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Title: Cognitive Impairment in Rheumatoid Arthritis: A Systematic Review

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Abstract

Objectives: Rheumatoid Arthritis (RA) is not commonly associated with central nervous system and brain changes. However a number of studies have reported high rates of cognitive impairment (CI) in adults with RA. The objective of this systematic review was to identify and explore the rates and types of CI in RA.

Methods: Multiple databases were searched including a time frame between 1994 to 2016 to identify studies that have included: (i) adults with RA; (ii) standardized neuropsychological tests; and (iii) sufficient information to ascertain the relationship between CI and demographic, clinical and psychology factors. Of 1,980 titles, 75 were retained at abstract level, 36 at full-text level and 15 studies in the final review. These were evaluated using a modified Newcastle-Ottawa Evaluation Scale and the findings were synthesized using a narrative approach.

Results: Ten out of 15 studies compared RA to other clinical and/or control groups. Based on summed effect size analyses, individuals with RA significantly under-performed on cognitive function tests compared to the control groups; particularly on verbal function, memory, and attention. Less clear differences were found between RA and other clinical groups. Some demographic (age, education), clinical (disease activity) and psychological (depression) factors were associated with CI but inconsistently so across studies. A number of limitations were identified: small and predominantly female samples, limited cognitive domain inclusion, lack of study details, and management of confounding variables.

Conclusions: There is evidence of CI in adults with RA. Further studies are required to confirm prevalence rates and examine potential mechanisms.

Significance and innovations

- Individuals with RA significantly underperform on cognitive function tests.
- Mechanisms of the association between RA and cognitive impairment are unclear.
- Age, education, disease activity and depression appear to be associated with cognitive impairment.
- Further research is required to confirm the rates and types of cognitive impairment in RA.

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis. It affects between 0.5 and 1% of the population and is more common in women and older adults [1, 2]. RA is a multisystem connective tissue disorder with common presentation including swollen, painful joints, fatigue and physical disability [3] with structural damage, systemic consequences [4] and depression [2].

Neuropsychological impairment is not usually associated with RA. However recent studies suggest there may be a link between RA and cognitive impairment and that even mild cognitive impairment (CI) can disrupt daily function for individuals with RA [5]. While some studies have found a link between RA and CI – specifically Alzheimer's disease and other dementias [6] – others have found no such link [7]. A large longitudinal population-based study found those with a history of RA were significantly more likely than those with other joint diseases to have developed CI over a period of 21 years [8]. The authors suggested the link between RA and cognitive decline might be due to inflammation within the brain. Further a high risk of cardiovascular comorbidity for patients with RA may also be implicated in CI, through mechanisms related to the metabolic syndrome and inflammatory proteins [6].

The pathogenic mechanisms of cognitive decline in RA are unknown [4]. It is possible that cognitive impairment may be associated with clinical features (e.g. pain, fatigue and sleep disturbance – as evidenced by research in chronic pain populations) [9] or psychological comorbidities (depression, anxiety) [10, 11, 12, 13] but the findings are inconsistent. Pain is known to impact cognition – particularly memory, mental flexibility and attention. This is due in part to the attention-occupying nature of chronic pain and possibly to the overlap between the brain regions that involve both pain and cognition [14]. Similarly depression can lead to reduced concentration [15] and executive function [16]. There are high levels of depression in RA [17] and CI may be a feature of depression.

RA is treated with a range of immunosuppressant agents that can lead to neurotoxicity when used long-term [18]. A commonly prescribed medication for RA is Methotrexate (MTX), which is highly effective [19] but might be associated with CI [20], mood changes and confusion [21]. Glucocorticoid therapy has been associated with an immediate impact on memory [22] and a possible cumulative influence on hippocampal function [23]. While there seems to be an association between glucocorticoid medication and CI in RA [24] the nature of that association remains undetermined.

Cognitive function encompasses a range of neuropsychological domains, including: orientation; attention/concentration; judgment/problem solving; memory; and verbal and visual/spatial function [25]. Impaired cognitive function may influence activities of daily life. In the context of RA it may also impact on treatment compliance and effectiveness and overall self-care [26, 27]. It follows that cognitive function may form an important indicator for assessment and monitoring as part of the overall management of RA.

Recent studies have suggested a substantial proportion of adults with RA may have CI but the prevalence rates, specific cognitive domains of impairment and clinical significance of such impairment are yet to be comprehensively determined.

This systematic literature review examined the rates and types of CI in adults with RA and set the following research questions:

1. What are the rates and types of CI among adults with RA?
2. Which demographic, clinical and psychological factors may be associated with CI in adults with RA?

In order to synthesize and evaluate findings, this systematic review included peer-reviewed studies based on formal observer-rated neuropsychological assessments. These are the ‘gold standard’ for assessing cognitive function.

Materials and Methods

This systematic review comprised five stages. Stage One involved a systematic search of the literature based on a combination of key words (Stage One: Database search) conducted by E.D and confirmed by T.M. Stages Two to Four were informed by the inclusion and exclusion criteria (Table 1). Stage Two involved a screening process in which two authors (T.M. and N.M.) screened the literature titles and abstracts for inclusion into the next stage. Stage Three involved two authors (T.M., P.K.) examining the full text articles, followed by a quality evaluation (Stage Four) conducted by three reviewers (T.M., P.K., S.C.) based on a revised Newcastle-Ottawa Quality Assessment Scale [28] (refer to supplementary material). Finally, data was synthesized (Stage Five) using a narrative approach by S.C and T.M. and then reviewed by N.M., P.C. and P.K.

Data sources and searches (Stage One)

To capture as many relevant citations as possible, a wide range of psychological, health, medical, and cross-disciplinary databases were searched to identify a broad range of literature examining the relationship between rheumatoid arthritis and cognitive function. These databases included: PsycINFO, PsycARTICLES, Psychology and Behavioral Sciences Collection, ProQuest Psychology Journals, PubMed, CINAHL Plus, Informit (health collection), ScienceDirect, Embase, Scopus, Web of Science, Cochrane Library, Alexander Street Press, National Technical Information Service, The Database of Abstracts of Reviews of Effects, and BIOSIS Previews. The search was limited to all literature related to the area of study, originally over the 20 years period January 1994 and December 2014 with update searches in 2015 and 2016. There was no restriction on study design or language of publication. Conference abstracts and poster presentations were included if there was sufficient details to allow appraisal of study quality. An example of an electronic search

strategy for PsycINFO is presented in Table 1. The full electronic search strategy is available online, accompanying this article.

The searches resulted in 1,980 citations from which relevant studies were selected for the review based on the presence of the search terms or related terms in the title and/or abstract. This screening process resulted in 1,488 citations being excluded as irrelevant and 421 duplicates were removed. A total of 71 titles were identified as relevant and were included in the second stage of the review.

TABLE 1 ABOUT HERE

Selection of Studies (Stages Two, Three and Four)

A set of pre-determined criteria for Stages Two, Three and Four is presented in Table 2. All non-empirical research including literature reviews, book sections and letters to the editor**,** as well as animal studies and studies with participants <18 years were excluded to focus on empirical studies with human, adult samples. Studies meeting the inclusion criteria for this review were published between 1994 and 2015, related to cognitive function assessment and rheumatoid arthritis, involved adults aged 18 years and over, and were published in any language as long as an English translation was available. For any articles where the abstract or full manuscript could not be located, the authors of these articles were contacted directly, requesting access to the abstract and/or full manuscript, with follow-up emails sent after two weeks of non-response.

TABLE 2 ABOUT HERE

Literature Screening – abstracts (Stage Two)

Two researchers (T.M. and N.M.) independently reviewed the 71 abstracts and recorded whether they accepted or rejected the abstract based on the pre-determined inclusion

criteria for Stage Two (Table 2). In the case of disagreement, consensus was reached after discussion between the two reviewers. Four additional abstracts were identified through the full-text screening in Stage Three and were added to these abstracts. Subsequently, of the 75 abstracts (refer to supplementary material), 38 were excluded for the following reasons: non-experimental studies (n = 9), non-human (n = 1) or non-adult-specific population (n = 5), non-RA-specific population (n = 3), no indication of cognitive function assessment (n = 1), grey literature only (n = 19).

Literature Screening – full-text (Stage Three)

Whilst grey literature such as poster presentations and conference abstracts had been included in Stage Two screening, once the authors confirmed that such articles had no full text (n = 2), they were excluded (at the commencement of Stage Three, prior to full text screening). Of the 35 abstracts (refer to supplementary material) that progressed to the full-text stage, only 15 were retained. Four papers were in languages other than English and only one of those had an official English translation version. The full papers were reviewed by two authors (T.M. and P.K.) for inclusion, based on the inclusion criteria in Table 2, including: the use of standardized, administered cognitive function assessment, sufficient demographic and clinical details on RA sample, and sufficient results details. The reference lists of the 35 papers were also reviewed and this identified a further four studies that met Stages One and Two inclusion criteria (as detailed above). Of the 36 full-text papers, 21 were removed from further consideration due to: lack of standardized cognitive function assessment (n = 8), duplication (more than one publication on the same dataset) (n = 6), and insufficient sample or results details (n = 7). The data from each individual study was then extracted and presented according the following items: demographics and clinical profile, study location, design and methodology, cognitive function assessment tools and cognitive impairment rates and types. Authors were contacted for clarification where information was missing.

Methodological Quality (Stage Four)

The 15 studies were then evaluated using a modified version of the Newcastle-Ottawa Evaluation Scale (NOS) [28] (refer to supplementary material) by three authors (T.M., K.P., & S.C.). The NOS is a scale developed to assess the design quality of non-randomized studies when reporting the results of meta-analyses and systematic reviews. The scale uses a 'star system' with each study appraised on three criteria: the selection of the study groups; the comparability of the groups, and ascertaining the outcome or exposure of interest for cohort or case-control studies respectively [28] and provides a score between 0-8. This evaluation scale provides an opportunity to identify risk of bias at the study design level that is then further examined at the data synthesis stage. Discrepancies across evaluations were resolved with discussion by the three authors.

Data synthesis (Stage Five)

Given the range of study designs, participant groups and assessment tools used across studies, and the overall small sample sizes, narrative review was determined to be the best option for summarizing the results. At this stage a risk of bias across studies was considered in relation to the studies' data management and quality of reporting of results. As a part of the data synthesis, studies were profiled and synthesized in terms of the number of cognitive domains they examined, data management and reporting, and consideration of confounding variables. In addition, effect sizes were calculated where possible and summed together to provide comparisons between RA and control and other clinical groups.

Results

Selection of studies

The full selection process, detailed in the methods section, is summarized in Figure 1.

FIGURE ONE ABOUT HERE

Methodological quality

The 15 studies were evaluated on the basis of sample selection, design and exposure. They ranged in total scores from 3.5 to 8 (possible range 0 – 8). The scores across the seven categories are presented in Table 3.

TABLE 3 ABOUT HERE

Study Characteristics

Fifteen studies reported on 749 participants with RA (Table 4). Sample sizes across studies ranged from 13 to 157 participants, with only three studies (Table 3: Studies #23, 29, & 30) with more than 100 participants. All but one study [31; test-retest 24 hours apart], were cross-sectional. Five studies [23, 29, 30, 31, 32] only included RA populations; four studies [33, 34, 35, 36] compared RA with control; and six studies included three [37, 38, 39, 40, 41) or four [42] comparison groups (RA, FM, SLE, MSD, SS and control). The majority of studies were conducted in the USA [23, 29, 30, 40] followed by Brazil [33, 35, 39] and Turkey [37, 38, 41] with the remaining studies being from Italy [32], Canada [42], Egypt [34], Australia [31] and Serbia [36].

Participants Characteristics

The majority (59% to 100%) of participants in the studies were female; the mean age ranged from 37.2 to 62.9 years (SD = 2.0 -13.5). Education levels ranged from mean 1.8 to 15.1 years across 10 studies with two not having provided details [34, 36] and three having provided only prevalence rates (over 8 years: #23; under 12 years: #31, 30).

Cognitive Impairment Prevalence

Of the 15 studies, three [30, 31, 33] stated the prevalence of cognitive impairment (30%, 0%, 31% respectively), while some only reported reduced scores [34, 40] or

impairment rates across individual tests [32] or combined groups' rates [42] (Table 4). The remaining studies [23, 29, 35, 36, 37, 38, 39, 41] did not report impairment rates.

TABLE 4 ABOUT HERE

Cognitive Domains Measured

Cognitive tests were grouped across six cognitive domains [43] (refer to supplementary material). Cognitive domains listed for each study are reported in Table 4. Across the 15 studies, four [35, 36, 37, 42] measured only one domain; two [29, 31] measured two domains; one measured three domains [23]; three [30 34, 39] measured four domains; and five [32, 33, 38, 40, 41] measured five domains. The most commonly measured domains were memory (13 studies) followed by judgment/problem solving (10 studies), attention/concentration (nine studies), and verbal function and visual-spatial organization (eight studies each), while orientation was not measured by any of the studies.

Cognitive Impairment Effect Sizes Analyses

Cognitive impairment was further examined in terms of Cohen's *d* analyses. Of 15 studies, eight included sufficient data to calculate standardized mean difference between RA and other clinical and control groups. These effect sizes were calculated across all available neuropsychological measures (refer to supplementary material) then totaled for each domain and group (RA, Control, other Clinical Groups) (Table 5). Effect sizes are broadly classified into small, medium and large indicators of standardized differences [44]. These may be interpreted as not noticeable (small), noticeable (medium) and clinically significant (large) [45].

Large median Cohen's *d* effect sizes were noted across three (Attention, Memory, Verbal Function) out of five domains between RA and Control. Similarly large effect sizes were noted in comparison between RA and non-CNS-SLE (although the two groups were not

aged matched, i.e. #39, 42) on one (Judgment) of the four domains as measured by Cohen's *d* and in a medium range for the other three domains. RA was outperformed by FMS (medium *d*) on Attention and MSc (small/marginal) but performed better than SS on three out of four domains (small to large *d*). All clinical groups across studies performed more poorly than the control group. Some groups were not age or education matched and, other than RA (n = 284) and Control (n = 180), their sample sizes were small (n = 20 to 33).

TABLE 5 ABOUT HERE

Confounding variables: Demographics

The majority of studies controlled for age, gender and education. Mean (SD) age for RA group ranged from 37.2 (3.2) to 62.9 (10.9). Some of those studies [23, 32, 39, 31] found age, and others found education [30, 41] to be associated with cognitive function. Younger and more educated participants performed better across some of the cognitive domains. Education ranged from mean of 1.84 to 15.11 with half of the studies in the range of 5-9 years of education. Some groups were not age or education matched [39, 42] and there was an overall pattern of the RA group being older than the control or other clinical groups [35, 39, 40, 41, 42].

Confounding variables: Clinical

The inclusion, measurement, and severity of clinical variables varied considerably across studies. The following variables were found to be associated with cognitive function: pain [23, 29, 31, 36, 38], disease activity [32, 33], fatigue [37], medication (prednisone/steroids, MTX) [40, 31, 30], biomarkers (IL-6, B and T cells) [34, 35, 40], and CVD risk factors [30]. A range of assessment tools was used across studies, prohibiting systematic comparison of clinical profile across samples.

Confounding variables: Psychological

Only two studies found depression (somatic symptoms) [40] and depression and anxiety [36] to relate to cognitive function. Some excluded participants based on their depression scores [32] others either did not include a depression measure [39] or did not report their scores [41]. The most commonly used depression scale was the Beck Depression Inventory (BDI) [32, 33, 34, 35, 36, 41] followed by the Hospital Anxiety and Depression Scale (HADS) [33, 37, 42]. Some studies used more than one measure (38: Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV) & overall well-being; 23: Center for Epidemiologic Studies Depression Scale (CES-D) & Multiple Affect Adjective Checklist-Revised (MAACL-R) = composite; 34: DSM-IV, BDI & Mini International Neuropsychiatric Interview (MINI); 35: BDI & Mini Mental State Examination (MMSE)) others used Arthritis Impact Measurement Scales (AIMS) [29], MMSE [39], and MINI [30] only. Given these measures and reporting differences, no comparison analyses of depression could be undertaken.

Biases at individual study and systematic review levels

The following potential biases were apparent across the studies: small sample sizes; lack of descriptive data; insufficient details about the skills/qualifications of test administrators; limitations in study design and appropriate analyses adjustments, narrow range of variables (demographic, clinical and neuropsychological) and use of convenient sampling.

Statistical analyses across studies were limited to effect size calculations for eight out of 15 studies and totaling of scores based on different measures of included domains. No other statistical analyses were possible based on the available data. The effect sizes should be interpreted cautiously as no adjustment was made for demographic, clinical and psychological differences across those studies.

According to the modified Newcastle-Ottawa Evaluation Scale (NOS) [28] the scores ranged from 3 to 7.5 out of 8 points, with an average of 5.3. The studies included participants with confirmed RA diagnosis, were age if not gender representative, and mostly matched on age via norms or control group. However a number of the studies failed to control for clinical or psychological variables in relation to cognitive function, were limited in the range of domains assessed (seven of 15 studies measured only one or two cognitive domains), and less than half provide impairment rates, scores and adequate findings explanations.

Discussion

The aim of this systematic review was to ascertain the levels of cognitive impairment in RA. According to the 15 studies that met the inclusion criteria, individuals with RA either perform more poorly at a range of cognitive assessment tasks than healthy controls, or perform at a level below age-related norms. The prevalence of cognitive impairment, however, could not be determined as only three studies included that information. The presence of cognitive impairment or at least poorer cognitive function varied across studies in terms of the domains. However, effect size calculations conducted on eight of the studies indicated clinically significant differences in cognitive function in RA compared to controls without RA. Those findings, notwithstanding methodological limitations, are significant and warrant further examination. Given the level of cognitive impairment identified in these studies, it may be necessary to assess and monitor cognitive function over time as part of the overall management of RA

Different explanations have been proposed for the apparent CI in RA. Given that other clinical groups included across the studies have also performed more poorly than healthy controls, this suggests that CI may not be specific to a particular condition but present across number of chronic, painful, inflammatory or autoimmune conditions. A number of

mechanisms may be involved in CI in RA including: chronic inflammation, medication (especially corticosteroids, methotrexate) and premature immunosenescence [35]. Findings from studies that have included neuroimaging data suggest brain involvement with structural and functional changes that may not clinically manifest but could be associated with rheumatoid vasculitis, chronic inflammation, demyelination [32, 34, 35]. Further, immune activities such as alternations in dehydroepiandrosterone (DHEA) metabolism also appear to be associated with CI particularly in relation to attention and learning, even when controlling for depression and in sample with mild disease activity [35, 40]. Medication may also impact on CI temporarily at single and accumulative dose levels [22, 23, 30, 31]. Finally, pain, fatigue, poor sleep and depression may be attentional distractions, and in turn impact on cognition [23, 33, 37]. How these biological, clinical and psychological variables interact in the development of CI is yet to be determined.

This review, however, identified a number of limitations across the studies that should be taken into consideration. These include the following: (1) small sample size across studies and in overall analysis of findings; (2) poor reporting of study details and CI in particular; (3) a lack of generalizability with predominantly female samples; (4) a limited range of cognitive domains inclusion; (5) lack of management of confounding variables (i.e. medication); (6) varied definitions of CI (i.e., number of tests with performance below norm/total number of tests); and (7) the use of established RA samples only. At the systematic review level, notable limitations include: (1) evaluation being limited to qualitative, narrative approach; and (2) overall effect size analyses conducted without controlling for confounding variables.

To our knowledge this is the first systematic review of CI in RA and its strength is in inclusion of only the studies that have used standardized neurocognitive assessment tools. Over half of these studies also included control groups – both healthy controls and other clinical groups to compare to RA. These are methodological strengths and while the findings

are mixed they provide a platform for further research with larger samples and stronger study designs. Such research should examine cognitive impairment at diagnosis and at regular intervals including flare-ups and medication changes; conduct comprehensive comparisons across age, gender, disease duration, and disease severity; and identify factors that may differ between RA patients with and without CI. The potential impact of CI, even at a sub-clinical level, is considerable. In relation to RA management, it is essential that future research seek to comprehensively assess CI levels, examine its etiology, and determine preventative and treatment measures.

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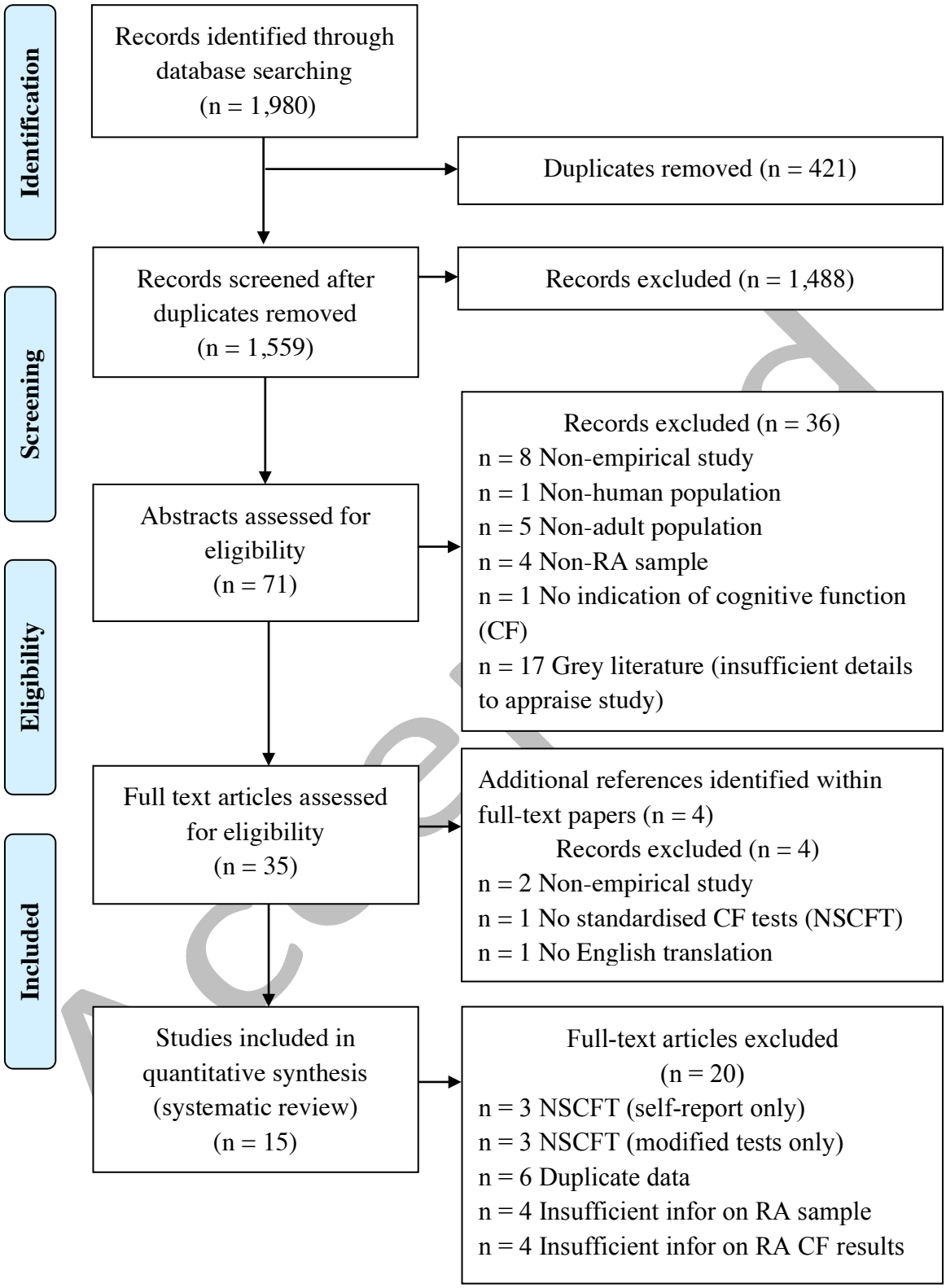

Figure 1. Flowchart: Literature Search and Studies Selection.

Table 1.

Electronic search strategy for PsycINFO database

Database	**Search #**	**Search strategy**	**Search Results**
PsychINFO (January 1994-December 2015)	1	Rheumat* Arthriti* AND Cognitive function*.ab	17
	2	Rheumat* Arthriti* AND Cognitive Impair*.ab	17
	3	Rheumat* Arthriti* AND Executive function*.ab	5
	4	Rheumat* Arthriti* AND Executive function* AND memory.ab	3
	5	Rheumat* Arthriti* AND Cognitive Impair* AND Memory.ab	6
	6	Rheumat* Arthriti* AND Cognitive function* AND Memory.ab	4
	7	Rheumat* Arthriti* AND Cognitive decline.ab	4
	8	Rheumat* Arthriti* AND Cognitive dysfunction.ab	7
	9	Rheumat* Arthriti* AND neurological function*.ab	1
	10	Rheumat* Arthriti* AND neurological impair*.ab	3
	11	Rheumat* Arthriti* AND neurological function* AND attention.ab	0
	12	Rheumat* Arthriti* AND neurological function* AND memory.ab	0
	13	Rheumat* Arthriti* AND neurological impair* AND attention.ab	1
	14	Rheumat* Arthriti* AND neurological impair* AND memory.ab	1
Total number of articles			69
Total number of duplicates			27
Potentially relevant (after screening titles and abstracts)			***19***

Table 2.

Inclusion and exclusion criteria for selection of the articles

Title and Abstract Inclusion Criteria
TITLE: includes words: (1) 'rheumatoid arthritis' or some variation of it (i.e. rheumatic disorders) AND/OR (2) 'cognitive function' or some variation of it (i.e. neurocognitive function, cognitive dysfunction) ABSTRACT: indicates: (1) Empirical study (2) Human sample, (3) Adult sample, (4) Rheumatoid arthritis sample (5) Cognitive function (6) Grey literature included if sufficiently detailed to appraise study quality (7) English version available
Full article Inclusion Criteria
(1) Sufficient demographic and clinical details on RA sample (2) Use of standardized, objective cognitive tests
Full article Exclusion Criteria
(1) Use of self- report/modified/computerized and/or neurological tests only (2) Duplicate data (3) Insufficient results details (i.e. cognitive function in RA results) (4) No objective measure of cognitive function

Table 3.

Modified Newcastle-Ottawa Quality Assessment of 15 Studies

Study[ref]	**Selection** 3 points			**Comparability** 2 points			**Exposure** 3 points		**Total** 8 points
	S1 1	**S2** 1	**S3** 1	**C1** (a) ½	**C2** ½	**C3** ½	**E1** 1½	**E2** 1½	

				(b) ½					
Abeare et al. (2010)[29]	1	1	0	0	0	0	½	½	3.0
Akdogan et al. (2013)[37]	1	½	0	1	½	½	0	½	4.0
Appenzeller et al. (2004)[33]	1	1	½	½	0	0	1 ½	1 ½	6.0
Bartolini et al. (2002)[32]	1	1	1	1	½	½	1 ½	1	7.5
Bilgici et al. (2014)[38]	1	½	½	½	0	0	1 ½	½	4.5
Brown et al. (2002)[23]	1	1	0	½	½	½	1	½	5.0
de Melo et al. (2012)[39]	1	½	1	0	0	0	1	1	4.5
Dick et al. (2002)[42]	1	1	½	½	0	0	0	1	4.0
Hamed et al. (2012)[34]	1	½	1	1	½	0	1	1	6.0
Kozora et al. (2001)[40]	1	½	1	1	½	½	1 ½	1	7.0
Meade et al. (2013)[31]	1	1	1	0	½	0	½	1½	5.5
Petersen et al. (2014)[35]	1	1	1	1	½	½	0	1	6.0
Shin et al. (2013)[30]	1	1	1	1	½	½	1 ½	1	7.5
Tomasević et al. (2011)[36]	1	1	1	1	0	0	0	½	4.5
Yilmaz et al. (2012)[41]	1	1	1	1	½	½	1 ½	½	7.0

Note: S1= Selection criterion 1; S2= Selection criterion 2; S3= Selection criterion 3; C1= Comparability criterion 1; C2= Comparability criterion 2; C3= Comparability criterion 3; E1= Exposure criterion 1; E2= Exposure criterion 2.