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

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

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Running title: Sjogren's impacting RA disease activity

Abstract

Objectives:

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

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.

Results:

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

Conclusion:

RA/SjS patients appear to have higher disease activity and more functional disability than patients with RA alone. The aetiology and clinical implications of this are unclear and warrant further investigation.

Keywords:

Sjögren's syndrome;

arthritis, rheumatoid;

outcome assessment, Health care;

patient reported outcome measures;

disability evaluation;

fatigue;

arthropathy, erosive

Key messages:

- Patients with RA/SjS may have higher disease activity than RA alone.
- The pathobiology and clinical implications of this require further investigation

Introduction

Rheumatoid arthritis (RA) is the most common rheumatic immune-mediated inflammatory disease (IMID). Poorly controlled disease activity is associated with disability and joint damage. Numerous disease-modifying treatments exist that are introduced in a trial-and-error approach with few pointers to indicate which patient may respond best to which treatment. Sjögren's syndrome (SjS) is another IMID that is

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

Methods

Search strategy and study selection

Our systematic review was performed following an a priori described protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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. 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.

Data extraction and quality evaluation

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

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.

Outcome evaluation

The primary outcome was a composite measure of RA disease activity: DAS28-ESR (Erythrocyte sedimentation rate), DAS28-CRP (C-reactive protein), SDAI or CDAI. Secondary outcomes were Swollen Joint Count (SJC), Tender Joint Count (TJC), Health Assessment Questionnaire-Disability Index (HAQ-DI) or modified Health Assessment Questionnaire (mHAQ), Visual Analogue Scale (VAS), joint damage indices and number of patients with damaged joints.

Statistical analysis

We performed a meta-analysis on observational or case control studies using a random effects model. Clinical parameters with less than 3 studies were considered inappropriate for statistical analysis. Heterogeneity of selected studies were assessed using the I2 statistic; I2 value of <25% indicates low heterogeneity, 25%–75% as moderate 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-statistics with a significance level of $p<0.10$. Publication bias was assessed with funnel plots (18). We did not perform meta-regression analysis because the number of obtainable 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.

Results

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).

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

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.

Meta-analysis of DAS28-ESR included 7 studies (23,26–31), with a total of 1920 RA and 320 RA/SjS patients. For one paper (27), the mean DAS28-ESR and SD were calculated using the provided data. The calculated data-distribution was not significantly skewed. We adopted a random effects model due to the high heterogeneity of studies ($I2 = 78.3\%$, $\tau2 = 0.38$, $P < 0.01$; Figure 2A). The difference between the two patient groups showed a strong trend to higher DAS28-ESR scores in RA/SjS with borderline statistical

significance (MD: 0.50; 95% CI [-0.008; 1.006] P = 0.05; Figure 2A).

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

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%, τ2 = 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.

Function

We found 4 papers with function data suitable for meta-analysis; 3 studies with HAQ-DI(26)(29)(34) and 1 study with mHAQ(23). Altogether, they included 693 RA and 126 RA/SjS patients. There was no significant heterogeneity of studies (I2 = 21.9%, τ2 < 0.0001, P = 0.2791; Figure 4). Function was worse in the RA/SjS group compared with RA alone (MD: 0.19; 95% CI [0.05; 0.34], P=0.009; Figure 4). We also performed subgroup analysis using papers with HAQ-DI data and studies with mHAQ data (Supplemental Fig 2). We observed no significant differences between studies with HAQ-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).

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).

Uhlig et al (23) reported that the RA/SjS patients had worse pain VAS scores (Mean=43.1, 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, 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, SD= 32.9, n= 39) than RA group (Mean=53.2, SD= 31.7, n= 191).

Meta-analysis of fatigue VAS included 638 RA and 112 RA/SjS (23,29,34). There was no significant heterogeneity of papers (I^2 = 42.6%, τ^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.

Joint damage

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 a clinical measure (23).

With the Sharp/van der Heijde method, Laroche et al. demonstrated that the RA/SjS group had more radiographic joint damage (n=39, median=15.4) compared with RA alone (n=39, median=13.9). However there was no statistical significance (p=0.79) (32). Brown et al. also described the same tendency; RA/SjS (n=85, median=47.5) having more radiographic joint damage than RA alone (n=744, median=17.0) (24). Using a less 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/SjS (n=46, Mean=1.8 SD=3.4) (23).

Three papers reported the percentage of patients with at least one damaged joint. (25,35,38). Yang et al used radiographic assessments, but was non-informative as all patients in both groups had at least one damaged joint (35). The other two papers assessed joint deformity clinically. He J et al. reported that RA/SjS patients (n=74, 60.8%) were 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 patients with ≥ 1 damaged joint in the RA/SjS group (36%) compared to RA alone (32%), although this did not reach statistical significance (p= 0.292) (38).

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

that patients with RA/SjS have higher DAS28-ESR scores (p=0.05). It is well-recognised that patients with SjS often have raised ESR, at least in part due to higher immunoglobulin levels, however CRP is typically normal except in the presence of certain extra-glandular features that may include inflammatory arthritis. Patients with SjS are also well-recognised to have a high symptom burden, including limb pain and fatigue, that negatively impacts health-related quality of life. It is therefore possible that these factors, ESR and symptoms, may be the drivers behind the observed higher DAS28-ESR scores. It is therefore of interest that we also found that patients with RA/SjS had a higher swollen joint count than those with RA alone. Further, although the DAS28-CRP meta-analysis did not reach statistical significance, it showed a similar numerical trend. Other papers we identified showed higher symptom burden, higher disability as measured by 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

is yet to be determined but is worthy of further research. Firstly, if there are pathobiological differences in RA processes between RA/SjS and RA alone, there may be a differential response to certain immunomodulators depending on the presence or absence of SjS. Secondly, in RA/SjS there are two autoimmune processes that may have a discordant or concordant response to any potential therapy, for example, anti-TNF has not been demonstrated to be efficacious in primary SjS (9,10). Thirdly, SjS-related pathobiology may influence drug-response through other means. For example, Chen et al utilised an autoantigen microarray in adalimumab treated RA patients and identified that the presence of anti-Ro60 antibodies were associated with formation of anti-drug antibodies and poor EULAR response (41), although this finding needs further validation in larger cohorts. The presence of anti-Ro antibodies also predicts a poorer response to abatacept (42), although again this needs validation in larger cohorts.

Our study has significant limitations meaning that we need to be cautious about our conclusions. The included studies showed statistically significant heterogeneity, although we compensated for this by selecting a conservative random effects model, as opposed to a fixed effects model, to evaluate statistical significance. Studies were mainly cross-sectional, and it was not possible to correct for factors that may have differed between 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, or if seropositivity was a confounding factor given the imbalance observed in some studies, as none of the analyses were stratified by autoantibody status. No SjS-specific outcome measures were available and SjS disease activity might also impact functional scores such as the HAQ.

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

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

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.

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

collection: TT, TC and BF. Data analysis: TT. Data interpretation: TT, TC and BF. Drafting of manuscript: TT, TC, FK, SB, HI, SM and BF. Full responsibility for the integrity of the work as a whole, from inception to published article: BF.

Funding TT received a grant from Japanese College of Rheumatology (JCR) as JCR-EULAR young rheumatologist training program. BAF and SJB have received support from the National Institute of Health Research (NIHR) Birmingham Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests BAF has undertaken consultancy for Novartis, BMS, Servier, Galapagos, Roche, UCB, Sanofi, Janssen and received research funding from Janssen, Servier, Galapagos, Celgene. SJB has undertaken consultancy in the past 3 years for Abbvie, BMS, Galapagos, Iqvia, J&J, Kiniksa and Novartis. FK is currently an employee of Roche.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data related to the study are included in the article or uploaded as supplementary data. All information related to the study are included in the article and uploaded as supplementary data.

References

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

https://doi.org/10.55563/clinexprheumatol/43z8gu

3. HAGA HJ, NADERI Y, MORENO AM, PEEN E. A study of the prevalence of sicca symptoms and secondary Sjögren's syndrome in patients with rheumatoid arthritis, and its association to disease activity and treatment profile. Int J Rheum Dis. 2012;15(3):284–8. https://doi.org/10.1111/j.1756-185X.2012.01717.x

4. CARMONA L, GONZÁLEZ-ALVARO I, BALSA A, ANGEL BELMONTE M, TENA X, SANMARTÍ R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis. 2003;62(9):897–900. http://dx.doi.org/10.1136/ard.62.9.897

5. HARROLD LR, SHAN Y, REBELLO S, et al. Prevalence of Sjögren's syndrome associated with rheumatoid arthritis in the USA: an observational study from the Corrona registry. Clin Rheumatol. 2020;39(6):1899–905. https://doi.org/10.1007/s10067-020-05004-8

6. RAMOS-CASALS M, BRITO-ZERÓN P, FONT J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum. 2007;36(4):246–55. https://doi.org/10.1016/j.semarthrit.2006.08.007

7. KOLLERT F, FISHER BA. Equal rights in autoimmunity: is Sjögren's syndrome ever 'secondary'? Rheumatology. 2020;59(6):1218–25. https://doi.org/10.1093/rheumatology/keaa009

8. CLOWSE MEB, WALLACE DJ, FURIE RA, et al. Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus: Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled Trials. Arthritis Rheumatol (Hoboken, NJ). 2017;69(2):362–75. https://doi.org/10.1002/art.39856

9. MARIETTE X, RAVAUD P, STEINFELD S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum. 2004;50(4):1270–6. https://doi.org/10.1002/art.20146

10. MAVRAGANI CP, NIEWOLD TB, MOUTSOPOULOS NM, PILLEMER SR, WAHL SM, CROW MK. Augmented interferon-alpha pathway activation in patients with Sjögren's syndrome treated with etanercept. Arthritis Rheum. 2007;56(12):3995–4004. https://doi.org/10.1002/art.23062

11. COOLES FAH, TARN J, LENDREM DW, et al. Interferon-α-mediated therapeutic resistance in early rheumatoid arthritis implicates epigenetic reprogramming. Ann Rheum Dis. 2022;81(9):1214–23. http://dx.doi.org/10.1136/annrheumdis-2022-222370

12. PAGE MJ, MCKENZIE JE, BOSSUYT PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71

13. BOOTH A. Prospero's progress and activities 2012/13. Syst Rev. 2013;2(111):1–3. https://doi.org/10.1186/2046-4053-2-111

14. ZENG X, ZHANG Y, KWONG JSW, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J Evid Based Med. 2015;8(1):2–10. https://doi.org/10.1111/jebm.12141

15. MODESTI PA, REBOLDI G, CAPPUCCIO FP, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. Fuchs FD, editor. PLoS One. 2016;11(1):e0147601.

https://doi.org/10.1371/journal.pone.0147601

16. HIGGINS JPT. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557

17. CUMPSTON MS, MCKENZIE JE, WELCH VA, BRENNAN SE. Strengthening systematic reviews in public health : guidance in the Cochrane Handbook for Systematic Reviews of Interventions , 2nd edition. 2022;44(4):588–92. https://doi.org/10.1093/pubmed/fdac036

18. EGGER M, SMITH GD, SCHNEIDER M, MINDER C. Bias in meta-analysis detected by a simple, graphical test. Br Med J. 1997;315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629

19. SHI J, LUO D, WAN X, et al. Detecting the skewness of data from the five-number summary and its application in meta-analysis. Stat Methods Med Res. 2023;096228022311720. https://doi.org/10.48550/arXiv.2010.05749

20. LUO D, WAN X, LIU J, TONG T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805. https://doi.org/10.1177/0962280216669183

21. WAN X, WANG W, LIU J, TONG T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14(1):135. https://doi.org/10.1186/1471-2288-14-135

22. BALDUZZI S, RÜCKER G, SCHWARZER G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Heal. 2019;22(4):153–60. http://dx.doi.org/10.1136/ebmental-2019-300117

23. UHLIG T, KVIEN TK, JENSEN JL, AXELL T. Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. Ann

Rheum Dis. 1999;58(7):415–22. http://dx.doi.org/10.1136/ard.58.7.415

24. BROWN LE, FRITS ML, IANNACCONE CK, WEINBLATT ME, SHADICK NA, LIAO KP. Clinical characteristics of RA patients with secondary SS and association with joint damage. Rheumatology. 2015;54(5):816–20. https://doi.org/10.1093/rheumatology/keu400

25. HE J, DING Y, FENG M, et al. Characteristics of Sjogren's syndrome in rheumatoid arthritis. Rheumatology. 2013;52(6):1084–9. https://doi.org/10.1093/rheumatology/kes374

26. MOERMAN R V., ARENDS S, MOSSEL E, KROESE FGM, VISSINK A, BOOTSMA H. 10-year follow-up of patients with rheumatoid arthritis and secondary Sjögren's syndrome or sicca symptoms in daily clinical practice. Clin Exp Rheumatol. 2020;38 Suppl 1(4):64–72. https://www.clinexprheumatol.org/abstract.asp?a=15517

27. KIM H, CHO S-K, KIM HW, et al. The Prevalence of Sjögren's Syndrome in Rheumatoid Arthritis Patients and Their Clinical Features. J Korean Med Sci. 2020;35(45):1–11. https://doi.org/10.3346/jkms.2020.35.e369

28. ROMANOWSKA-PRÓCHNICKA K, OLESIŃSKA M, PARADOWSKA-GORYCKA A, et al. Discrepancies in assessment of patients with rheumatoid arthritis and secondary Sjögren's syndrome by DAS28-ESR and DAS28-CRP. Cent Eur J Immunol. 2016;41(2):188–94. https://doi.org/10.5114/ceji.2016.60994

29. LINS E SILVA M, CARVALHO CN, CARVALHO A DE AT, LEÃO JC, DUARTE ALP, GUEIROS LA. Effect of Xerostomia on the Functional Capacity of Subjects with Rheumatoid Arthritis. J Rheumatol. 2016;43(10):1795–800. https://doi.org/10.3899/jrheum.151211

30. OLIVEIRA HF, DE SOUZA TR, CARVALHO CN, et al. Serologic profile and clinical markers of Sjögren syndrome in patients with rheumatoid arthritis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(6):628–35. http://dx.doi.org/10.1016/j.oooo.2015.02.479

31. HE J, DING Y, FENG M, et al. Characteristics of Sjögren's syndrome in rheumatoid arthritis. Rheumatology (Oxford). 2013;52(6):1084–9. https://doi.org/10.1093/rheumatology/kes374

32. LAROCHE M, DEGBOE Y, CONSTANTIN A. Sjögren's syndrome associated with erosive rheumatoid arthritis alters its prognosis and long-term therapeutic response: a case–control study. Rheumatol Int. 2023;43(2):363–6. https://doi.org/10.1007/s00296-021-05074-0

33. ZHANG H, ZHANG H, GAO D, XIE W, GENG Y, ZHANG Z. Overlapping Sjogren's syndrome reduces the probability of reaching target in rheumatoid arthritis patients: a propensity score matched real-world cohort from 2009 to 2019. Arthritis Res Ther. 2020;22(1):100. https://doi.org/10.1186/s13075-020-02189-w

34. MELO TS, SILVA ML E, SILVA JÚNIOR ML DE M, DUARTE AP, GUEIROS LA. Characterization of clinical, laboratory, IL-6 serum levels, and IL-6-174 G/C genetic polymorphisms in patients with rheumatoid arthritis and Sjögren's syndrome. Rev Assoc Med Bras. 2021;67(11):1600–4. https://doi.org/10.1590/1806-9282.20210665

35. YANG H, BIAN S, CHEN H, et al. Clinical characteristics and risk factors for overlapping rheumatoid arthritis and Sjögren's syndrome. Sci Rep. 2018;8(1):1–7. http://dx.doi.org/10.1038/s41598-018-24279-1

36. VILLANI E, GALIMBERTI D, PAPA N DEL, NUCCI P, RATIGLIA R. Inflammation in dry eye associated with rheumatoid arthritis: Cytokine and in vivo confocal microscopy study. Innate Immun. 2013;19(4):420–7. https://doi.org/10.1177/1753425912471692

37. HARROLD LR, SHAN Y, REBELLO S, et al. Disease activity and patient-reported outcomes in patients with rheumatoid arthritis and Sjögren's syndrome enrolled in a large observational US registry. Rheumatol Int. 2020;40(8):1239–48. https://doi.org/10.1007/s00296-020-04602-8

38. SANTOSH K, DHIR V, SINGH S, et al. Prevalence of secondary Sjögren's syndrome in Indian patients with rheumatoid arthritis: a single-center study. Int J Rheum Dis. 2017;20(7):870–4. https://doi.org/10.1111/1756-185X.13017

39. ANAYA J-M. The diagnosis and clinical significance of polyautoimmunity. Autoimmun Rev. 2014;13(4–5):423–6. https://doi.org/10.1016/j.autrev.2014.01.049

40. TRUTSCHEL D, BOST P, MARIETTE X, et al. Variability of Primary Sjögren's Syndrome Is Driven by Interferon-α and Interferon-α Blood Levels Are Associated With the Class II HLA–DQ Locus. Arthritis Rheumatol. 2022;74(12):1991–2002. https://doi.org/10.1002/art.42265

41. CHEN P-K, LAN J-L, CHEN Y-M, et al. Anti-TROVE2 Antibody Determined by Immune-Related Array May Serve as a Predictive Marker for Adalimumab Immunogenicity and Effectiveness in RA. J Immunol Res. 2021;2021:6656121. https://doi.org/10.1155/2021/6656121

42. ENDO Y, KOGA T, KAWASHIRI S, et al. Significance of anti-Ro/SSA antibodies in the response and retention of abatacept in patients with rheumatoid

arthritis: a multicentre cohort study. Scand J Rheumatol. 2021;50(1):15–9.
https://doi.org/10.1080/03009742.2020.1772361

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

*ACPA: Anti-Citrullinated Protein/Peptide Antibody, Duration: RA disease duration, N: Number of Seropositive Patients, N/A: No Data Available, NOS: Newcastle–Ottawa Scale, NS: Not Significant, +ve: Positive, RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, T: Total Number of Patients with Data Available. * Based on IgG. #Calculated by Chi-square test when p value not presented in cited papers.*

Figure Legends

Figure 1: Flow diagram of study selection

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

Figure 3: Forest plots from the meta-analysis of swollen (A) and tender (B) joint counts

Figure 4: Forest plot from the meta-analysis of function (HAQ-DI and mHAQ)

Figure1: Flow diagram of the eligible studies selection

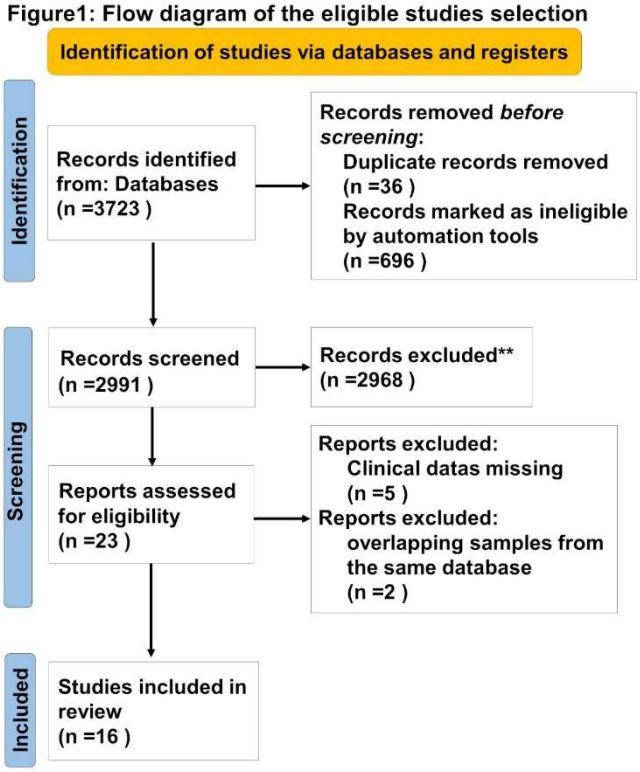


Figure2A: Forest plots of the meta-analysis on DAS28-ESR

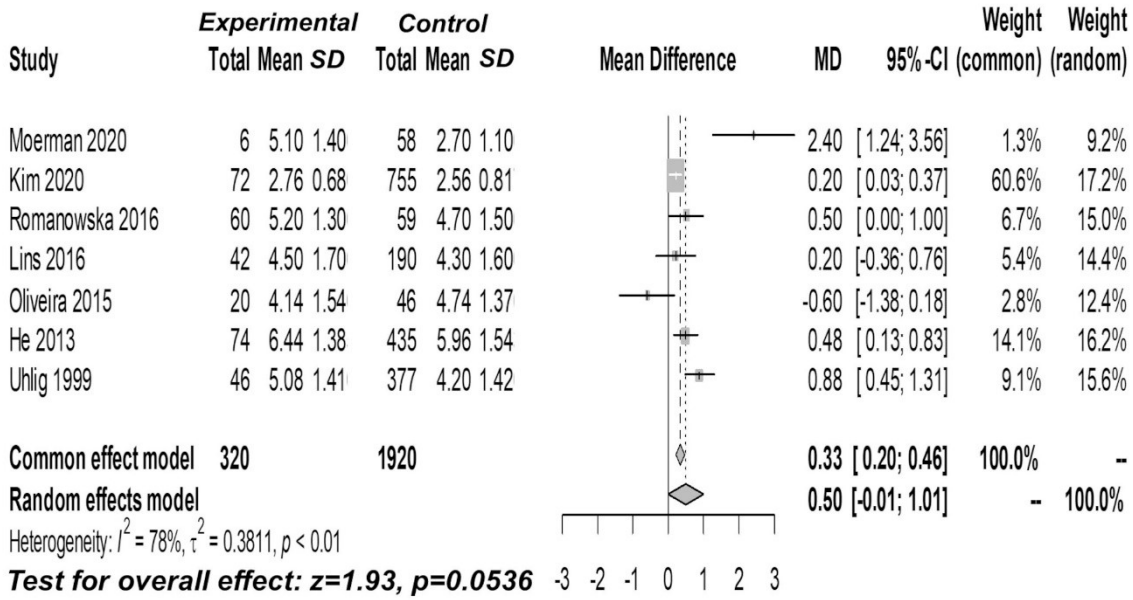
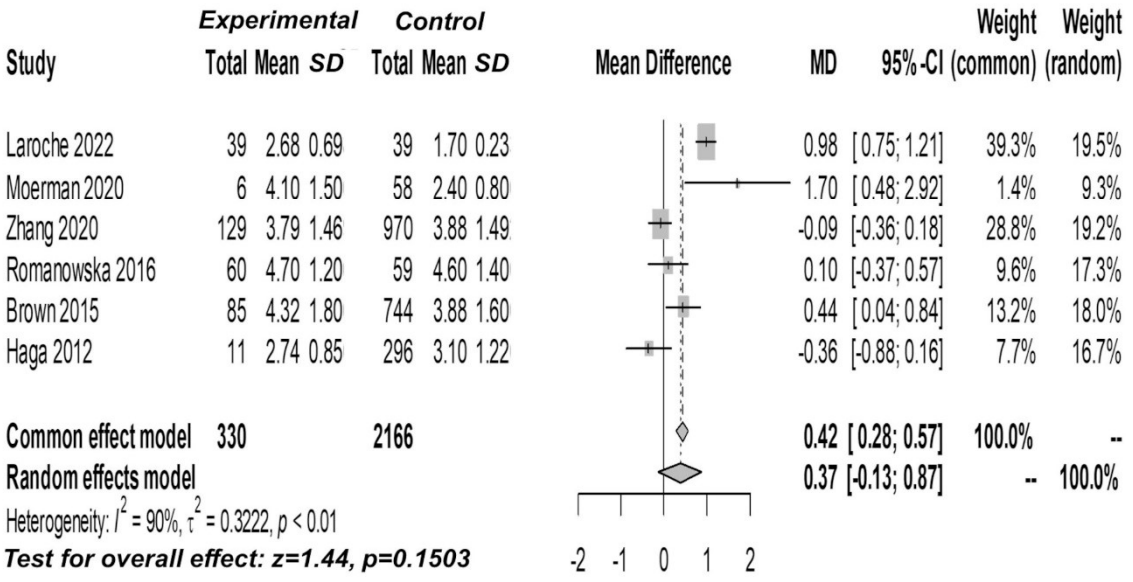


Figure2B: Forest plots of the meta-analysis on DAS28-CRP



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

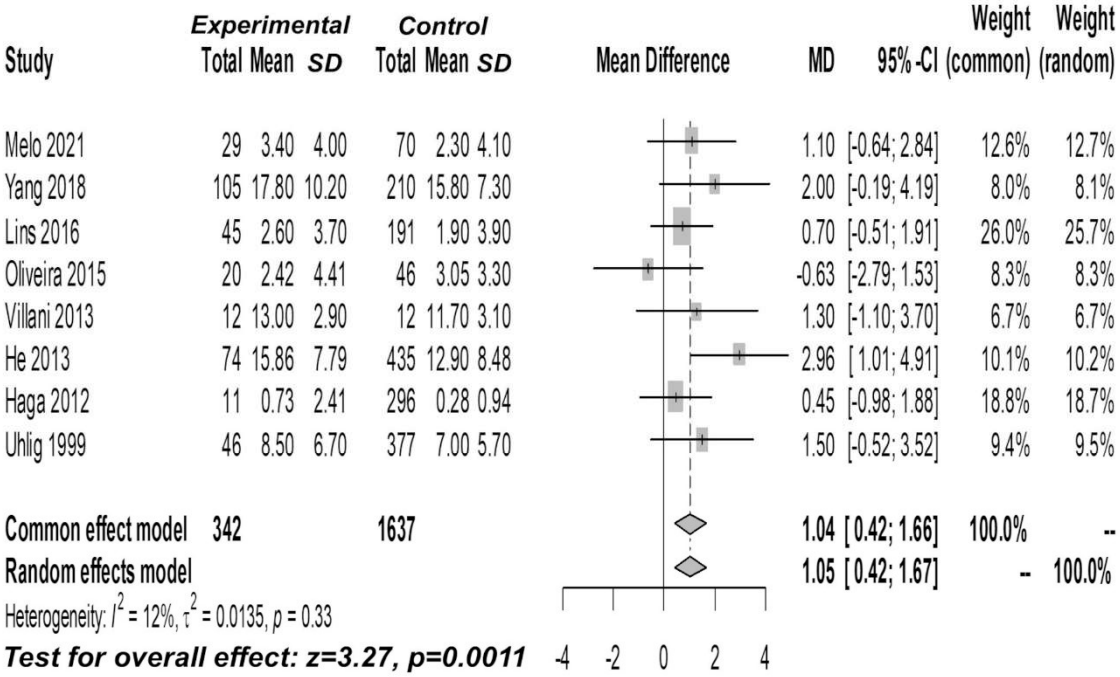
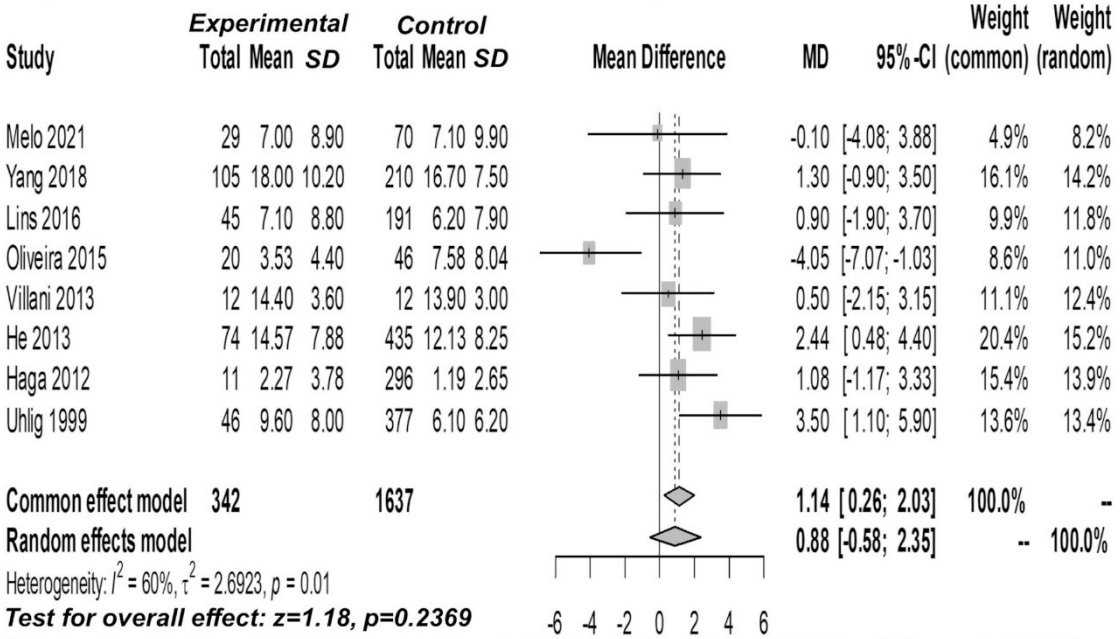
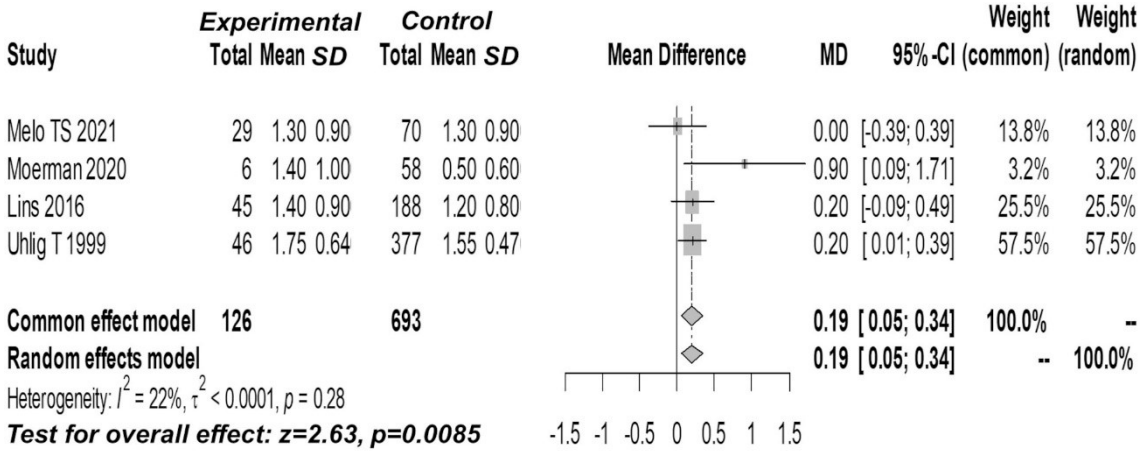


Figure3B: Forest plots of the meta-analysis on TJC



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)

Supplementary Information

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

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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%)

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%)

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%)

N:Number of Patients, T: Total Number of Patients with Data Available, %: Proportion with Comorbidities, N/A: No Data Available, RA: Rheumatoid Arthritis, SjS: Sjögren Syndrome, HT: Hypertension, CVD: Cardio Vascular Disease, COPD: Chronic Obstructive Pulmonary Disease, ILD: Interstitial Lung Disease, PF: Pulmonary Fibrosis, I:involvement

**Only proportions are available.*

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

	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

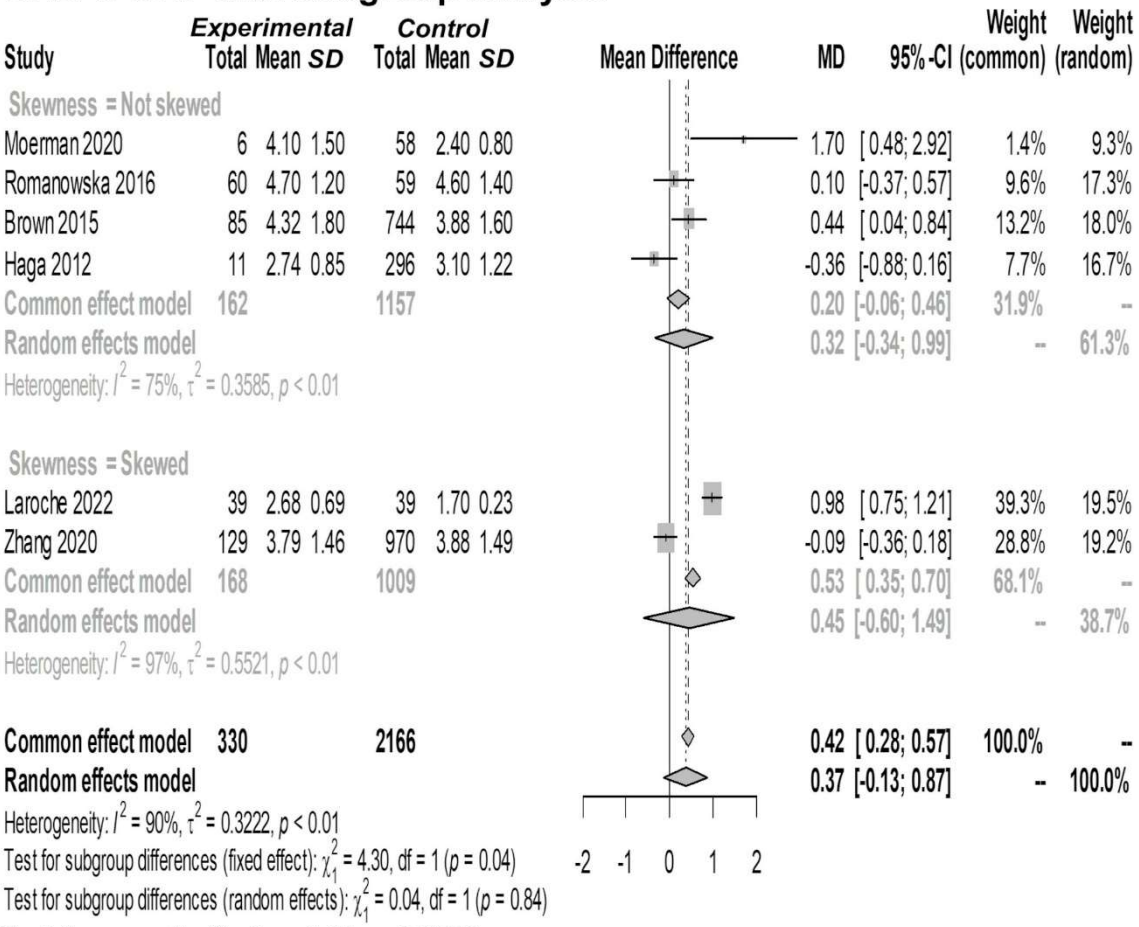
	Sulfasalazine	Tacrolimus
References	**N/T(%); RA, RA/SjS, p**	**N/T(%); RA, RA/SjS, p**
Kim	31/744 (4.1%), 3/72 (4.2%) p=0.980	92/744 (12.2%), 4/72 (5.6%), p=0.093
Haga	96/296 (32.4%), 5/11 (45.5%) p= NS	N/A

	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

	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,

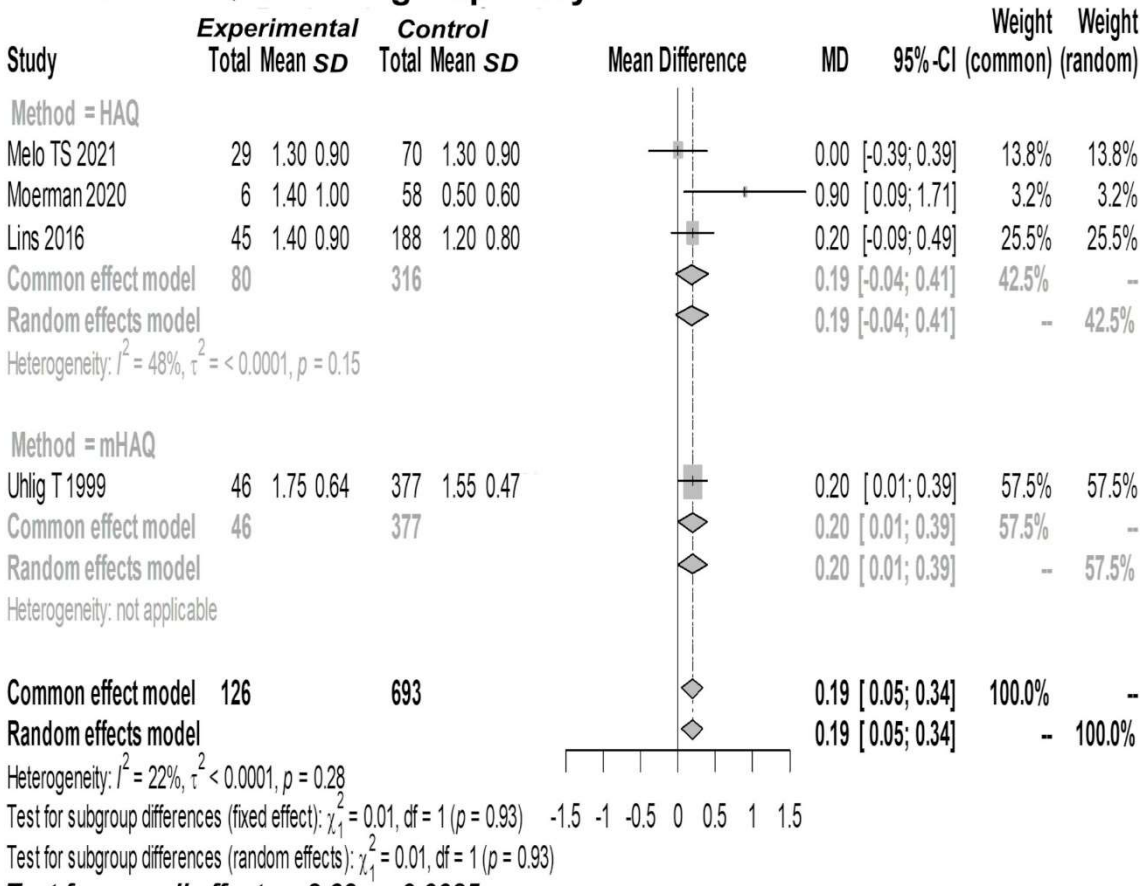
Supplementary Figure1: Forest plots of the meta-analysis on DAS28-CRP with subgroup analysis



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)

Supplementary Figure2: 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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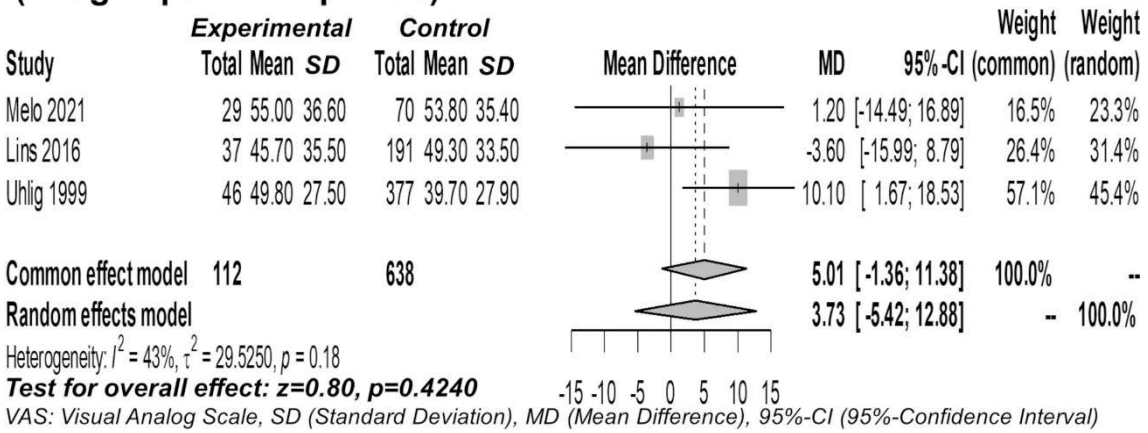
Supplementary Figure3: Forest plots of the meta-analysis on VAS (Fatigue patient reported)



VAS: Visual Analog Scale, SD (Standard Deviation), MD (Mean Difference), 95%-CI (95%-Confidence Interval)