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**Cognitive impairment in the immune-mediated inflammatory diseases compared with age-matched controls: systematic review and meta-regression**

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Key words: rheumatoid arthritis, disability, epidemiology, outcomes research, psychology

**Abstract**

**Objectives:** To compare the magnitude of cognitive impairment against age-expected levels across the immune mediated inflammatory diseases (IMIDs: systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], axial spondyloarthritis [axSpA], psoriatic arthritis [PsA], psoriasis [PsO]).

**Methods:** A pre-defined search strategy was implemented in Medline, Embase and Psychinfo on 29/05/2021. Inclusion criteria were: (i) observational studies of an IMID, (ii) healthy control comparison, (iii) measuring cognitive ability (overall, memory, complex attention/executive function, language/verbal fluency), and (iv) sufficient data for meta-analysis. Standardised mean differences (SMD) in cognitive assessments between IMIDs and controls were pooled using random-effects meta-analysis. IMIDs were compared using meta-regression.

**Results:** In total, 65 IMID groups were included (SLE: 39, RA: 19, axSpA: 1, PsA: 2 PsO: 4), comprising 3141 people with IMIDs and 9333 controls. People with IMIDs had impairments in overall cognition (SMD: -0.57 [95% CI -0.70, -0.43]), complex attention/executive function (SMD -0.57 [95% CI -0.69, -0.44]), memory (SMD -0.55 [95% CI -0.68, -0.43]) and language/verbal fluency (SMD -0.51 [95% CI -0.68, -0.34]). People with RA and people with SLE had similar magnitudes of cognitive impairment in relation to age-expected levels. People with neuropsychiatric SLE had larger impairment in overall cognition compared with RA.

**Conclusions:** People with IMIDs have moderate impairments across a range of cognitive domains. People with RA and SLE have similar magnitudes of impairment against their respective age-expected levels, calling for greater recognition of cognitive impairment in both conditions. To further understand cognition in the IMIDs, more large-scale, longitudinal studies are needed.

[Words: 245]

The immune mediated inflammatory diseases (IMIDs) represent a diverse collection of diseases whose mechanisms share common inflammatory pathways (e.g. cytokine dysregulation, such as tumour necrosis factor alpha)[1]. The IMIDs have a global prevalence of 5-7%[2], and include conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and psoriasis (PsO).

Cognitive impairment is a condition characterised by impairment in mental processing such as orientation, attention, problem-solving abilities, memory, and executive functions[3]. For some IMIDs, cognitive impairment has been well characterised. A 2018 meta-analysis reported a prevalence of 38% across 35 studies of people with SLE[4], and a second meta-analysis of 10 studies of people with SLE reported moderate impairments in terms of attention, memory and verbal fluency compared with controls without SLE[5]. A systematic review of studies of people with RA reported large effects on attention, problem solving, memory, verbal function and visuospatial tasks compared with controls[6]. A review of studies of people with PsO included six studies, five of which reported an association between PsO and increased risk of cognitive impairment[7]. Fewer studies have focused on PsA and axSpA, but poorer cognitive performance has been reported in these conditions compared with controls[8-10]. Therefore, cognitive impairment appears to be a significant issue across the IMIDs.

Despite this, the relative magnitude of cognitive impairment across the IMIDs is far from clear, and raises the question whether cognitive impairment is related to long term systemic inflammation, or whether impairment is an intrinsic feature of particular IMIDs. A systematic review by Al Rayes et al (2018) identified 8 studies directly comparing the prevalence of cognitive impairment between people with SLE and RA, with a pooled risk ratio of 1.80 (95% CI 1.30, 2.49), indicating greater prevalence in people with SLE[4]. However, age is a strong predictor of cognitive ability[11]. In many of the studies in Al Rayes et al, the people with RA had similar ages to the participants with SLE. As the average age of onset of SLE is lower than RA, these people with RA age-matched to the SLE participants will be younger than typical RA cohorts. This means these people with RA may have less cognitive impairment than would be expected in typical RA cohorts, as the people in these studies were younger. Furthermore, these comparisons only focused on the prevalence of impairment, rather than the magnitude of impairment. Contrary to the Al Rayes et al review, Meade et al's systematic review reported larger effect estimates in people with RA in terms of the magnitude of cognitive impairment compared with SLE[6], but this was from just two studies and these studies did not match for age[12 13]. Direct comparisons between the other IMIDs have not been performed.

Using meta-regression techniques, the relative magnitude of cognitive impairment across the IMIDs can be indirectly assessed by comparing the average size of impairment in each IMID compared with age-matched healthy controls. This indirect comparison will illustrate which IMID has the greatest impairment in cognitive ability compared with people without an IMID of a similar age. Therefore, the aims of this project were (i) to estimate the magnitude of cognitive impairment in people with IMIDs by identifying all studies comparing cognitive ability in a sample of people with IMIDs with a sample of healthy controls, and (ii) use meta-regression to compare indirectly the magnitude of cognitive impairment across the IMIDs.

**Methods**

A systematic review was performed using the Medline, Embase and Psychinfo databases, including studies published up to 29/05/2021 using a predefined search strategy based on previous reviews (see Supplementary Table 1)[5-7]. The inclusion criteria were: (1) observational studies including an IMID (RA, SLE, axSpA, PsA, PsO), (2) a healthy control comparison group, (3) measuring cognitive ability (see below for cognitive domains included), and (4) at a minimum reporting mean and standard deviation

[SD] of cognitive assessment scores in the IMID and controls groups, or other summary statistics from which means and SDs could be estimated [see statistical analysis section]). Exclusion criteria included: (1) studies of children, (2) interventional studies, (3) reviews or editorials, (4) conference abstracts / unpublished dissertations, and (5) not published in English and no translation available. Studies that only reported the number of people with cognitive impairment (i.e. prevalence not magnitude of impairment) were also excluded. Furthermore, where multiple publications reported on the same sample of participants, the study with the largest sample size was included (see below for further details). This review was designed and reported according to the PRISMA guidelines[14].

The search strategy (Supplementary Table 1) included both text and MESH terms to identify studies assessing cognitive ability in the included IMIDs. This strategy was implemented using OVID across the three databases and yielded 2693 abstracts. After duplicates were removed by EndNote X9, the titles and abstracts of the remaining 2228 abstracts were screened by two reviewers (JMG, TT). Disagreements were discussed between reviewers until a final decision was made. Of the identified abstracts, 2090 did not meet inclusion criteria (Figure 1), leaving 138 full texts which were read by the same two reviewers. Of these, 56 studies were included in the review. The reference lists of four published reviews were screened[4-7], which resulted in five additional papers being included. Finally, a relevant study by the authorship team which was published 27/06/2021 was also included[15].

The data from each included full text were extracted by one reviewer onto a standardised form. This included information regarding:

- Study design,
- Inclusion/exclusion criteria,
- Number of participants included,
- Demographics (age, gender, education, number of people with IMIDs and HCs),
- Diagnosis of the participants (including disease duration when reported),
- Matching on age, gender, education and/or any other characteristics,
- Cognition data of the participants.

The cognition measures were grouped into four domains based on categorisations from a previous review of cognition in SLE[5]: overall cognition, complex attention/executive function, memory, language/verbal fluency. Memory was further subdivided into four categories based on two criteria: immediate/delayed recall and verbal/non-verbal memory. Several publications reported multiple assessments within these domains. To avoid double counting the studies in the meta-analyses, the frequency of all assessments within each domain was used to define a hierarchy of assessments (i.e. the assessments used more frequently across all the included studies were given higher priority. Ties in ranks were checked, and no study reported two assessments with tied ranks). If a publication reported two assessments within a cognition domain, the assessment ranked higher in the hierarchy was used (assessment hierarchies in the Supplementary Materials).

In several instances, multiple publications were identified by an author team using ostensibly the same sample, or a later publication reported results from a new sample of participants merged with a previously recruited sample (e.g. [16-21]). To avoid double counting in the meta-analyses, where this occurred the publication with the largest sample size was used.

Quality assessment was performed using an adapted version of the Newcastle-Ottawa case-control study assessment[22], rating each study based on sample representativeness, sample size justification, description of non-respondents, ascertainment of IMID status, recruitment of controls, matching on age, matching on other variables, and use of validated cognitive assessment instruments.

*Statistical analysis*

The baseline characteristics of the people with an IMID and HCs were summarised using random effects meta-analysis. For each cognitive assessment, the standardised mean difference between people with an IMID and HCs was calculated and pooled using random effects meta-analysis, stratified by IMID diagnosis. Meta-analyses were carried out in all studies, and limited to studies that reported matching on age. Further analyses were conducted on studies that also matched on gender and education. For the majority of scales, higher scores indicated better cognition. Where this was not the case (e.g. trail making task B), scales were reversed to allow consistent interpretation of pooled SMDs. Studies reporting extremely large SMDs (>2) or with inconsistent reporting of results were not included[23-26]. Funnel plots were created to assess publication bias.

Meta-regression was used to compare across the IMID diagnoses. Rather than comparing the raw scores on the cognitive assessments attained by the people with each IMIDs diagnosis (which would be biased by age), the meta-regression compares across the IMIDs the magnitude of impairment of each IMID against age-matched healthy controls (i.e. the meta-regression regresses the differences in cognitive ability (the SMDs) between the participants with IMIDs and healthy control reported from each study against IMID diagnosis; Figure 2 illustrates the comparisons made in the meta-regression analysis). The results of the meta-regression can be interpreted as a comparison of the magnitude of impairment in cognitive ability of each IMID over each IMID's respective age-expected level (i.e. based on each study's healthy controls).

Several studies reported demographic or cognition data as median and range or interquartile range rather than mean and SDs. To include these studies in the meta-analyses, means and standard deviations were estimated using published formulae[27]. Furthermore, some studies reported IMIDs in subgroups. To avoid double counting controls, these IMID subgroups were combined using published formulae[28]. Several studies reported assessments of more than one memory dimension. These were pooled using multi-level meta-analysis. Sensitivity analyses limiting meta-analyses to studies scoring ≥4 and ≥5 out of 8 on the Newcastle-Ottawa quality assessment scale and a comparison of neuropsychiatric SLE (NPSLE) and RA were also conducted. Assessment of agreement between the reviewers was performed using Stata version 14 (College Station, TX, USA) and meta-analysis and meta-regression analyses using R version 3.6.0 (packages: tidyverse[29], estmeansd[30], meta[31], metafor[32], esc[33]).

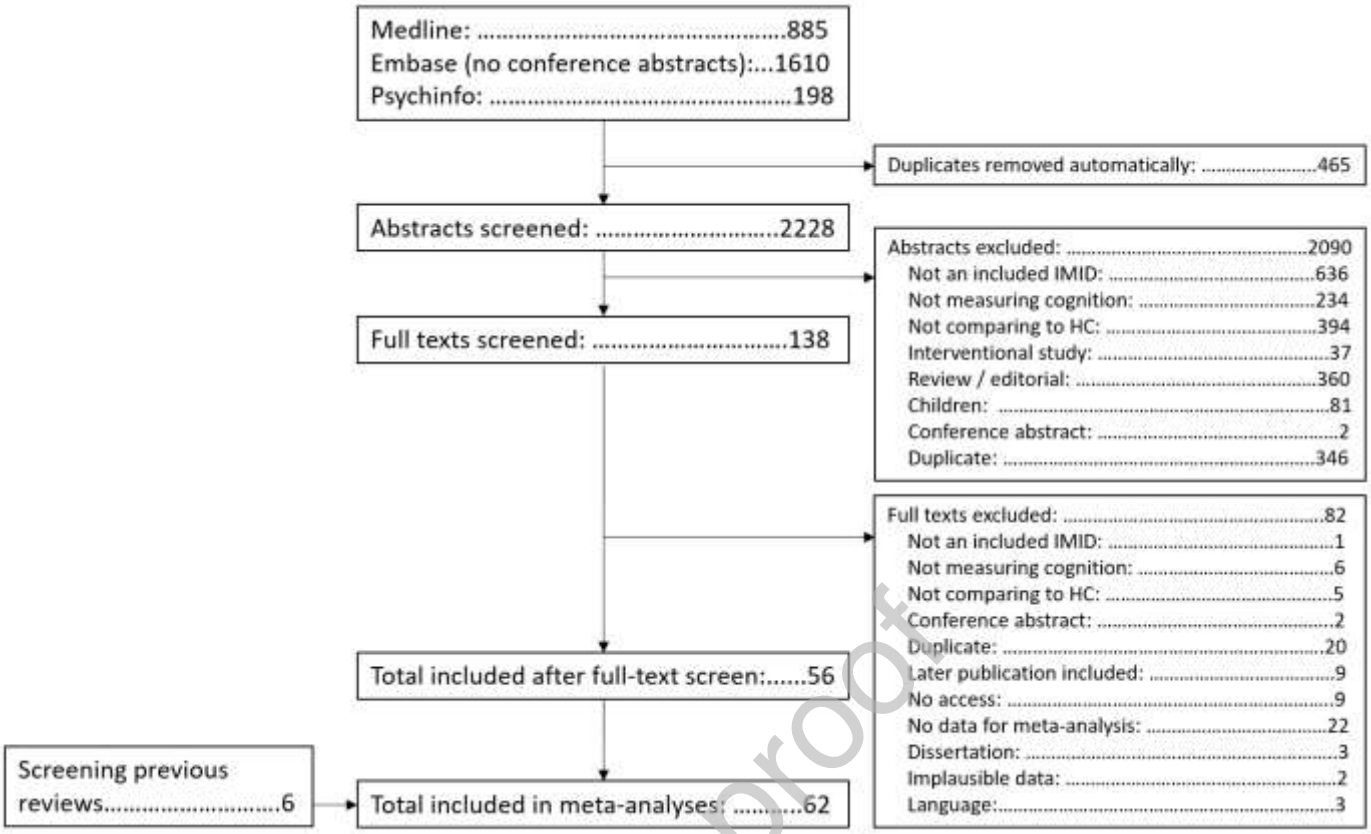


*Figure 1 – PRISMA flow-diagram of study selection*

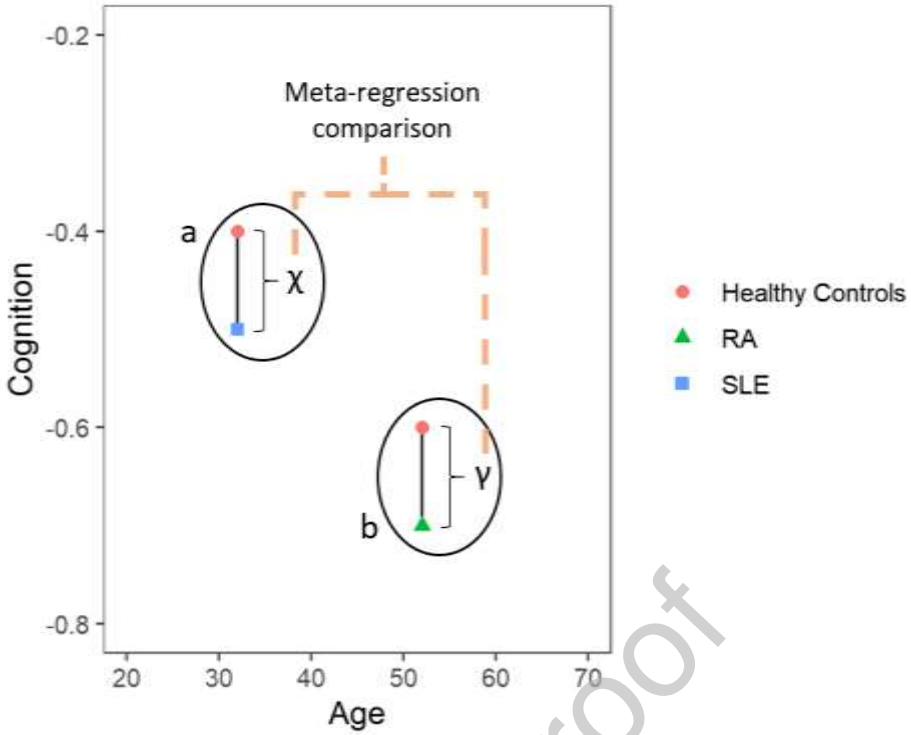


*Figure 2 – Illustrative diagram of the meta-regression*

RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

The figure illustrates the comparisons made in the meta-regression analysis (hypothetical data). The red circles indicate healthy controls matched on age with RA (green triangles) and SLE (blue squares) (RA and SLE chosen as examples). Lower scores indicate more cognitive impairment. The circle *a* represents the meta-analysis of SLE vs age-matched healthy controls, and therefore the effect χ is the magnitude of impairment in SLE compared with age-matched controls (i.e. people with SLE have lower scores on cognitive assessments and therefore more cognitive impairment). The circle *b* represents the meta-analysis of RA vs age-matched healthy controls, and therefore the effect γ is the magnitude of impairment in RA compared with age-matched controls. Simply comparing RA (green triangle) with SLE (blue square) would be biased by age. Instead, the meta-regression analysis compares the sizes of effects χ and γ – the interpretation of the meta-regression coefficient of this particular analysis would be how much more impaired are people with SLE over healthy people of a similar age (to people with SLE – red circle in *a*), compared with the impairment in RA over healthy people of a similar age (to people with RA – red circle in *b*)

**Results**

*Description of included studies*

Overall, 62 studies were included across the meta-analyses[9 10 13 15 21 25 26 34-88] (Figure 1). There were 65 IMID participant groups (three studies included two separate IMID groups), comprising: SLE = 39, RA = 19, PsO = 4, PsA = 2, axSpA = 1. In total, 3141 people with an IMID were included (SLE = 1642, RA = 928, PsO = 398, PsA = 133, axSpA = 40), compared with 9333 controls. All continents were represented other than Oceania and Antarctica (North America = 18, Asia = 17, Europe = 16, South America = 8, Africa = 3); the highest number of studies from a single country was the USA (N = 14).

The SLE participants had lower pooled mean age compared with the other IMIDs, and people in the IMID groups were slightly older than their corresponding control groups (Table 1). This difference was reduced when limiting to studies matching on age (Table 1). There was a higher proportion of women in the SLE (95.7%) and RA (96.6%) groups compared with the other IMIDs, and there were few differences in the proportion of women between the IMID and control groups (primarily as many studies only included women) (Table 1). People in the IMID groups had lower education than controls, and people with RA had lower education than people with SLE (Table 1). This trend remained when examining only studies that reported matching on education. Furthermore, people with RA had longer disease duration on average compared with the SLE samples (Table 1).

*Meta-analyses of cognitive ability stratified by IMID diagnosis*

In total, 38 comparisons from 37 studies (one included an RA and an SLE group) reported data on assessments of overall cognition (N comparisons: SLE = 19, RA = 13, PsO = 3, PsA = 2, axSpA = 1). The most commonly included scales were the Mini-Mental State Exam (N=16), The Montreal Cognitive Assessment (N=6) and the Wechsler Intelligence Scale - Full Scale IQ (N=6, Supplementary Table 3 for all included assessments). People with IMIDs had significant impairments on instruments aiming to summarise overall cognition (SMD: -0.57 [95% CI -0.70, -0.43], Figure 3 & Table 2). Similar results were seen when restricting to studies that matched on age (Table 2), and when restricting to studies that also matched on gender and education (Supplementary Table 4).

For complex attention/executive function, 42 studies were included (N comparison: SLE = 28, RA = 11, PsO = 2, PsA = 0, axSpA = 1). The most commonly included scales were the Trail Making Task – B (N=15), Paced Auditory Serial Addition Task (N=5), and the Stroop Interference Task (N=5, Supplementary Table 6 for all included assessments). Similar to overall cognition, people with IMIDs had significant impairments in complex attention/executive function compared with controls (SMD -0.57 [95% CI -0.69, -0.44], Figure 4 & Table 2). Similar results were seen when restricting to studies that reported matching (Table 2 & Supplementary Table 7).

Memory assessments were defined based on whether they were verbal or non-verbal and whether they involved immediate or delayed recall (assessments in Supplementary Table 9). People with IMIDs had moderate impairment in all memory domains (Table 2 and Figure 5), although these estimates were dominated by studies of SLE, particularly the non-verbal assessments (% of studies which assessed people with SLE: verbal immediate = 65.5%, verbal delayed = 69.2%, non-verbal immediate = 88.2%, non-verbal delayed = 88.8%). Again, similar results were seen when limiting to studies which matched people with IMIDs and controls on age (Table 2), gender, and education (Supplementary Table 10). Combining all reported memory assessments in a multi-level meta-analysis, results from 90 memory assessments across 39 studies showed moderate impairment in memory in the IMIDs against controls (SMD -0.55 [95% CI -0.68, -0.43], Supplementary Table 12).

In total, 26 comparisons reported results on language/verbal fluency assessments. The most common assessment included was the animal naming test (N=14) followed by the Controlled Oral Word Association Test (N=5, Supplementary Table 14). People with IMIDs had moderate-sized impairments in language/verbal fluency (SMD -0.51 [95% CI -0.68, -0.34], Table 2 and Figure 6), with similar results when limiting to studies which matched on age (SMD -0.55 [95% CI -0.71, -0.39]) as well as gender and education (Supplementary Table 15).

Funnel plots were created to assess potential publication bias (Supplementary Figures 1-7). In general, publication bias appears limited, with the exception of the verbal immediate meta-analysis (Supplementary Figure 3), in which several small-scale studies reported large effects with no small-scale studies reporting small effects, indicating the possibility the small-scale studies showing no effect have not been published.

*Meta-regression comparing the magnitude of cognitive ability across the IMIDs*

Meta-regression was used to perform indirect comparisons across the IMIDs (Table 3). Due to a lack of studies, the only meaningful comparisons are between RA and SLE. RA and SLE had similar magnitudes of impairment against respective age-expected levels in overall cognition (difference in standardised means [95% CI]: -0.09 [-0.40, 0.22]), whereas people with RA had worse cognition over age-expected levels compared with SLE in complex attention/executive function, memory and language/verbal fluency (difference in standardised means [95% CI]: complex attention/executive function: -0.36 [-0.72, -0.01]; memory: -0.67 (-1.08, -0.25); language/verbal fluency: -0.42 [-0.80, -0.04]). Sensitivity analyses restricted to studies matching on gender and education produced similar results, albeit with wider confidence intervals (Supplementary Tables 5, 8, 11, 13 and 16).

*Sensitivity analysis – NPSLE vs RA*

Many of the samples of people with SLE had mixed populations including both NPSLE and non-NPSLE participants. In sensitivity analysis, studies where 100% of the sample were people with NPSLE or studies where data for an NPSLE subgroup were also presented were selected (N = 11[16 40 41 45 47 53 57 64 67 70 89], two studies included here were not included in the main meta-analysis as later publications on the same sample were selected[16 89]) and compared against studies of people with RA. People with NPSLE had worse overall cognition scores compared with people with RA (SMD [95% CI]: NPSLE = -1.08 [-1.41, -0.75]; RA = -0.56 [-0.80, -0.33]; difference in standardised means RA vs NPSLE [95% CI] = 0.54 [0.08, 0.99]), but the other cognitive domains were similar between the two IMIDs (Supplementary Tables 17 and 18).

*Sensitivity analysis – Quality assessment*

The mean quality rating was 4.6 out of 8 (SD 1.3; description of quality assessment in Supplementary Table 19). The majority of studies (97%) used validated assessments, whereas only very few studies performed a priori sample size calculations (7%) or provided information on non-responders (18%), and only 29% of studies used controls recruited through the community, with many studies using family members of the cases as controls, or staff at the authors' university or hospitals (Supplementary Table 20 and 21). Limiting studies to those which scored ≥4 or ≥5 out of 8 made little difference to the overall findings (Supplementary Tables 22 and 23).

Table 1 – Demographic characteristics pooled across studies

| Variable | IMID | IMID pooled value (95% CI) | HC pooled value (95% CI) | Pooled mean difference / RR (95% CI) |
|---|---|---|---|---|
| **Age [all studies], years** | SLE | 38.0 (36.1, 39.9) | 36.0 (34.3, 37.7) | 1.7 (0.7, 2.7) |
| | RA | 52.1 (46.8; 57.3) | 50.9 (44.8, 57.1) | 1.0 (0.2, 1.7) |
| | axSpA | 49.3 (44.6, 54.0) | 48.8 (44.0, 53.6) | 0.5 (-6.2, 7.2) |
| | PsA | 54.7 (25.4, 83.9) | 53.6 (-3.5, 110.7) | 1.9 (-24.6, 28.4) |
| | PsO | 47.9 (27.5, 68.4) | 47.0 (26.4, 67.7) | 0.6 (-0.8, 2.0) |
| **Age [age-matched], years** | SLE | 37.6 (35.5, 39.7) | 36.0 (34.1, 37.8) | 1.4 (0.4, 2.3) |
| | RA | 54.5 (47.8, 61.1) | 54.8 (48.0, 61.6) | 0.6 (0.3, 0.9) |
| | axSpA | 49.3 (44.6, 54.0) | 48.8 (44.0, 53.6) | 0.5 (-6.2, 7.2) |
| | PsA | 57.4 (53.0 (61.7) | 58.2 (54.1, 62.3) | -0.8 (-6.8, 5.2) |
| | PsO | 40.9 (38.4, 43.4) | 41.1 (36.7, 45.5) | -0.4 (-5.1, 4.3) |
| **Proportion women [all studies], %** | SLE | 95.7% (93.4, 97.3) | 94.8% (91.2, 97.0) | RR 1.01 (0.99, 1.02) |
| | RA | 96.6% (88.3, 99.1) | 96.7% (86.2, 99.3) | RR 1.00 (0.99, 1.01) |
| | axSpA | 47.5% (32.7, 62.7) | 45.0% (30.5, 60.4) | RR 1.06 (0.66, 1.69) |
| | PsA | 41.4% (7.0, 86.9) | 46.4% (5.1, 93.3) | RR 0.90 (0.23, 3.54) |
| | PsO | 56.1% (32.1, 77.6) | 63.3% (29.1, 87.9) | RR 0.88 (0.69, 1.13) |
| **Proportion women [sex matched], %** | SLE | 95.3% (92.2, 97.2) | 95.3% (91.2, 97.6) | RR 1.00 (0.99, 1.01) |
| | RA | 97.1% (84.9, 99.5) | 97.0% (84.1, 93.9) | RR 1.00 (0.99, 1.01) |
| | axSpA | 47.5% (32.7, 62.7) | 45.0% (30.5, 60.4) | RR 1.06 (0.66, 1.69) |
| | PsA | 46.0% (30.8, 61.9) | 44.4% (29.3, 60.7) | RR 1.03 (0.62, 1.71) |
| | PsO | 56.1% (32.1, 77.6) | 62.9% (30.5, 60.4) | RR 0.88 (0.69, 1.13) |
| **Education [all studies], years** | SLE | 13.3 (12.2, 14.4) | 14.0 (12.9, 15.0) | -0.6 (-1.3, 0.0) |
| | RA | 10.5 (9.0, 12.1) | 12.0 (10.3, 13.6) | -1.3 (-1.8, -0.8) |
| | axSpA | - | - | - |
| | PsA | 13.1 (12.3, 13.8) | 13.9 (12.7, 15.0) | -0.8 (-2.2, 0.6) |
| | PsO | 10.0 (8.4, 11.6) | 9.0 (7.7, 10.3) | 1.0 (-1.1, 3.1) |
| **Education [education matched], years** | SLE | 12.8 (10.6, 14.9) | 12.7 (10.9, 14.5) | 0.1 (-0.9, 1.0) |
| | RA | 9.5 (7.1, 11.9) | 10.7 (8.5, 12.8) | -1.0 (-1.8, -0.1) |
| | axSpA | - | - | - |
| | PsA | - | - | - |
| | PsO | - | - | - |
| **Disease duration, years** | SLE | 8.8 (7.2, 10.3) | - | - |
| | RA | 10.5 (9.2, 11.8) | - | - |
| | axSpA | 13.2 (10.0, 16.4) | - | - |
| | PsA | 9.6 (7.9, 11.3) | - | - |
| | PsO | 12.9 (-26.5, 52.3) | - | - |

Differences between the pooled values of the of the IMID and HCs and the pooled mean differences are due to differences in the weighting parameter (e.g. for IMID pooled value, the weighting parameter is defined based on the number of IMID participants only, whereas the weighting parameter in the pooled mean difference column is defined based on the IMID and the control sample size)

axSpA = axial spondyloarthritis, CI = confidence interval, HC = healthy control, IMID = immune mediated inflammatory disease, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, RR = risk ratio, SLE = systemic lupus erythematosus

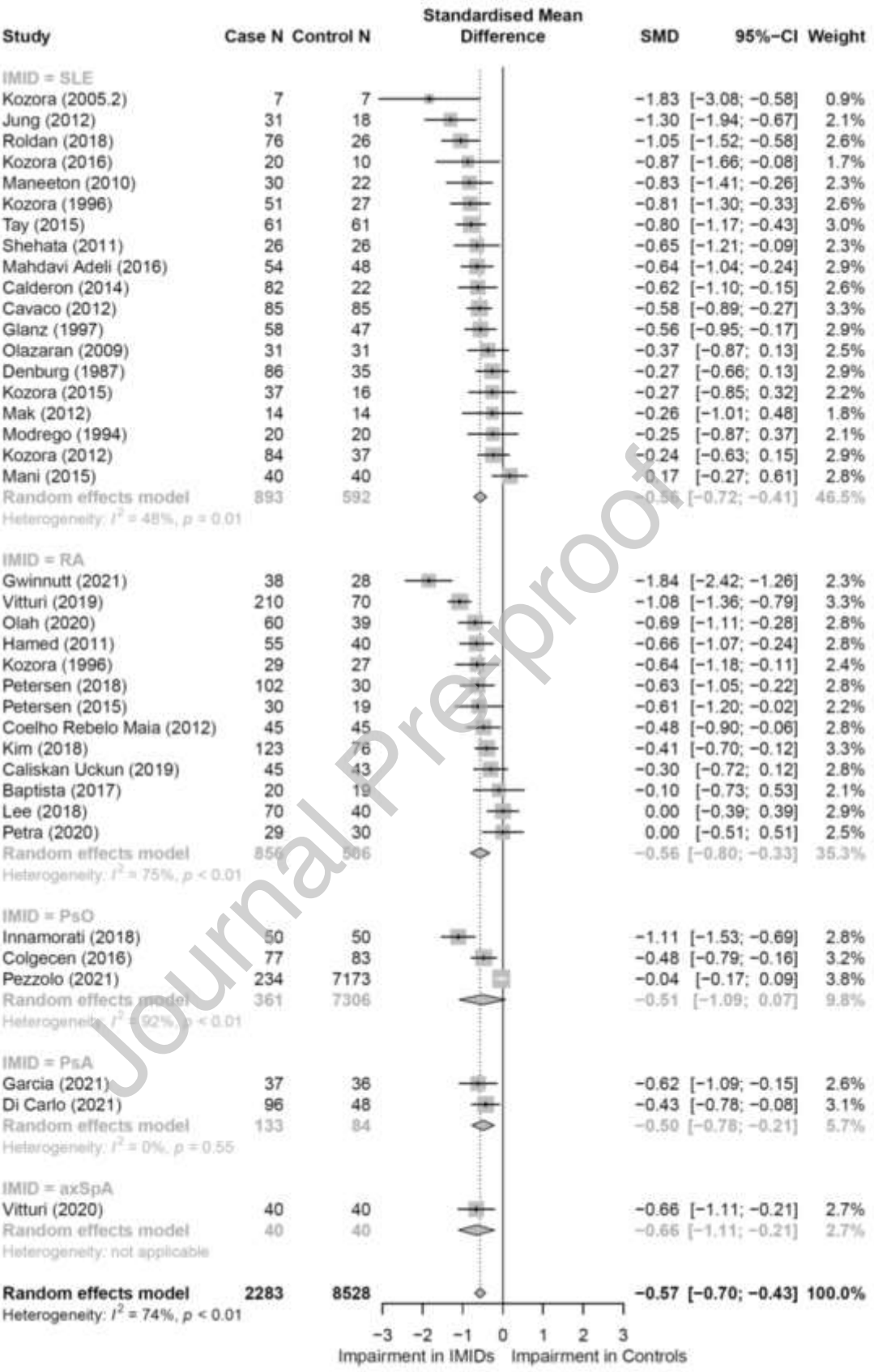


*Figure 3 – Forest plot of meta-analysis of studies reporting assessments of overall cognition*

*axSpA = axial spondyloarthritis, CI = confidence interval, IMID = immune mediated inflammatory disease, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SMD = standardised mean difference*

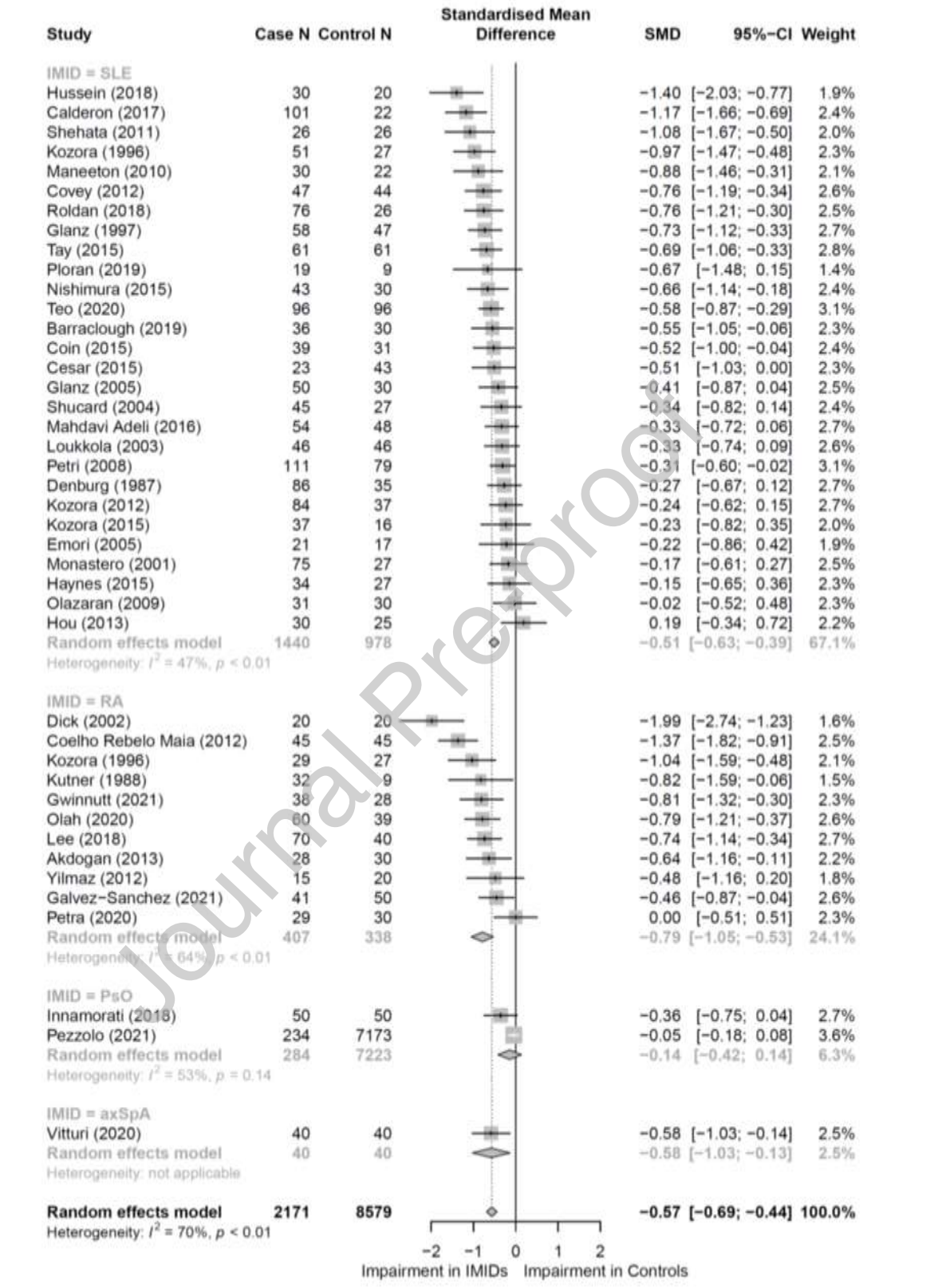


*Figure 4 – Forest plot of meta-analysis of studies reporting assessments of complex attention/executive function*

*axSpA = axial spondyloarthritis, CI = confidence interval, IMID = immune mediated inflammatory disease, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SMD = standardised mean difference*

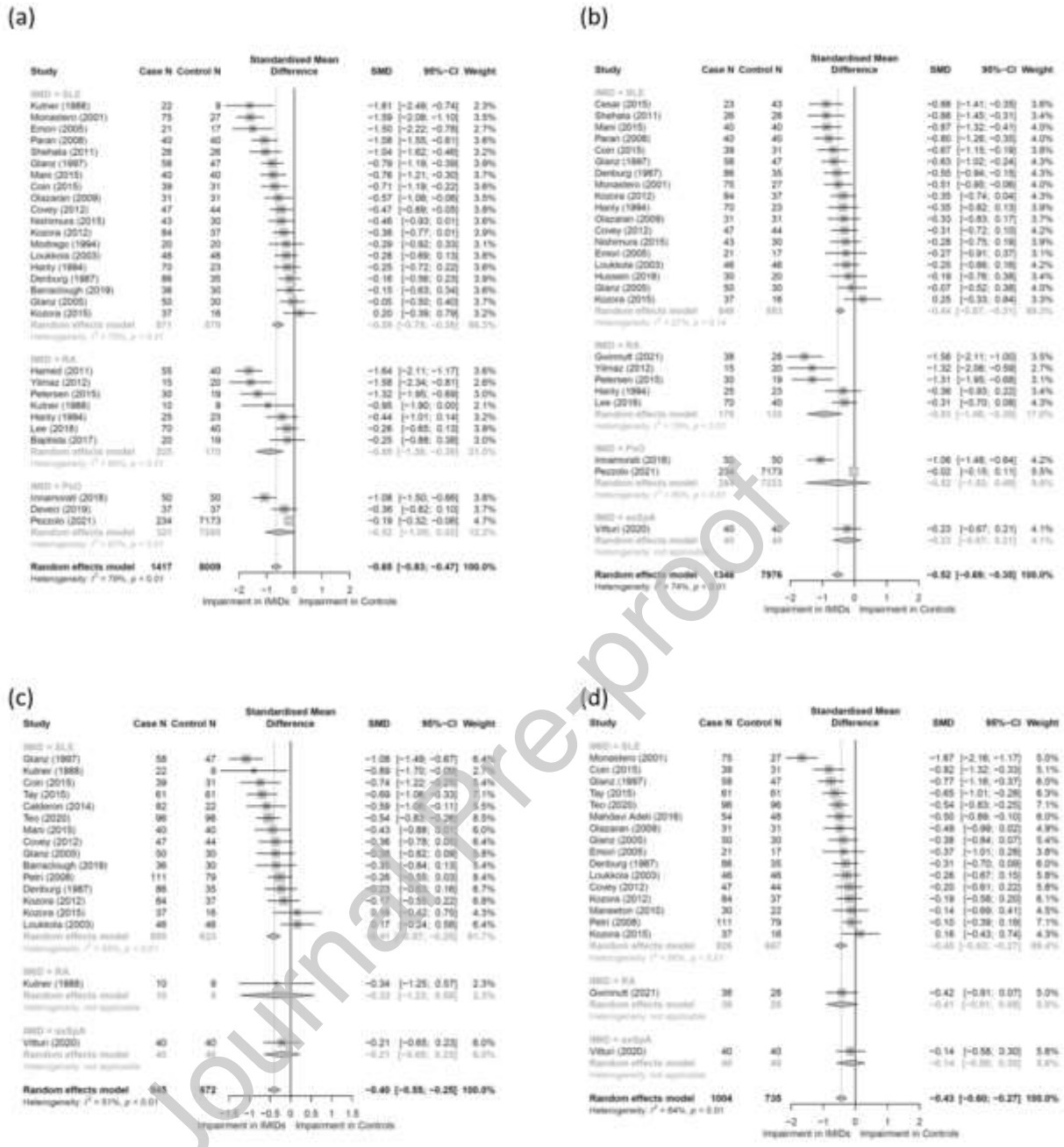


*Figure 5 – Forest plot of meta-analysis of studies reporting assessments of memory – (a) verbal immediate, (b) verbal delayed, (c) non-verbal immediate, (d) non-verbal delayed*

*axSpA = axial spondyloarthritis, CI = confidence interval, IMID = immune mediated inflammatory disease, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SMD = standardised mean difference*

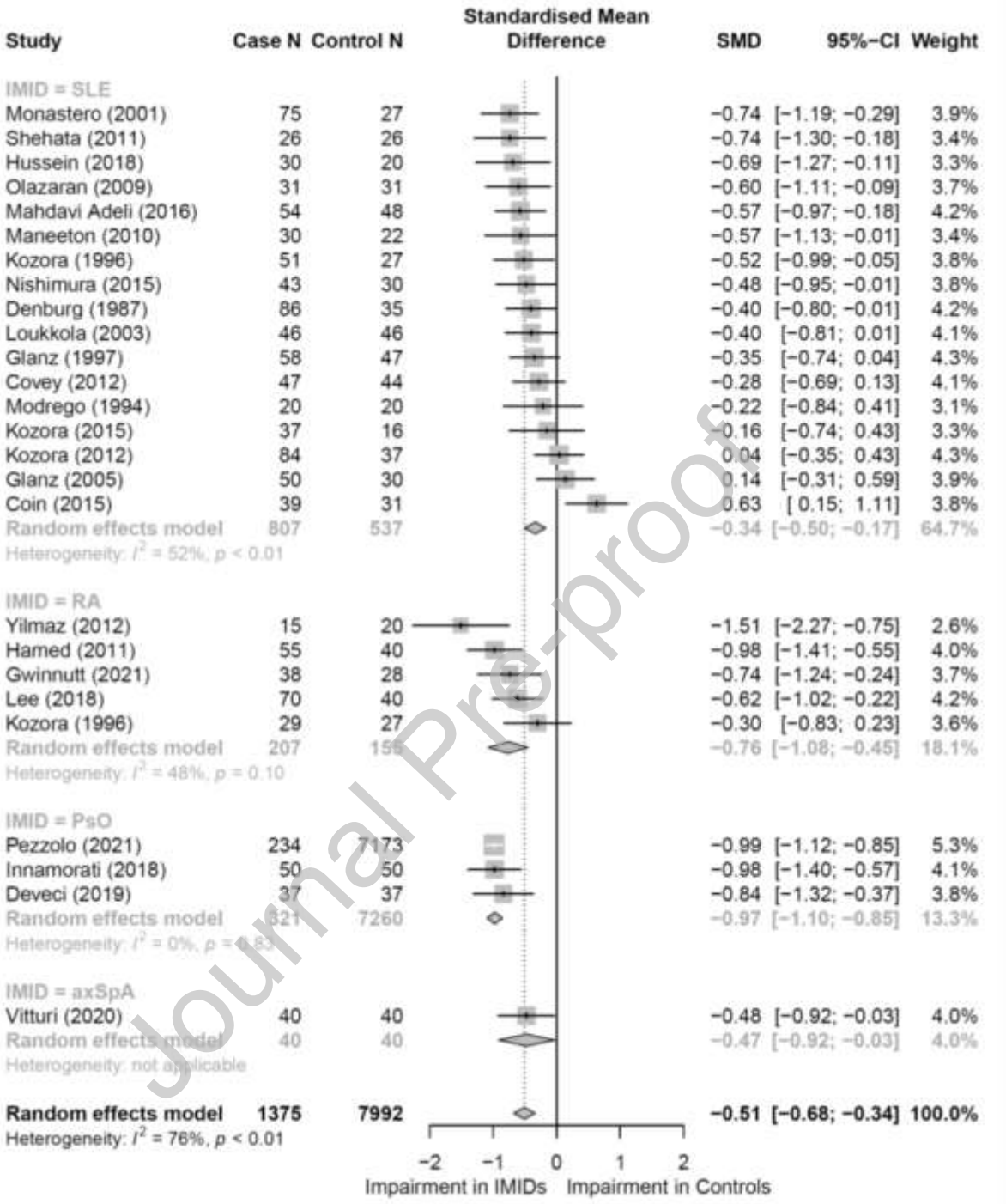


*Figure 6 – Forest plot of meta-analysis of studies reporting assessments of language / verbal fluency*

*axSpA = axial spondyloarthritis, CI = confidence interval, IMID = immune mediated inflammatory disease, PsA = psoriatic arthritis, PsO = psoriasis, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus, SMD = standardised mean difference*

Table 2 – Results of meta-analyses

| | | Standardised mean difference (95% Confidence Interval) [N studies] | | | | | |
|---|---|---|---|---|---|---|---|
| | | All IMIDs | Systemic lupus erythematosus | Rheumatoid arthritis | Axial spondyloarthritis | Psoriatic arthritis | Psoriasis |
| **Overall cognition** | All | -0.57 (-0.70, -0.43) [38] | -0.56 (-0.72, -0.41) [19] | -0.56 (-0.80, -0.33) [13] | -0.66 (-1.11, -0.21) [1] | -0.50 (-0.78, -0.21) [2] | -0.51 (-1.09, 0.07) [3] |
| | Age-matched | -0.61 (-0.75, -0.48) [29] | -0.55 (-0.72, -0.38) [14] | -0.64 (-0.90, -0.38) [11] | -0.66 (-1.11, -0.21) [1] | -0.61 (-1.08, -0.14) [1] | -0.77 (-1.39, -0.16) [2] |
| **Complex attention / executive function** | All | -0.57 (-0.69, -0.44) [42] | -0.51 (-0.63, -0.39) [28] | -0.79 (-1.05, -0.53) [11] | -0.58 (-1.03, -0.13) [1] | - | -0.14 (-0.42, 0.14) [2] |
| | Age-matched | -0.60 (-0.74, -0.45) [31] | -0.52 (-0.67, -0.37) [22] | -0.89 (-1.30, -0.47) [7] | -0.58 (-1.03, -0.14) [1] | - | -0.36 (-0.75, 0.04) [1] |
| **Verbal memory (immediate)** | All | -0.65 (-0.83, -0.47) [29] | -0.59 (-0.79, -0.38) [19] | -0.88 (-1.38, -0.39) [7] | - | - | -0.52 (-1.05, 0.02) [3] |
| | Age-matched | -0.75 (-1.01, -0.49) [18] | -0.61 (-0.90, -0.32) [12] | -1.18 (-1.82, -0.54) [4] | - | - | -0.72 (-1.42, -0.02) [2] |
| **Verbal memory (delayed)** | All | -0.52 (-0.69, -0.35) [26] | -0.44 (-0.57, -0.31) [18] | -0.93 (-1.48, -0.38) [5] | -0.23 (-0.67, 0.21) [1] | - | -0.52 (-1.52, 0.49) [2] |
| | Age-matched | -0.57 (-0.79, -0.35) [17] | -0.39 (-0.56, -0.21) [12] | -1.40 (-1.76, -1.03) [3] | -0.23 (-0.67, 0.21) [1] | - | -1.05 (-1.47, -0.63) [1] |
| **Non-Verbal memory (immediate)** | All | -0.40 (-0.55, -0.25) [17] | -0.41 (-0.57, -0.25) [15] | -0.32 (-1.23, 0.58) [1] | -0.21 (-0.65, 0.23) [1] | - | - |
| | Age-matched | -0.33 (-0.50, -0.17) [11] | -0.34 (-0.52, -0.16) [10] | - | -0.21 (-0.65, 0.23) [1] | - | - |
| **Non-Verbal memory (delayed)** | All | -0.43 (-0.60, -0.27) [18] | -0.45 (-0.63, -0.27) [16] | -0.41 (-0.91, 0.08) [1] | -0.14 (-0.58, 0.30) [1] | - | - |
| | Age-matched | -0.42 (-0.62, -0.22) [14] | -0.44 (-0.66, -0.22) [12] | -0.41 (-0.91, 0.08) [1] | -0.14 (-0.58, 0.30) [1] | - | - |
| **Memory (all) §** | All | -0.55 (-0.68, -0.43) [90] | -0.50 (-0.62, -0.37) [68] | -0.86 (-1.28, -0.44) [14] | -0.19 (-0.75, 0.36) [3] | - | -0.51 (-1.34, 0.32) [5] |
| | Age-matched | -0.60 (-0.77, -0.42) [60] | -0.48 (-0.64, -0.31) [46] | -1.17 (-1.63, -0.70) [8] | -0.19 (-0.75, 0.36) [3] | - | --0.74 (-2.26, 0.79) [3] |
| **Language / verbal fluency** | All | -0.51 (-0.68, -0.34) [26] | -0.34 (-0.50, -0.17) [17] | -0.76 (-1.08, -0.45) [5] | -0.47 (-0.92, -0.03) [1] | - | -0.97 (-1.10, -0.85) [3] |
| | Age-matched | -0.55 (-0.71, -0.39) [19] | -0.40 (-0.57, -0.23) [12] | -0.82 (-1.24, -0.41) [4] | -0.47 (-0.92, -0.03) [1] | - | -0.91 (-1.22, -0.60) [2] |

§ numbers in square brackets represent number of memory assessments, rather than number of studies

Table 3 – Results of meta-regression

| | | Mean difference in pooled effect sizes (95% Confidence Interval) | | | | |
|---|---|---|---|---|---|---|
| | | Systemic lupus erythematosus | Rheumatoid arthritis | Axial spondyloarthritis | Psoriatic arthritis | Psoriasis |
| **Overall cognition** | All | Ref. | -0.01 (-0.28, 0.31) | -0.08 (-0.91, 0.75) | 0.06 (-0.52, 0.65) | 0.09 (-0.37, 0.55) |
| | Age-matched | Ref. | -0.09 (-0.40, 0.22) | -0.11 (-0.89, 0.67) | -0.06 (-0.85, 0.73) | -0.21 (-0.75, 0.33) |
| **Complex attention / executive function** | All | Ref. | -0.28 (-0.53, -0.02) | -0.07 (-0.75, 0.61) | - | 0.34 (-0.08, 0.77) |
| | Age-matched | Ref. | -0.36 (-0.72, -0.01) | -0.06 (-0.85, 0.73) | - | 0.17 (-0.59, 0.93) |
| **Verbal memory (immediate)** | All | Ref. | -0.29 (-0.75, 0.16) | - | - | 0.08 (-0.50, 0.66) |
| | Age-matched | Ref. | -0.58 (-1.21, 0.05) | - | - | -0.10 (-0.88, 0.68) |
| **Verbal memory (delayed)** | All | Ref. | -0.47 (-0.90, -0.04) | 0.22 (-0.59, 1.03) | - | -0.02 (-0.56, 0.52) |
| | Age-matched | Ref. | -1.02 (-1.47, -0.58) | 0.16 (-0.41, 0.74) | - | -0.67 (-1.22, -0.11) |
| **Non-Verbal memory (immediate)** | All | Ref. | 0.08 (-0.96, 1.11) | 0.21 (-0.45, 0.87) | - | - |
| | Age-matched | Ref. | - | 0.13 (-0.47, 0.73) | - | - |
| **Non-Verbal memory (delayed)** | All | Ref. | 0.03 (-0.75, 0.82) | 0.31 (-0.45, 1.06) | - | - |
| | Age-matched | Ref. | 0.02 (-0.80, 0.85) | 0.30 (-0.50, 1.10) | - | - |
| **Memory (all)** | All | Ref. | -0.36 (-0.69, -0.03) | 0.30 (-0.45, 1.06) | - | 0.00 (-0.46, 0.46) |
| | Age-matched | Ref. | -0.67 (-1.08, -0.25) | 0.28 (-0.45, 1.02) | - | -0.28 (-0.85, 0.30) |
| **Language / verbal fluency** | All | Ref. | -0.43 (-0.77, -0.10) | -0.14 (-0.78, 0.51) | - | -0.61 (-0.96, -0.26) |
| | Age-matched | Ref. | -0.42 (-0.80, -0.04) | -0.07 (-0.70, 0.55) | - | -0.51 (-0.97, -0.05) |

**Discussion**

This analysis of 62 studies assessing cognition in the IMIDs illustrates that the IMIDs are associated with moderate impairments across a range of cognitive domains compared with healthy controls. Furthermore, this analysis revealed that people with SLE and RA had similar levels of cognitive impairment compared against their age-expected norms. These findings persisted when limiting analyses to studies that matched on age, as well as gender and education. People with NPSLE did have greater impairment on overall cognition assessments compared with RA, but similar scores across the other domains. These analyses illustrate the substantial burden people with an IMID have in terms of cognitive impairment, and may indicate the need to monitor cognitive ability in these conditions, and to develop effective interventions. Furthermore, greater awareness that cognitive impairment is an important symptom across all the IMIDs is essential for improved management. The European Alliance of Associations for Rheumatology (EULAR) published recommendations for NPSLE in 2010[90]; an update covering all IMIDs may soon be needed.

The finding that SLE and RA had comparable magnitudes of cognitive impairment compared with age-expected levels was surprising, as this goes against the work of other reviews[4]. Our analysis used an indirect comparison method rather than identifying studies that directly compared people with SLE and RA, which meant more studies could be included and mitigates the limitation of having one IMID group who are younger than representative cohorts of that IMID; important given the differences in average age of onset between RA and SLE. Whilst the age-matched analysis removes the confounding effects of age, there could be other differences between the people with IMIDs and controls driving this finding. For example, the people with RA in the studies included in this review had lower levels of education than their controls. Furthermore, all studies included prevalent cases; the people with RA within this review had longer disease duration compared with the people with SLE, and therefore had been exposed to inflammation for a longer period of time, which could explain some of the findings. We also did not look at the effects of treatment or other clinical factors such as depression and disease activity, which could have affected the results[91-93]. There were far fewer studies of people with axSpA, PsA and PsO, and therefore the magnitude of impairment in these conditions is less clear. More research is needed on the cognitive ability of people with these conditions.

This study has a number of strengths. The use of meta-regression to compare indirectly the magnitude of cognitive impairment across the IMIDs circumvents the issue of having one of the IMID populations with an abnormal age-distribution, which has hampered previous direct comparisons. However, there are limitations to this review, including the small amounts of double counting of some controls in meta-analyses where a study is included with two IMID populations but only one control group (and therefore the control group is featured twice in the analysis). As only very few studies included more than one IMID group, this is not likely to significantly affect the results. On the other hand, efforts were made to limit the double-counting of people with IMIDs by attempting to exclude multiple publications reporting on the same sample. Due to the reporting within included studies, it is sometimes not easy to confirm whether two publications by the same authors did use the same or nested samples, or whether the two samples were just recruited using similar methods. Therefore, potentially some studies were excluded when in fact they reported on a unique sample of people with IMIDs. Only a limited number of cognitive domains were included in this review. Some studies did report measures on other cognitive domains (e.g. reactions times, visuospatial skills), however these were relatively few and any cross-IMID comparison would be a challenge as a result. Therefore, the choice was made to focus on the cognitive domains most widely studied across the included publications. No date restrictions were imposed on the included studies, given the relatively small amount of data available on cognition in the IMIDs. However, changes in available treatments,

management strategies, and secular changes in disease severity could be influencing the results. Lastly, all studies had a cross-sectional design and included prevalent IMID cases, meaning that change over time could not be assessed. It is currently unclear if cognitive impairment is apparent at diagnosis or whether this impairment develops over time. Longitudinal assessment of cognitive ability in the IMIDs is urgently needed.

Several mechanisms have been put forward to explain the apparent cognitive impairment in the IMIDs. Inflammation is thought to be a key component promoting long-term cognitive decline[94], and therefore the long-term inflammatory burden of these conditions may be resulting directly in cognitive impairment. Indeed, an association between the presence of pro-inflammatory cytokines and cognitive impairment in RA and SLE has been reported[75 95]. Cardiovascular disease is also a well-documented risk factor for cognitive impairment, and the IMIDs are associated with increased occurrence of cardiovascular disease[96 97]. Associations between the presence of cardiovascular risk factors or history of cardiovascular events and cognitive impairment have been reported in RA[98] and SLE[99]. On the other hand, risk factors for cognitive impairment are likely differential between people with IMIDs and controls (e.g. smoking status) and it is unclear whether IMID status acts as a mediator in the relationship between these risk factors and impairment, or whether risk factors are directly causing cognitive impairment, irrespective of diagnosis. Furthermore, symptoms of the IMIDs could be promoting this impairment. Pain, fatigue and depression are common symptoms in the IMIDs, and all these factors are associated with cognitive impairment in the general public, other chronic conditions[100], and the IMIDs[6 101 102]. Greater understanding of the occurrence and mechanisms of cognitive impairment in the IMIDs may lead to intervention development. Trials of new anti-inflammatory treatments in the IMIDs should include measures of cognitive ability as secondary outcomes, given the relationship between inflammation and cognition. For example, inhibition of tumour necrosis factor-alpha (TNF-α) resulted in lower cognitive impairment in animal models[103], and there is some evidence that anti-TNF treatment and other disease modifying treatments are associated with lower risk of dementia[104-107]. Lifestyle interventions may also be useful for improving cognition in the IMIDs, given the association between lifestyle facets (e.g. physical activity level, obesity, and smoking) and cognitive impairment[108-110] and therefore should be evaluated in the IMIDs.

In conclusion, people with IMIDs have substantial deficits in cognitive ability compared with people of a similar age without an IMID. The magnitude of impairment against age expected levels was similar between people with SLE and people with RA, indicating the need for greater awareness of cognitive impairment in these conditions. There were fewer studies of people with axSpA, PsA and PsO, and therefore more research is required to understand how people with these diseases are affected by cognitive impairment. Greater understanding regarding the causes and longitudinal trajectories of cognitive impairment across the IMIDs is also needed, which could lead to intervention development.

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**CONTRIBUTORS**

Review of manuscript: JMG, TT, MB, SMMV, MH, AM; Study concept and design: JMG; Acquisition of data: JMG, TT; Analysis and interpretation of data: JMG, TT, MB, SMMV, MH, AM;

**COMPETING INTERESTS**

None declared

**DATA ACCESS STATEMENT**

No novel data created as part of this project

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