

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

Tomizawa, Takuya; Cox, Tobias; Kollert, Florian; Bowman, Simon J.; Itu, Hiromu; Matsuda, Shuichi; Fisher, Benjamin A.

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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
4 Authors: Takuya Tomizawa^{1,2,3,4}, Tobias Cox^{1,2}, Florian Kollert^{1,2,5}, Simon J. Bowman^{1,2},
5 Hiromu Ito⁴, Shuichi Matsuda⁴, Benjamin A. Fisher^{1,2*}

6
7 *Authors' affiliations:*

8 ¹ *Rheumatology Research Group, Institute of Inflammation and Ageing, College of*
9 *Medical and Dental Sciences, University of Birmingham*

10 ² *National Institute for Health Research (NIHR), Birmingham Biomedical Research*
11 *Centre and Department of Rheumatology, University Hospitals Birmingham NHS*
12 *Foundation Trust, Birmingham, UK*

13 ³ *Department of Orthopaedic Surgery, Terni Hospital, Terni, Japan*

14 ⁴ *Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine,*
15 *Kyoto, Japan*

16 ⁵ *Department of Rheumatology, Immunology, and Allergology, Inselspital, University*
17 *Hospital Bern, Bern, Switzerland*

18
19 *Corresponding author:

20 Rheumatology Research Group, Institute of Inflammation and Ageing, College of
21 Medical and Dental Sciences, University of Birmingham, Birmingham, UK

22 E-mail: B.Fisher@bham.ac.uk

23
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:**

32 We searched Web of Science (Core Collection, FSTA, Medline), PubMed and Cochrane
33 databases, without language restriction. Studies reporting RA disease activity scores, joint
34 counts, visual analogue scales (VAS), disability and joint damage, and comparing RA and
35 RA/SjS were selected. Outcomes reported in at least 3 studies in which the diagnosis of
36 SjS fulfilled classification criteria underwent meta-analysis, using a random effects model
37 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
43 -0.008-1.006; $p = 0.05$), higher swollen joint count scores (mean difference 1.05, 95% CI
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/SjS) might define a disease subset with differing
79 pathophysiology and treatment response (7). The preferential SLE outcomes with
80 epratuzumab for a SLE/SjS 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
88 limb pain and fatigue. Elevated ESR and symptom burden due to SjS might impact the
89 measurement of composite scores of RA disease activity.

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

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

97

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
103 number CRD 42022377490) (13). We searched Web of Science (Core Collection, FSTA,
104 Medline), PubMed, Cochrane databases up to September 2022 to find studies comparing
105 the RA clinical outcomes of RA alone with RA/SjS. There were no restrictions on age,
106 sex or duration of the study. There were no geographic or language limitations. Two
107 authors (TT and TC) independently selected studies based on titles and abstracts.
108 Afterward, full-text articles were acquired for those studies assumed to satisfy the
109 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.

111 We included the following search terms: ‘rheumatoid arthritis’, ‘Sjögren’, ‘secondary’,
112 ‘overlap’, ‘disease activity’, ‘erosions’, ‘disability’, ‘DAS (Disease activity score) 28’,
113 ‘SDAI (Simplified Disease Activity Index)’ and ‘CDAI (Clinical Disease Activity Index)’.
114 We excluded single case reports. Studies where either the 2002 American-European
115 Consensus Group (AECG), 2012 provisional American College of Rheumatology (ACR),
116 or 2016 ACR/European Alliance of Associations for Rheumatology (EULAR)
117 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

121 study such as author, year of publication, study design, study place, sample size, diagnosis
122 of RA and SjS and classification criteria used, age and gender of patients were collected.
123 We evaluated the quality of evidence of studies with the Newcastle-Ottawa Scale (NOS)
124 (14,15). The maximum NOS score is 9 points and studies achieving 0-3, 4-6 or 7-9 points
125 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
141 heterogeneity of studies with the Tau-squared method (17) and using Cochran's Q-
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)

145 and 95% CI were calculated with mean value and standard deviation (SD) of RA and
146 RA/SjS patients. When data were not presented as means and standard deviations, we
147 estimated with the median, first quartile, third quartile, and sample size (19–21). If data
148 were skewed, we performed subgroup analyses of studies with skewed data and no
149 skewed data for examination of the effect of skewed data on results. Statistical analyses
150 were performed with R commander (manova; R Ver 2.7-1) (22). All statistical tests
151 adapted a two-sided p-value of 0.05 for significance except for the Q-statistics.

152

153 **Results**

154 *Study Selection*

155 We identified 3723 references through the literature search of which we removed 36
156 duplicates (n=36) and 696 ineligible (n =696) articles prior to screening. A further 2991
157 titles and abstracts were excluded after primary screening. After reviewing the remaining
158 23 full text articles, we excluded 5 studies without enough data and 2 studies with
159 overlapping samples from the same database. Finally, 16 full-text papers met all eligibility
160 criteria (Figure 1).

161

162 *Characteristics of the included studies*

163 Table 1 shows the characteristics of the 16 included observational papers (5 cohort studies,
164 5 case–control studies and 6 cross-sectional studies) with a total of 21108 RA patients and
165 8614 RA/SjS patients. All papers were published between 1999 and 2022, with 6 studies
166 in Europe, 2 studies in North America, 3 studies in South America, 5 papers in East Asia,
167 1 paper in South Asia. The method of SjS diagnosis was described in all the studies except
168 Uhlig et al. (23). However, this paper contained a group with low tear and saliva flow that

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

173 The mean age of RA and RA/SjS patients were 58.5 and 61.1 years. The proportions of
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/SjS 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*

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

186

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 ($I^2 = 78.3\%$,
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 ($I^2 = 90\%$, $\tau^2 = 0.32$, $P < 0.01$; Figure 2B). There was no
198 significant difference despite a numerical trend to higher scores in the RA/SjS 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 ($Q = 0.04$, $p = 0.84$).

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

208

209

210 *Joint Counts*

211 For meta-analysis of SJC we utilized 8 studies (3,23,29–31,34–36) comprising 1637 RA
212 and 342 RA/SjS patients. We observed no significant heterogeneity of studies ($I^2 = 12\%$,
213 $\tau^2 = 0.014$, $P = 0.33$; Figure 3A). There was a statistically significant higher SJC in
214 RA/SjS compared with RA alone (MD: 1.05; 95% CI [0.42; 1.67], $P = 0.001$; Figure 3A).

215 We included 8 studies (3,23,29–31,34–36) in the meta-analysis of TJC with a total of
216 1637 RA and 342 RA with SjS patients. There was significant heterogeneity between

217 studies ($I^2 = 60\%$, $\tau^2 = 2.6923$, $P = 0.01$; Figure 3B). We found no significant difference
218 between RA patients and RA/SjS patients, despite a numerical trend to higher counts in
219 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
225 RA/SjS patients. There was no significant heterogeneity of studies ($I^2 = 21.9\%$, $\tau^2 <$
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).

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

237

238 *VAS*

239 Studies with groups meeting SjS classification criteria and reporting VAS data included
240 2 papers with patient-reported pain VAS (3,23), 3 studies with patient-reported fatigue

241 VAS (23,29,34), 2 papers with patient global assessment VAS (patient's global
242 assessment)(23,29), and only 1 study with physician global assessment VAS(23).

243

244 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
246 these findings, with their RA/SjS group having worse scores (Mean=39.00, SD=28.68,
247 n=11) than those with RA alone (Mean= 29.13, SD= 23.81, n=296).

248 Uhlig et al (23) also reported that the RA/SjS group (Mean= 2.91, SD= 0.98, n= 46) had
249 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
251 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

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

261

262

263 *Joint damage*

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

265 radiographic joint damage (24,32) and only one paper with a damaged joint count as a
266 clinical 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–
273 18) between RA alone (n=377, Mean=1.8, SD=3.5) and RA/SjS (n=46, Mean=1.8
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,
280 45.3%) (25). Meanwhile, Santosh et al. demonstrated a numerically higher percentage of
281 patients with ≥ 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**

285 The coexistence of more than one autoimmune disease is common (39) but the impact of
286 one autoimmune disease on the disease activity or outcomes of a second is rarely
287 examined. Various small studies have suggested that RA disease activity may be higher
288 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.

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

306 There are potential implications related to our findings. Uncontrolled disease activity in
307 RA is associated with joint damage, disability, and higher risk for subsequent joint
308 replacement. Although there are numerous therapies used to control disease activity in
309 RA, these are typically introduced in the order of their historical introduction into
310 medicine, with no reliable predictors of response to specific therapies and primary
311 nonresponse rates of at least 30%; both factors leading to cycling through treatments.
312 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 SjS (9,10). Thirdly, SjS-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
331 identify if our observations applied equally to RF or ACPA positive and negative patients,
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 HAQ.

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
339 explore differences in some outcomes or to adjust for confounders, co-morbidities,
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
344 upon objective evidence of SjS, as well as reflecting ‘real-world’ clinical practice, it is
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**

354 We have identified that RA disease activity is higher in RA/SjS patients. Whilst we need
355 to be cautious in our interpretation, we believe our findings are important for raising
356 awareness and stimulating further research to characterise the underlying biological
357 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
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375 **Data availability statement** All data related to the study are included in the article or uploaded as
376 supplementary data. All information related to the study are included in the article and uploaded as
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378 **References**

- 379 1. KASSAN SS, MOUTSOPOULOS HM. Clinical Manifestations and Early
380 Diagnosis of Sjögren Syndrome. Arch Intern Med. 2004;164(12):1275.
381 doi:10.1001/archinte.164.12.1275
- 382 2. MANFRÈ V, CHATZIS LG, CAFARO G, et al. Sjögren's syndrome: one year in
383 review 2022. Clin Exp Rheumatol. 2022;40(12):2211–24.

- 384 <https://doi.org/10.55563/clinexprheumatol/43z8gu>
- 385 3. HAGA HJ, NADERI Y, MORENO AM, PEEN E. A study of the prevalence of
386 sicca symptoms and secondary Sjögren's syndrome in patients with rheumatoid
387 arthritis, and its association to disease activity and treatment profile. *Int J Rheum*
388 *Dis.* 2012;15(3):284–8. <https://doi.org/10.1111/j.1756-185X.2012.01717.x>
- 389 4. CARMONA L, GONZÁLEZ-ALVARO I, BALSA A, ANGEL BELMONTE M,
390 TENA X, SANMARTÍ R. Rheumatoid arthritis in Spain: occurrence of extra-
391 articular manifestations and estimates of disease severity. *Ann Rheum Dis.*
392 2003;62(9):897–900. <http://dx.doi.org/10.1136/ard.62.9.897>
- 393 5. HARROLD LR, SHAN Y, REBELLO S, et al. Prevalence of Sjögren's
394 syndrome associated with rheumatoid arthritis in the USA: an observational
395 study from the Corrona registry. *Clin Rheumatol.* 2020;39(6):1899–905.
396 <https://doi.org/10.1007/s10067-020-05004-8>
- 397 6. RAMOS-CASALS M, BRITO-ZERÓN P, FONT J. The overlap of Sjögren's
398 syndrome with other systemic autoimmune diseases. *Semin Arthritis Rheum.*
399 2007;36(4):246–55. <https://doi.org/10.1016/j.semarthrit.2006.08.007>
- 400 7. KOLLERT F, FISHER BA. Equal rights in autoimmunity: is Sjögren's syndrome
401 ever 'secondary'? *Rheumatology.* 2020;59(6):1218–25.
402 <https://doi.org/10.1093/rheumatology/keaa009>
- 403 8. CLOWSE MEB, WALLACE DJ, FURIE RA, et al. Efficacy and Safety of
404 Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus:
405 Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled
406 Trials. *Arthritis Rheumatol (Hoboken, NJ).* 2017;69(2):362–75.
407 <https://doi.org/10.1002/art.39856>

- 408 9. MARIETTE X, RAVAUD P, STEINFELD S, et al. Inefficacy of infliximab in
409 primary Sjögren's syndrome: results of the randomized, controlled Trial of
410 Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum.*
411 2004;50(4):1270–6. <https://doi.org/10.1002/art.20146>
- 412 10. MAVRAGANI CP, NIEWOLD TB, MOUTSOPOULOS NM, PILLEMER SR,
413 WAHL SM, CROW MK. Augmented interferon-alpha pathway activation in
414 patients with Sjögren's syndrome treated with etanercept. *Arthritis Rheum.*
415 2007;56(12):3995–4004. <https://doi.org/10.1002/art.23062>
- 416 11. COOLES FAH, TARN J, LENDREM DW, et al. Interferon- α -mediated
417 therapeutic resistance in early rheumatoid arthritis implicates epigenetic
418 reprogramming. *Ann Rheum Dis.* 2022;81(9):1214–23.
419 <http://dx.doi.org/10.1136/annrheumdis-2022-222370>
- 420 12. PAGE MJ, MCKENZIE JE, BOSSUYT PM, et al. The PRISMA 2020 statement:
421 an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
422 <https://doi.org/10.1136/bmj.n71>
- 423 13. BOOTH A. Prospero's progress and activities 2012/13. *Syst Rev.* 2013;2(111):1–
424 3. <https://doi.org/10.1186/2046-4053-2-111>
- 425 14. ZENG X, ZHANG Y, KWONG JSW, et al. The methodological quality
426 assessment tools for preclinical and clinical studies, systematic review and meta-
427 analysis, and clinical practice guideline: A systematic review. *J Evid Based Med.*
428 2015;8(1):2–10. <https://doi.org/10.1111/jebm.12141>
- 429 15. MODESTI PA, REBOLDI G, CAPPUCCIO FP, et al. Panethnic Differences in
430 Blood Pressure in Europe: A Systematic Review and Meta-Analysis. Fuchs FD,
431 editor. *PLoS One.* 2016;11(1):e0147601.

- 432 <https://doi.org/10.1371/journal.pone.0147601>
- 433 16. HIGGINS JPT. Measuring inconsistency in meta-analyses. *BMJ*.
434 2003;327(7414):557–60. <https://doi.org/10.1136/bmj.327.7414.557>
- 435 17. CUMPSTON MS, MCKENZIE JE, WELCH VA, BRENNAN SE. Strengthening
436 systematic reviews in public health : guidance in the Cochrane Handbook for
437 Systematic Reviews of Interventions , 2nd edition. 2022;44(4):588–92.
438 <https://doi.org/10.1093/pubmed/fdac036>
- 439 18. EGGER M, SMITH GD, SCHNEIDER M, MINDER C. Bias in meta-analysis
440 detected by a simple, graphical test. *Br Med J*. 1997;315(7109):629–34.
441 <https://doi.org/10.1136/bmj.315.7109.629>
- 442 19. SHI J, LUO D, WAN X, et al. Detecting the skewness of data from the five-
443 number summary and its application in meta-analysis. *Stat Methods Med Res*.
444 2023;096228022311720. <https://doi.org/10.48550/arXiv.2010.05749>
- 445 20. LUO D, WAN X, LIU J, TONG T. Optimally estimating the sample mean from
446 the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods
447 Med Res*. 2018;27(6):1785–805. <https://doi.org/10.1177/0962280216669183>
- 448 21. WAN X, WANG W, LIU J, TONG T. Estimating the sample mean and standard
449 deviation from the sample size, median, range and/or interquartile range. *BMC
450 Med Res Methodol*. 2014;14(1):135. <https://doi.org/10.1186/1471-2288-14-135>
- 451 22. BALDUZZI S, RÜCKER G, SCHWARZER G. How to perform a meta-analysis
452 with R: a practical tutorial. *Evid Based Ment Heal*. 2019;22(4):153–60.
453 <http://dx.doi.org/10.1136/ebmental-2019-300117>
- 454 23. UHLIG T, KVIEN TK, JENSEN JL, AXELL T. Sicca symptoms, saliva and tear
455 production, and disease variables in 636 patients with rheumatoid arthritis. *Ann*

- 456 Rheum Dis. 1999;58(7):415–22. <http://dx.doi.org/10.1136/ard.58.7.415>
- 457 24. BROWN LE, FRITS ML, IANNACONE CK, WEINBLATT ME, SHADICK
458 NA, LIAO KP. Clinical characteristics of RA patients with secondary SS and
459 association with joint damage. *Rheumatology*. 2015;54(5):816–20.
460 <https://doi.org/10.1093/rheumatology/keu400>
- 461 25. HE J, DING Y, FENG M, et al. Characteristics of Sjogren’s syndrome in
462 rheumatoid arthritis. *Rheumatology*. 2013;52(6):1084–9.
463 <https://doi.org/10.1093/rheumatology/kes374>
- 464 26. MOERMAN R V., ARENDS S, MOSSEL E, KROESE FGM, VISSINK A,
465 BOOTSMA H. 10-year follow-up of patients with rheumatoid arthritis and
466 secondary Sjögren’s syndrome or sicca symptoms in daily clinical practice. *Clin*
467 *Exp Rheumatol*. 2020;38 Suppl 1(4):64–72.
468 <https://www.clinexprheumatol.org/abstract.asp?a=15517>
- 469 27. KIM H, CHO S-K, KIM HW, et al. The Prevalence of Sjögren’s Syndrome in
470 Rheumatoid Arthritis Patients and Their Clinical Features. *J Korean Med Sci*.
471 2020;35(45):1–11. <https://doi.org/10.3346/jkms.2020.35.e369>
- 472 28. ROMANOWSKA-PRÓCHNICKA K, OLESIŃSKA M, PARADOWSKA-
473 GORYCKA A, et al. Discrepancies in assessment of patients with rheumatoid
474 arthritis and secondary Sjögren’s syndrome by DAS28-ESR and DAS28-CRP.
475 *Cent Eur J Immunol*. 2016;41(2):188–94. <https://doi.org/10.5114/ceji.2016.60994>
- 476 29. LINS E SILVA M, CARVALHO CN, CARVALHO A DE AT, LEÃO JC,
477 DUARTE ALP, GUEIROS LA. Effect of Xerostomia on the Functional Capacity
478 of Subjects with Rheumatoid Arthritis. *J Rheumatol*. 2016;43(10):1795–800.
479 <https://doi.org/10.3899/jrheum.151211>

- 480 30. OLIVEIRA HF, DE SOUZA TR, CARVALHO CN, et al. Serologic profile and
481 clinical markers of Sjögren syndrome in patients with rheumatoid arthritis. *Oral*
482 *Surg Oral Med Oral Pathol Oral Radiol*. 2015;119(6):628–35.
483 <http://dx.doi.org/10.1016/j.oooo.2015.02.479>
- 484 31. HE J, DING Y, FENG M, et al. Characteristics of Sjögren’s syndrome in
485 rheumatoid arthritis. *Rheumatology (Oxford)*. 2013;52(6):1084–9.
486 <https://doi.org/10.1093/rheumatology/kes374>
- 487 32. LAROCHE M, DEGBOE Y, CONSTANTIN A. Sjögren’s syndrome associated
488 with erosive rheumatoid arthritis alters its prognosis and long-term therapeutic
489 response: a case–control study. *Rheumatol Int*. 2023;43(2):363–6.
490 <https://doi.org/10.1007/s00296-021-05074-0>
- 491 33. ZHANG H, ZHANG H, GAO D, XIE W, GENG Y, ZHANG Z. Overlapping
492 Sjogren’s syndrome reduces the probability of reaching target in rheumatoid
493 arthritis patients: a propensity score matched real-world cohort from 2009 to
494 2019. *Arthritis Res Ther*. 2020;22(1):100. [https://doi.org/10.1186/s13075-020-](https://doi.org/10.1186/s13075-020-02189-w)
495 [02189-w](https://doi.org/10.1186/s13075-020-02189-w)
- 496 34. MELO TS, SILVA ML E, SILVA JÚNIOR ML DE M, DUARTE AP,
497 GUEIROS LA. Characterization of clinical, laboratory, IL-6 serum levels, and
498 IL-6-174 G/C genetic polymorphisms in patients with rheumatoid arthritis and
499 Sjögren’s syndrome. *Rev Assoc Med Bras*. 2021;67(11):1600–4.
500 <https://doi.org/10.1590/1806-9282.20210665>
- 501 35. YANG H, BIAN S, CHEN H, et al. Clinical characteristics and risk factors for
502 overlapping rheumatoid arthritis and Sjögren’s syndrome. *Sci Rep*. 2018;8(1):1–
503 7. <http://dx.doi.org/10.1038/s41598-018-24279-1>

- 504 36. VILLANI E, GALIMBERTI D, PAPA N DEL, NUCCI P, RATIGLIA R.
505 Inflammation in dry eye associated with rheumatoid arthritis: Cytokine and in
506 vivo confocal microscopy study. *Innate Immun.* 2013;19(4):420–7.
507 <https://doi.org/10.1177/1753425912471692>
- 508 37. HARROLD LR, SHAN Y, REBELLO S, et al. Disease activity and patient-
509 reported outcomes in patients with rheumatoid arthritis and Sjögren’s syndrome
510 enrolled in a large observational US registry. *Rheumatol Int.* 2020;40(8):1239–
511 48. <https://doi.org/10.1007/s00296-020-04602-8>
- 512 38. SANTOSH K, DHIR V, SINGH S, et al. Prevalence of secondary Sjögren’s
513 syndrome in Indian patients with rheumatoid arthritis: a single-center study. *Int J*
514 *Rheum Dis.* 2017;20(7):870–4. <https://doi.org/10.1111/1756-185X.13017>
- 515 39. ANAYA J-M. The diagnosis and clinical significance of polyautoimmunity.
516 *Autoimmun Rev.* 2014;13(4–5):423–6.
517 <https://doi.org/10.1016/j.autrev.2014.01.049>
- 518 40. TRUTSCHEL D, BOST P, MARIETTE X, et al. Variability of Primary
519 Sjögren’s Syndrome Is Driven by Interferon- α and Interferon- α Blood Levels Are
520 Associated With the Class II HLA–DQ Locus. *Arthritis Rheumatol.*
521 2022;74(12):1991–2002. <https://doi.org/10.1002/art.42265>
- 522 41. CHEN P-K, LAN J-L, CHEN Y-M, et al. Anti-TROVE2 Antibody Determined
523 by Immune-Related Array May Serve as a Predictive Marker for Adalimumab
524 Immunogenicity and Effectiveness in RA. *J Immunol Res.* 2021;2021:6656121.
525 <https://doi.org/10.1155/2021/6656121>
- 526 42. ENDO Y, KOGA T, KAWASHIRI S, et al. Significance of anti-Ro/SSA
527 antibodies in the response and retention of abatacept in patients with rheumatoid

528 arthritis: a multicentre cohort study. *Scand J Rheumatol.* 2021;50(1):15–9.

529 <https://doi.org/10.1080/03009742.2020.1772361>

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533 Table 1: Characteristics of included studies

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

Yang 2018	Case Control	China	Single	210, 105	N/A, 4.0 p=N/A	168/210 (79.0%), 93/105 (88.6%) p=0.06	173/210 (82.3%), 72/94 (76.6%) p=0.10	5
Laroche 2022	Case Control	France	Single	39, 39	16.1, 16.9 p=0.89	N/A	N/A	6
Romanowska 2016	Cross Sectional	Poland	Single	59, 60	N/A, N/A p= N/A	30/59 (51%), 46/56 (82%) p=0.0004#	46/59 (78%), 28/31 (90%) p=0.15#	7
Santosh 2017	Cross Sectional	India	Single	199, 11	6.7, 9.2 p=0.13	162/188 (86%), 10/11 (91%) p=1.0	N/A	7
Kim 2020	Cross Sectional	Korea	Single	755, 72	8.0, 7.5 p=0.45	520/748 (69.5%), 61/72 (84.7%) p=0.007	606/730 (83.0%), 66/72 (91.7%) p=0.06	7
Haga 2012	Cross Sectional	Denmark	Single	296, 11	10.6, 10.9 p=NS	N/A	N/A	6
Villani 2013	Cross Sectional	Italy	Single	12, 12	13.5, 13.7 p=N/A	11/12 (92%), 9/12 (75%) p=0.27#	N/A	5
Melo 2021	Cross Sectional	Brazil	Single	70, 29	9.1, 10.9 p=0.54	N/A	N/A	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

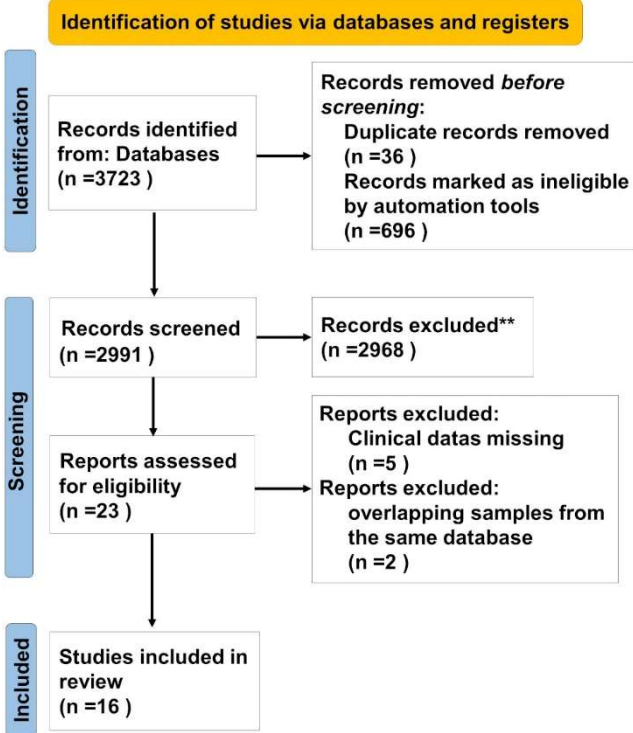
539 Figure 2: Forest plots from the meta-analysis of DAS28-ESR (A) and DAS28-CRP (B)
540 composite disease outcome scores

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)

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Figure1: Flow diagram of the eligible studies selection



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

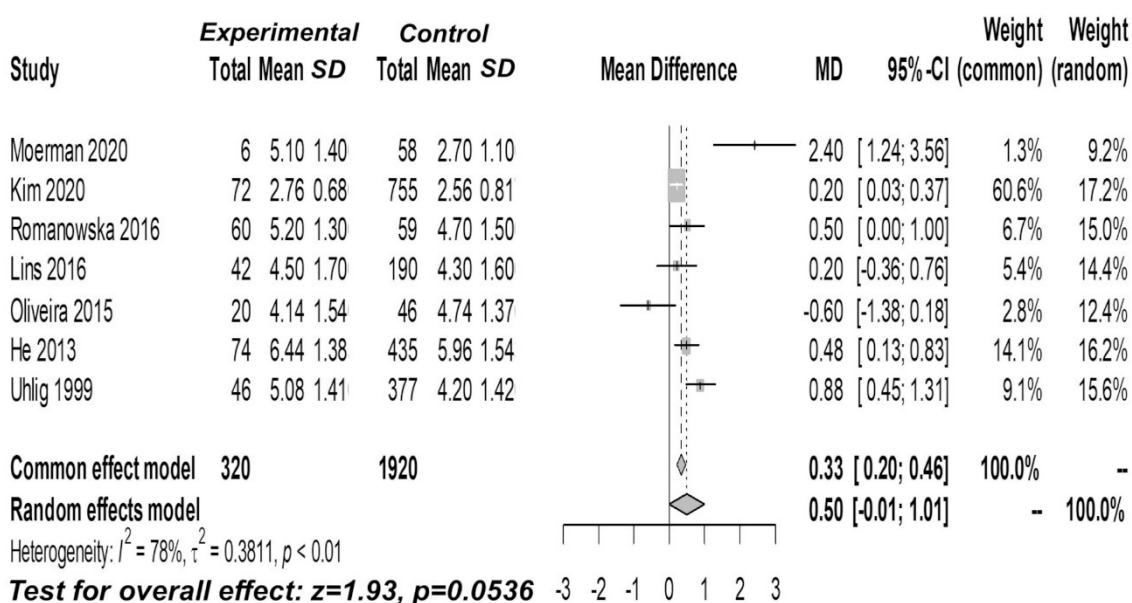
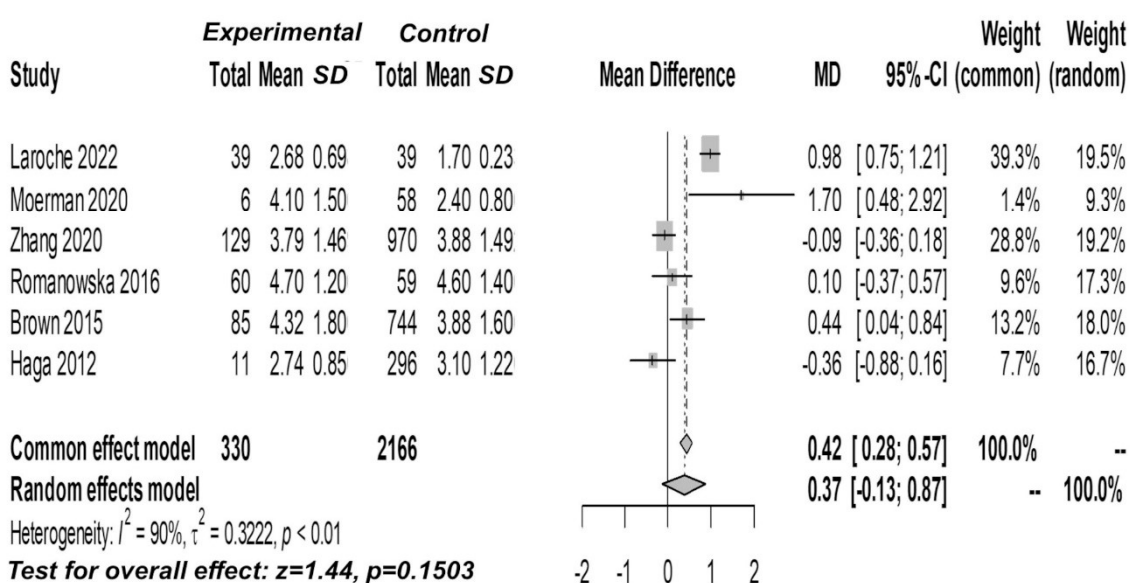


Figure2B: Forest plots of the meta-analysis on DAS28-CRP



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)

Figure3A: Forest plots of the meta-analysis on SJC

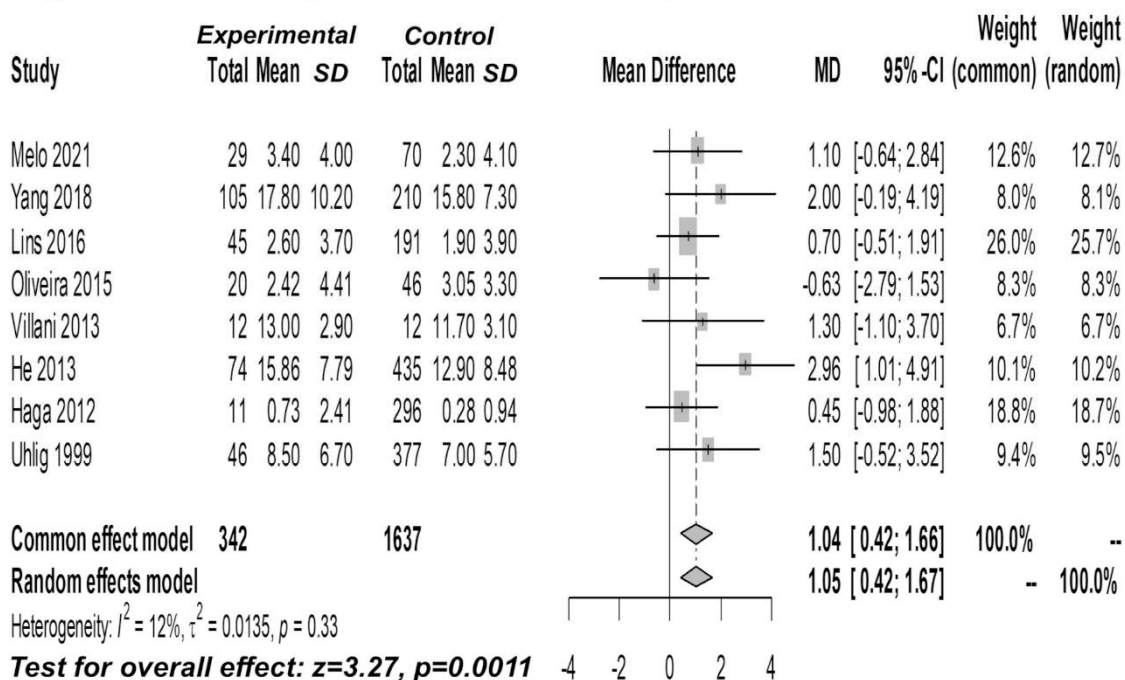
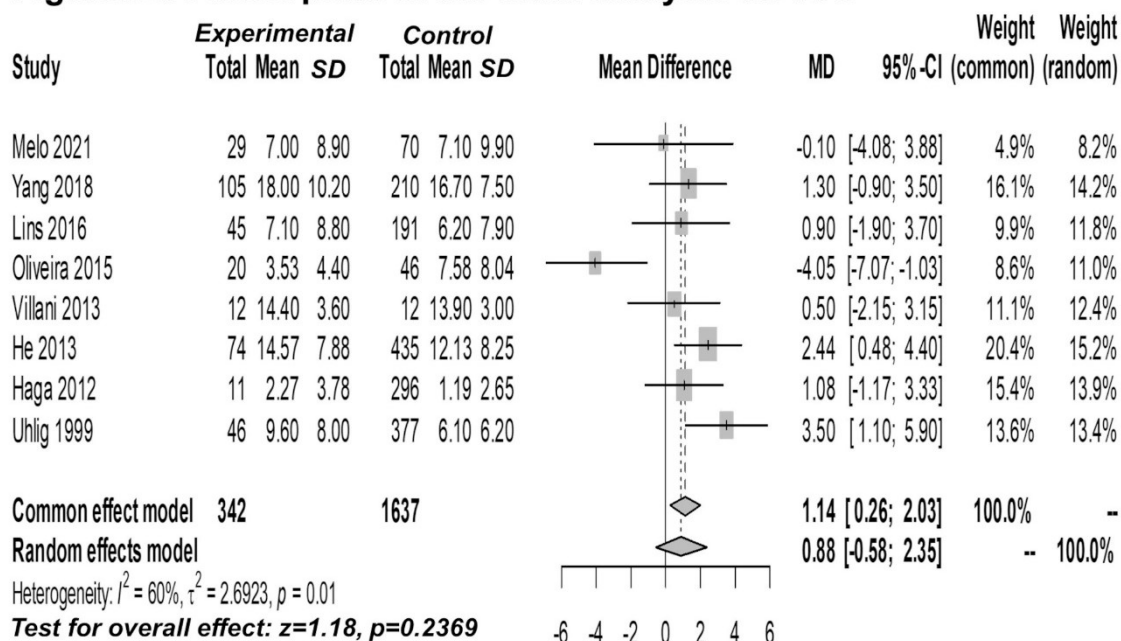
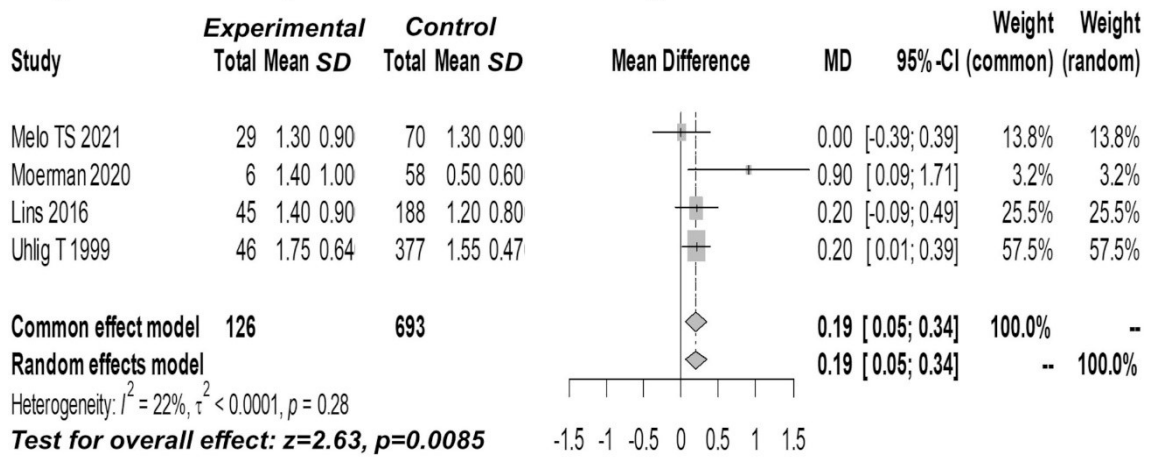


Figure3B: Forest plots of the meta-analysis on TJC



SJC: Swollen Joint Count, TJC: Tender Joint Count, SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)

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



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

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554 **Supplementary Information**

555

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

558

559 Authors: Takuya Tomizawa^{1,2,3,4}, Tobias Cox^{1,2}, Florian Kollert^{1,2,5}, Simon J. Bowman^{1,2},
560 Hiromu Ito⁴, Shuichi Matsuda⁴, Benjamin A. Fisher^{1,2*}

561

562 *Authors' affiliations:*

563 ¹ *Rheumatology Research Group, Institute of Inflammation and Ageing, College of*
564 *Medical and Dental Sciences, University of Birmingham*

565 ² *National Institute for Health Research (NIHR), Birmingham Biomedical Research*
566 *Centre and Department of Rheumatology, University Hospitals Birmingham NHS*
567 *Foundation Trust, Birmingham, UK*

568 ³ *Department of Orthopaedic Surgery, Terni Hospital, Terni, Japan*

569 ⁴ *Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine,*
570 *Kyoto, Japan*

571 ⁵ *Department of Rheumatology, Immunology, and Allergology, Inselspital, University*
572 *Hospital Bern, Bern, Switzerland*

573

574 **Corresponding author:*

575 *Rheumatology Research Group, Institute of Inflammation and Ageing, College of*
576 *Medical and Dental Sciences, University of Birmingham, Birmingham, UK*

577 E-mail: B.Fisher@bham.ac.uk

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

References	Harrold 2020	Kim 2020
	N/T(%); RA, RA/SjS	N/T(%); RA, RA/SjS
HT	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%)

579

References	Yang 2018	He 2016
	N/T(%); RA, RA/SjS	N/T(%); RA, RA/SjS
HT	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.*

586

587 **Supplementary Table2: Characteristics of RA therapy**

	MTX	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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	Anti-TNF	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

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	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

590

	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

591

	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

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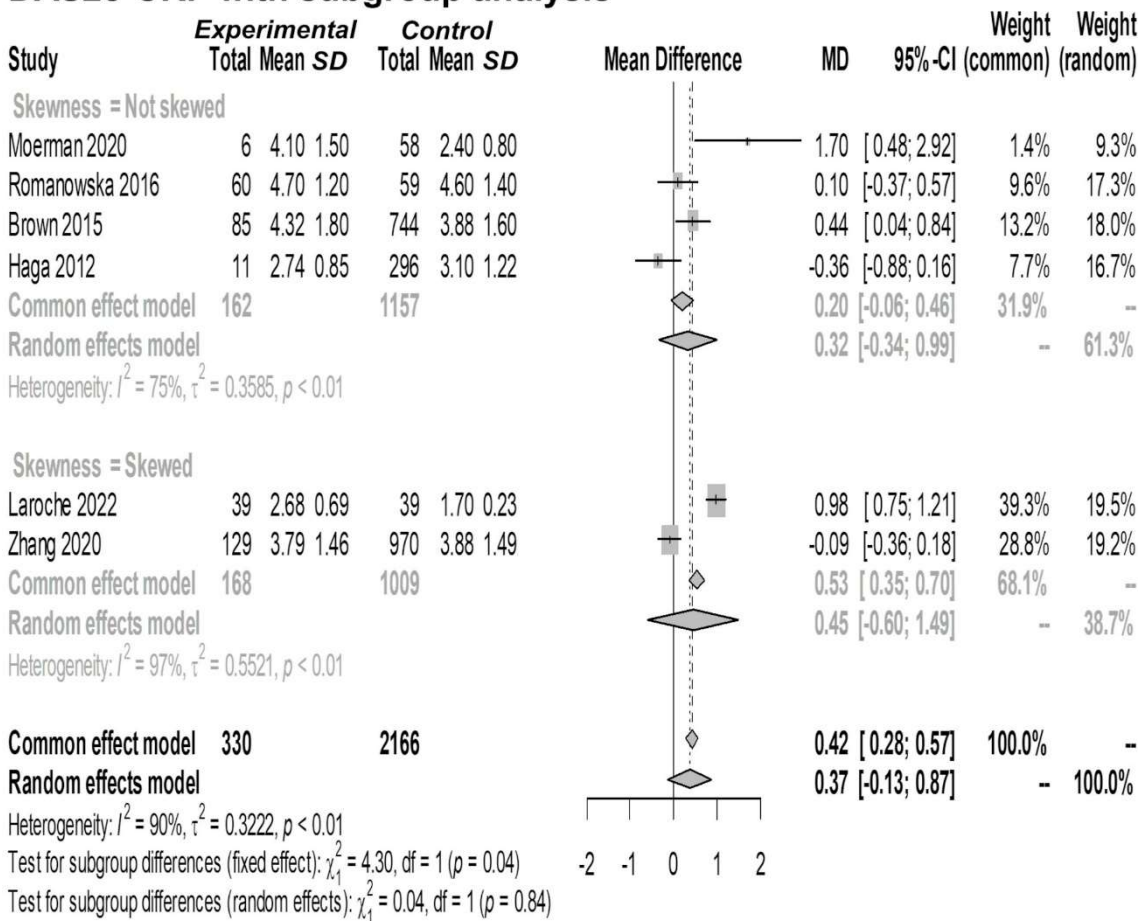
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RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, N: Number of Patients, T: Total Number of Patients Data Available, %: Proportion with Comorbidities, p: p value, N/A: No Data Available, NS: Not Significant, MTX: methotrexate, TNF: tumor necrosis factor,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

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



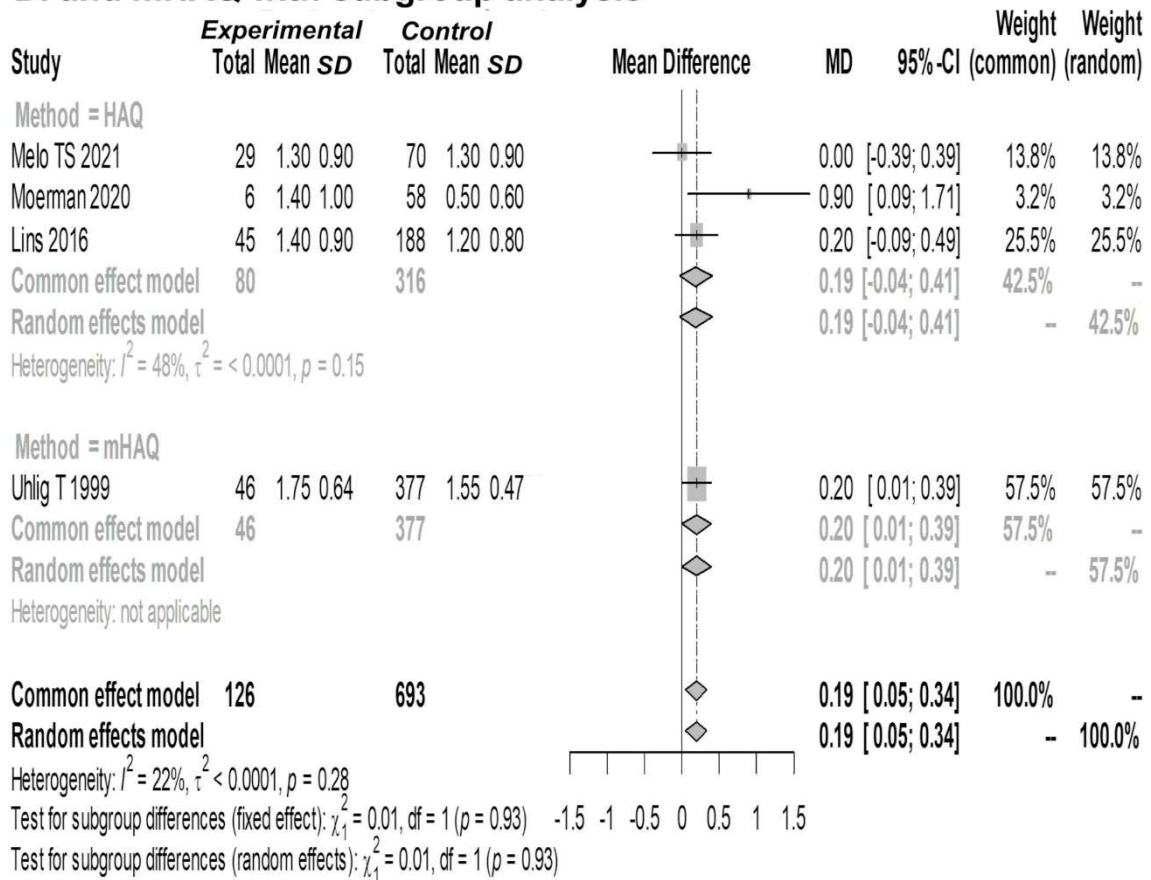
Test for overall effect: $z=1.44$, $p=0.1503$

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 Figure 2: Forest plots of the meta-analysis on HAQ-DI and mHAQ with subgroup analysis



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

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

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

