 12\%$ ,	<b>Ι 342</b> Ι τ <sup>2</sup> = 0.01	35, p =	0.33	1637		Γ			1.04 1.05	[ 0.42; 1.66] [ 0.42; 1.67]	100.0% 	 100.0%
Test for overa	all eff	ect:	z=3	.27, p	<b>=</b> 0.00	<b>)11</b> -4	-2	024				

### Figure3A: Forest plots of the meta-analysis on SJC

### Figure3B: Forest plots of the meta-analysis on TJC

Study	Expe Total	e <i>rime</i> Mean	ental SD	C Total	o <i>ntro</i> Mean s	l SD	Mean Differe	nce MD	95% -	Weight CI (common)	Weight (random)
Melo 2021	29	7.00	8.90	70	7.10	9.90		-0.10	[-4.08; 3.8	8] 4.9%	8.2%
tang 2016	105	7 10	10.20 0.00	210	6.20	7.00		- 1.30 - 0.00	[-0.90, 3.3	0] 10.1%	14.2%
Oliveira 2015	45 20	3.53	4.40	46	7.58	7.90 8.04	<u> </u>	-4.05	[-7.07; -1.0	0] 9.9% 3] 8.6%	11.0%
Villani 2013	12	14.40	3.60	12	13.90	3.00		- 0.50	[-2.15; 3.1	5] 11.1%	12.4%
He 2013	74	14.57	7.88	435	12.13	8.25		2.44	[0.48; 4.4	0] 20.4%	15.2%
Haga 2012	11	2.27	3.78	296	1.19	2.65		- 1.08	[-1.17; 3.3	3] 15.4%	13.9%
Uhlig 1999	46	9.60	8.00	377	6.10	6.20		+ 3.50	[1.10; 5.9	0] 13.6%	13.4%
Common effect mode	342			1637				1.14	[0.26; 2.0	3] 100.0%	-
Random effects mode Heterogeneity: $I^2 = 60\%$ ,	e <b>l</b> t <sup>2</sup> = 2.69	23, p =	0.01					0.88	[-0.58; 2.3	5]	100.0%

Test for overall effect: z=1.18, p=0.2369

Test for overall effect: z=1.18, p=0.2369-6-4-20246SJC: Swollen Joint Count, TJC: Tender Joint Count, SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)

Study	Expe Total	<i>rimental</i> Mean SD	Co Total	ontrol Mean SD	Mean	Difference	MD	95% -CI	Weight (common)	Weight (random)
Melo TS 2021 Moerman 2020 Lins 2016 Uhlig T 1999	29 6 45 46	1.30 0.90 1.40 1.00 1.40 0.90 1.75 0.64	70 58 188 377	1.30 0.90 0.50 0.60 1.20 0.80 1.55 0.47	-	+	0.00 0.90 0.20 0.20	[-0.39; 0.39] [ 0.09; 1.71] [-0.09; 0.49] [ 0.01; 0.39]	13.8% 3.2% 25.5% 57.5%	13.8% 3.2% 25.5% 57.5%
Common effect model Random effects model Heterogeneity: $l^2 = 22\%$ , Test for overall	<b>126</b>   1 1 2 2 0.000 0 000 0 000	)1, p = 0.28 :: <b>z=2.63,</b>	693 p=0.0	0085	-1.5 -1 -0.5	0 0.5 1	0.19 0.19 1.5	[ 0.05; 0.34] [ 0.05; 0.34]	100.0% 	 100.0%

### Figure4: Forest plots of the meta-analysis on HAQ-DI and mHAQ

HAQ-DI: Health Assessment Questionnaire-Disability Index, mHAQ: modified Health Assessment Questionnaire, 552 SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)

### 554 Supplementary Information

555

### 556 The impact of concomitant Sjogren's disease on rheumatoid arthritis 557 disease activity: a systematic review and meta-analysis

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References	Harrold 2020	Kim 2020
	N/T(%); RA, RA/SjS	N/T(%); RA, RA/SjS
НТ	5214/16658 (31.3%), 2909/7870 (37.0%)	183/755 (24.2%), 9/72 (12.5%)
CVD	1710/16658 (10.3%),1219/7870 (15.5%)	N/A
Maligancy	1821/16658 (15.5%),1223/7870 (10.9%)	16/755 (2.1%), 3/72 (4.2%)
Infection	845/16658 (5.1%) ,795/7870 (10.1%)	N/A
Diabetes	1416/16658 (8.5%), 775/7870 (9.8%)	70/755 (9.3%), 1/72 (1.4%)
Asthma	590/16658 (3.5%), 403/7870 (5.1%)	N/A
COPD	355/16658 (2.1%), 270/7870 (3.4%)	N/A
ILD / PF	81/16658 (0.5%), 81/7870 (1.0%)	33/735 (4.4%), 1/72 (1.4%)

### 578 Supplementary Table 1: Comorbidities within included studies

579

References	<b>Yang 2018</b>	He 2016
	N/T(%); RA, RA/SjS	N/T(%); RA, RA/SjS
НТ	N/A	132/435 (30.3%), /74 (28.4%)
CVD	N/A	17/435 (3.9%), 7/74 (9.5%)
Diabetes	N/A	45/435 (10.3%), 5/74 (6.8%)
ILD / PF	43/210 (20.4%),45/105 (42.8%)	51/435 (11.7%), 33/74 (44.6%)
Renal I	25/210 (11.9%),15/105 (14.3%)	N/A (4.81%), N/A (14.9%)*
Nervous I	8/210 (3.8%), 9/105 (8.6%)	10/435 (0.23%), 20/74 (2.7%)

580

References

Lins 2016

	N/T(%); RA, RA/SjS
HT	24/162 (14.8%), 15/39 (38.5%)
Diabetes	10/162 (6.2%), 5/39 (12.8%)

581 N:Number of Patients, T: Total Number of Patients with Data Available, %: Proportion with

582 Comorbidities, N/A: No Data Available, RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, HT:

583 Hypertension, CVD: Cardio Vascular Disease, COPD: Chronic Obstructive Pulmonary Disease, ILD:

584 Interstitial Lung Disease, PF: Pulmonary Fibrosis, I:involvement

585 *\*Only proportions are available.* 

### 587 Supplementary Table2: Characteristics of RA therapy

	МТХ	Steroid
References	N/T(%); RA, RA/SjS, p	N/T(%) p; RA, RA/SjS, p
Brown	350/744 (47.1%), 41/85 (48.2%), p= 0.09	N/A
Lins	N/A	103/162 (63.6%), 26/39 (66.7%), p= 0.718
Yang	N/A	29/210 (13.8%), 89/105 (84.8%), p <0.001
Laroche	17/39 (43.6%), 9/39 (23.1%), p= 0.05	3/39 (7.7%), 17/39 (43.6%), p= 0.0001
Kim	214/744 (28.3%), 23/72 (31.9%), p= 0.519	328/744 (43.4%), 37/74 (51.4%), p= 0.195
Haga	207/296 (69.9%), 7/11 (63.6%), p= NS	87/296 (29.4%), 3/11 (27.3%), p=NS

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	<b>Anti-TNF</b>	Ritximab
References	N/T(%); RA, RA/SjS, p	N/T(%); RA, RA/SjS, p
Brown	263/744 (35.4%), 39/85 (45.9%), p= 0.06	N/A
Laroche	22/39 (56.4%), 10/39 (25.6%), p= 0.006	1/39 (2.6%), 13/39 (33.3%), p=0.0006
Kim	79 /744 (10.5%), 4/72 (5.6%) p=0.185	N/A

	Sulfasalazine	Tacrolimus
References	N/T(%); RA, RA/SjS, p	N/T(%); RA, RA/SjS, p
Kim	31/744 (4.1%), 3/72 (4.2%) p=0.980	92/744 (12.2%), 4/72 (5.6%), p=0.093
Haga	96/296 (32.4%), 5/11 (45.5%) p= NS	N/A

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	Anti-IL6	JAK I
References	N/T(%); RA, RA/SjS, p	N/T(%); RA, RA/SjS, p
Laroche	3/39 (7.7%), 5/39 (12.8%), p=0.7	7/39 (13.9%), 3/39 (7.7%), p=0.3

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	Leflunomide	Hydroxychloroquine
References	N/T(%); RA, RA/SjS, p	N/T(%); RA, RA/SjS, p
Kim	163/744 (21.6%), 21/72 (29.2%), p=0.140	135/744 (17.9%), 15/72 (20.8%), p=0.535

RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, N:Number of Patients, T: Total Number of Patients
Data Available, %: Proportion with Comorbidities, p: p value, N/A: No Data Available, NS: Not
Significant, MTX: methotrexate, TNF: tumor necrosis factor, IL: Interleukin, JAK I: Janus Kinase
Inhibitor,

## Supplementary Figure1: Forest plots of the meta-analysis on DAS28-CRP with subgroup analysis

04	Expe	rimental	Co	ontro			Maaa	D:#		МР	050/ 01	Weight	Weight
Study	lotal	imean SD	lotal	mean	SD		wean	Difference	;	MD	95%-01	(common)	(random)
Skewness = Not ske	wed							3					
Moerman 2020	6	4.10 1.50	58	2.40	0.80			3		1.70	[ 0.48; 2.92]	1.4%	9.3%
Romanowska 2016	60	4.70 1.20	59	4.60	1.40			- <b>1</b>		0.10	[-0.37; 0.57]	9.6%	17.3%
Brown 2015	85	4.32 1.80	744	3.88	1.60			+		0.44	[ 0.04; 0.84]	13.2%	18.0%
Haga 2012	11	2.74 0.85	296	3.10	1.22		-	-		-0.36	[-0.88; 0.16]	7.7%	16.7%
Common effect mode	162		1157					$\diamond$		0.20	[-0.06; 0.46]	31.9%	
Random effects mode	)							$\Leftrightarrow$		0.32	[-0.34; 0.99]	**	61.3%
Heterogeneity: $I^2 = 75\%$ ,	$\tau^2 = 0.35$	85, p < 0.01											
								ŝ					
Skewness = Skewed													
Laroche 2022	39	2.68 0.69	39	1.70	0.23					0.98	[0.75; 1.21]	39.3%	19.5%
Zhang 2020	129	3.79 1.46	970	3.88	1.49					-0.09	[-0.36; 0.18]	28.8%	19.2%
Common effect mode	168		1009					$\diamond$		0.53	[0.35; 0.70]	68.1%	
Random effects mode	)							$\Leftrightarrow$		0.45	[-0.60; 1.49]	-	38.7%
Heterogeneity: $I^2 = 97\%$ .	$\tau^2 = 0.55$	21. p < 0.01											
0 ,		1						1					
Common effect mode	330		2166					\$		0.42	[ 0.28: 0.57]	100.0%	
Random effects mode	el .							$\diamond$		0.37	[-0.13: 0.87]	-	100.0%
Heterogeneity: $l^2 = 90\%$	$\tau^2 = 0.32$	22 n < 0.01									,		
Test for subgroup differen	nces (fixe	d effect): $v^2 = 1$	430 df=	:1(n=	0.04)	-2	-1	0 1	2				
Test for subgroup differen	nces (ran	dom effects): 1	$v^2 = 0.04$	df = 1	(n = 0.84)	-2	-1	VI	2				
rootion oubgroup differen	ioco (idii	uoni circoto). j	4 - 0.0 <del>1</del> ,	u - 1	(p = 0.04	1							

Test for overall effect: z=1.44, p=0.1503

DAS28-CRP (Disease Activity Score 28 - C-reactive protein), SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)

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### Supplementary Figure2: Forest plots of the meta-analysis on HAQ-DI and mHAQ with subgroup analysis

Study	<i>Expe</i> Total	erimental Mean SD	Co Total	ntrol Mean	sD	Mean Difference	MD	95% -CI	Weight (common)	Weight (random)
Method = HAQ										
Melo TS 2021	29	1.30 0.90	70	1.30	0.90		0.00	[-0.39; 0.39]	13.8%	13.8%
Moerman 2020	6	1.40 1.00	58	0.50	0.60	+ •	- 0.90	[0.09; 1.71]	3.2%	3.2%
Lins 2016	45	1.40 0.90	188	1.20	0.80	+#-	0.20	[-0.09; 0.49]	25.5%	25.5%
Common effect mode	80		316			$\diamond$	0.19	[-0.04; 0.41]	42.5%	
Random effects mode	el					$\diamond$	0.19	[-0.04; 0.41]		42.5%
Heterogeneity: $I^2 = 48\%$ ,	τ <sup>2</sup> = < 0.(	0001, p = 0.15								
Method = mHAQ										
Uhlig T 1999	46	1.75 0.64	377	1.55	0.47		0.20	[0.01; 0.39]	57.5%	57.5%
Common effect mode	I 46		377			$\diamond$	0.20	[ 0.01; 0.39]	57.5%	
Random effects mode	el					$\diamond$	0.20	[ 0.01; 0.39]		57.5%
Heterogeneity: not applica	able									
Common effect mode	I 126		693			\$	0.19	[ 0.05; 0.34]	100.0%	-
Random effects mode	el					$\diamond$	0.19	[0.05; 0.34]		100.0%
Heterogeneity: $l^2 = 22\%$ ,	τ <sup>2</sup> < 0.00	01, p = 0.28								
Test for subgroup differer	nces (fixe	ed effect): $\chi_1^2$ =	0.01, df =	= 1 (p =	0.93)	-1.5 -1 -0.5 0 0.5 1 1.5	j			
Test for subgroup differer	nces (ran	idom effects): ;	( <sup>2</sup> = 0.01,	, df = 1 (	p = 0.9	3)				
Tost for overall	offor	t. 7=2 62	n=0 (	0085						

Test for overall effect: z=2.63, p=0.0085

HAQ-DI: Health Assessment Questionnaire-Disability Index, mHAQ: modified Health Assessment Questionnaire, 502 SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)

### Supplementary Figure3: Forest plots of the meta-analysis on VAS (Fatigue patient reported)

	- Experimental	Control				Weight	Weight
Study	Total Mean SD	Total Mean SD	Mean Difference	MD	95%-CI	(common)	(random)
Melo 2021	29 55.00 36.60	70 53.80 35.40		1.20	[-14.49; 16.89]	16.5%	23.3%
Lins 2016	37 45.70 35.50	191 49.30 33.50		-3.60	[-15.99; 8.79]	26.4%	31.4%
Uhlig 1999	46 49.80 27.50	377 39.70 27.90		- 10.10	[ 1.67; 18.53]	57.1%	45.4%
Common effect model	112	638	$\sim$	5.01	[-1.36; 11.38]	100.0%	-
Random effects mode	1			3.73	[-5.42; 12.88]	-	100.0%
Heterogeneity: $l^2 = 43\%$ .	$t^2 = 29.5250, p = 0.18$						

**Test for overall effect:** z=0.80, p=0.4240 -15 -10 -5 0 5 10 15 VAS: Visual Analog Scale, SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval) 604