SYSTEMATIC REVIEW

REVISED Frailty in people with rheumatoid arthritis: a systematic review of observational studies [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Frailty, an age-related decline in physiological reserve, is an increasingly important concept in the management of chronic diseases. The implications of frailty in people with rheumatoid arthritis are not well understood. We undertook a systematic review to assess prevalence of frailty in people with rheumatoid arthritis, and the relationship between frailty and disease activity or clinical outcomes.
Methods: We searched four electronic databases (January 2001 to April 2021) for observational studies assessing the prevalence of frailty (any frailty measure) in adults (≥18 years) with rheumatoid arthritis, or analysing the relationship between frailty and disease activity or clinical outcomes (e.g. quality of life, hospitalisation or mortality) in people with rheumatoid arthritis. Study quality was assessed using an adapted Newcastle-Ottawa Scale. Screening, quality assessment and data extraction were performed independently by two reviewers. We used narrative synthesis.
Results: We identified 17 analyses, from 14 different populations. 15/17 were cross-sectional. Studies used 11 different measures of frailty. Frailty prevalence ranged from 10% (frailty phenotype) to 36% (comprehensive rheumatologic assessment of frailty) in general adult populations with rheumatoid arthritis. In younger populations (<60 or <65 years) prevalence ranged from 2.4% (frailty phenotype) to 19.9% (Kihon checklist) while in older populations (>60 or >65) prevalence ranged from 31.2% (Kihon checklist) to 55% (Geriatric 8 tool). Frailty was cross-sectionally associated with higher disease activity (10/10 studies), lower physical function (7/7 studies) and longer disease duration (2/5 studies), and with hospitalization and osteoporotic fractures (1/1 study, 3.7 years follow-up).
Conclusion: Frailty is common in rheumatoid arthritis, including those aged <65 years, and is associated with a range of adverse features. However, these is heterogeneity in how frailty is measured. We found

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Any reports and responses or comments on the article can be found at the end of the article.

few longitudinal studies making the impact of frailty on clinical outcomes over time and the extent to which frailty is caused by rheumatoid arthritis unclear.

Keywords
Rheumatoid arthritis, frailty, epidemiology

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REVISED **Amendments from Version 1**

We have revised the paper in response to the comments of both peer reviewers. Full details of all changes are listed and quoted in the posted response to each of their comments. Briefly, we have given more description of the rationale for assessing frailty in studies of RA, clarified our inclusion criteria with regard to frailty measures, expanded the description of the Newcastle-Ottawa scale adaptation, given details of the software used to produce summary data, updated the rheumatoid arthritis criteria in Table 1 for two studies, added minimum age of recruitment for all studies, added a MOOSE checklist to the online repository, given more detail on the results of the quality appraisal, discussed factors that might influence frailty prevalence in more detail, provided more text on potential clinical implications, and clarified the wording in the sections highlighted by the reviewers.

Any further responses from the reviewers can be found at the end of the article

Introduction

Rheumatoid arthritis is the most common chronic inflammatory arthropathy, the incidence of which increases with age[1–3]. While advances in treatment of rheumatoid arthritis have resulted in marked improvement in outcomes and prognosis, rheumatoid arthritis continues to cause significant symptom burden, loss of function, morbidity, and reduced quality of life[1,3]. Frailty has been highlighted as an emerging concept in our understanding of the impact of musculoskeletal disorders[2]. Frailty is an age-related state of increased vulnerability leading to decompensation in response to physiological stress[4]. While most studies have focused on people aged over 65 years, frailty is also prevalent and associated with adverse health outcomes in younger populations[5]. Many measures exist to quantify frailty, of which the most widely used are the frailty phenotype[6] (a physical measure assessed by grip strength, walking speed, exhaustion, weight loss, and low physical activity) and the frailty index[7,8] (a cumulative count of age-related deficits including long term conditions, symptoms, functional limitation and physiological markers). Both constructs have potential overlap with features associated with rheumatoid arthritis.

Despite a rapid expansion of frailty research in the last two decades, including in the context of specific index conditions[9], research on frailty in the context of inflammatory diseases in general, and rheumatoid arthritis in particular, is relatively recent[2,10]. Frailty has been reported to be prevalent in people with rheumatoid arthritis, including relatively young individuals (i.e. <65 years)[11]. Others have explored associations between frailty and functional limitations in rheumatoid arthritis[12]. However, the diversity of measures used to quantify frailty, and overlap between features of rheumatoid arthritis and frailty constructs, means that understanding the relationship between frailty and rheumatoid arthritis requires careful consideration. This is important as frailty measures are increasingly being advocated to aid risk stratification and identification of high-risk populations in a range of clinical contexts. The utility and appropriateness of such an approach in people with rheumatoid arthritis therefore requires careful consideration of the relationship between frailty and this condition.

This systematic review seeks to synthesise data from observational studies of frailty in people with rheumatoid arthritis. We aim to assess (i) what frailty measures have been used in published studies including people with rheumatoid arthritis, (ii) what is the prevalence of frailty in people with rheumatoid arthritis across a range of ages, (iii) what is the association between frailty and features of rheumatoid arthritis such as disease activity, functional limitation, and duration, and (iv) what is the association between frailty and adverse health outcomes (e.g. hospitalisation, mortality or quality of life) in people with rheumatoid arthritis.

Methods

This systematic review was conducted according to a pre-specified protocol (PROSPERO: CRD42021251960) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13].

Eligibility criteria

Criteria for inclusion, defined according to PECOS (Population, Exposure, Comparator, Outcome, Setting and Study design)[14], including outcomes of interest are detailed in Table 1. Criteria were deliberately broad in terms of setting, frailty definition, and outcomes. Briefly, studies must include adults (≥18 years) with rheumatoid arthritis and assess frailty, although we expect studies may mainly involve 'older' populations. Studies were considered regardless of frailty measure, to allow comparison between different methods of identifying frailty. These could include validated measures of frailty (e.g. frailty phenotype or frailty index), adaptations of these measures where the adaptation was described, or unvalidated measures intended to capture frailty as long as the criteria used to define frailty within the study were fully described. We did not exclude studies on the basis of the criteria used to define rheumatoid arthritis (i.e. validated criteria, physician diagnosis, medical record/clinical codes or self-reported definitions were all eligible for inclusion). We included studies in any setting (community, outpatient, or inpatient). Observational studies with cross-sectional or cohort designs were eligible for inclusion. Experimental studies were excluded. When examining the association between frailty and clinical outcomes in those with rheumatoid arthritis, studies were expected to report the association between frailty and the outcome of interest. As in previous reviews of frailty[15,16], considered studies that describe this either as the association with the presence or absence of frailty or the association between the degree of frailty and the outcome.

Information sources and screening

We searched Medline, Embase, Web of Science Core Collection and Scopus databases from 2001 (as this was the date of the original description of the frailty phenotype and frailty index definitions[6,7]) to 8th April 2021 using a combination of keywords and Medical Subject Headings. The search structure was 'rheumatoid arthritis' and 'frail'. The full search strategy can be found in the Box 1. Two independent reviewers (PH and HM) screened all titles and abstracts and assessed full texts of all relevant articles for eligibility. Inter-rater agreement was high (kappa statistic 98%). Disagreements were resolved by consensus, involving a third reviewer if necessary. Hand-searching reference lists of relevant articles and forward-citation searching using Web of Science were also used to supplement electronic database searches. We did not attempt to contact study authors for additional information where this was not reported.

Table 1. Inclusion Criteria.

PECOS component	Description
Population	Adults (≥ 18 years old) with rheumatoid arthritis
Exposure	Frailty as assessed by any frailty measure
Comparator	People with rheumatoid arthritis not classified as frail
Outcomes	Primary outcome • Frailty prevalence Secondary outcomes: • Mortality • Hospital admission • Major Adverse Cardiovascular Events • Admission to long-term care facility • Quality of life • Fractures • Disease activity (e.g. Disease Activity Score in 28 joints; DAS-28) • Physical impairment or disability (e.g. Health Assessment Questionnaire – Disability Index; HAQ-DI)
Settings	Community (including care home/nursing home) Outpatient clinic Inpatient
Study design	Cross sectional or cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies, Grey literature. Studies not published in English.

Box 1. Search Strategy for Medline (adapted for other databases)

1. Exp Arthritis, Rheumatoid/
2. (felty$ adj2 syndrome).tw
3. (caplan$adj2 syndrome).tw
4. Rheumatoid nodule.tw
5. (Sjogren$ adj2 syndrome).tw
6. (sicca adj2 syndrome).tw
7. Still$ disease.tw
8. (arthritis adj2 rheumat$).tw
9. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
10. Frail$.tw
11. Exp Frailty/
12. Exp Frail Elderly/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
14. 10 or 11 or 12
15. 13 and 14

Data extraction and quality assessment

Data were extracted from each of the eligible studies using a piloted data extraction form (PH and HM). Data extracted included details of the published study (publication reference, aim, setting), population (sample eligibility, recruitment method, age and sex), criteria used to define rheumatoid arthritis (e.g. American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria[17], self-report, electronic medical records, etc.), frailty measure, any adaptation of the frailty measure used in the study, prevalence of frailty, and the association between frailty and clinical outcomes. For outcomes, we extracted data on the method used to assess the outcome, timeframe or length of follow-up, the magnitude of the association along with measure of uncertainty, and any adjustment for potential confounders. Where there was variation between studies in the assessment of similar outcomes we presented this data in supplementary tables. We used a version of the Newcastle-Ottawa tool, previously adapted to assess observational studies of frailty[15], to quantify risk of bias (criteria shown in Box 2). The Newcastle-Ottawa scale is frequently used to assess quality of observational studies. Previous reviews have also adapted elements of the scale to reflect the studies of interest to the review itself. For this review, we used an adaptation previously developed for observational studies of frailty. This adaptation altered the 'exposure' component of the was altered to award two points if a study used validated measure of frailty implemented according to its original description. One point was awarded if studies used an alternative measure of frailty (e.g. an adapted or non-validated measure of frailty) but the criteria were described in sufficient detail to allow the assessment to be replicated. This adaptation was to reflect the fact that there is no 'gold-standard' measure of frailty and that frailty is assessed using a diverse range of measures within the literature. The scale was applied to all studies (cross sectional or longitudinal), with only the first 5 elements of the scale being relevant to the cross-sectional studies. This approach was taken to allow an identical approach to quality assessment for prevalence estimates from cross sectional or (baseline of) longitudinal studies. Quality was assessed independently by two reviewers (PH and HM) with disagreements resolved by discussion and involving a third reviewer if necessary. Studies were not excluded on the basis of the quality assessment.

Box 2. The Newcastle-Ottawa Scale Adaptation for studies assessing the prevalence and impact of frailty

1 – Representativeness of the exposed (i.e. frail) cohort

a) Truly representative (one star)

b) Somewhat representative (one star)

c) Selected group

d) No description of the derivation of the cohort

2 – Selection of the non-exposed (i.e. non-frail) cohort

a) Drawn from the same community as the exposed cohort (one star)

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3 – Ascertainment of exposure

a) Validated measurement tool for frailty (two stars)

b) Non-validated measurement tool, but the tool is available or described (one star)

c) No description of measurement tool

4 – Non-respondents

a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory (one star)

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory

c) No description of the response rate of the characteristics of the responders and non-responders

5 – Demonstration that outcome of interest was not present at the start of the study

a) Yes (one star)

b) No

Comparability:

1 – Comparability of the cohorts on the basis of the design or analysis being controlled for confounders

a) The study controls for age and sex (one star)

b) The study controls for other factors (one star)

c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcomes:

1 – Assessment of outcomes

a) Independent assessment (one star)

b) Record linkage (one star)

c) Self-report

d) No description

e) Other

2 – Follow-up long enough for outcomes to occur

a) Yes (one star)

b) No

3 – Adequacy of follow-up of cohorts

a) Complete follow-up: all subjects accounted for (one star)

b) Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20% or description of those lost suggested no different from those followed (one star)

c) Follow-up rate less than 80% and no description of those lost

d) No statement

Synthesis

Findings of the included studies were summarised using a narrative synthesis. Extracted data for each study were collected on .csv files. Methodological and demographic details of each study, along with quality assessment, were summarised using tables. Prevalence estimates were plotted stratified by age-group of the sample and with reference to the frailty measure used for each estimate using the *ggplot2* package in R. Confidence intervals were calculated for each prevalence estimate. Findings related to other outcomes (characteristics of rheumatoid arthritis or clinical outcomes) were summarised using a Harvest plot[18,19]. Harvest plots can be used to display heterogenous data across a range of outcomes. Findings are displayed on a matrix with each bar representing a study. The position of the bar on the matrix indicates the relationship between frailty and a specific outcome (i.e. positive association, negative association, or no association with frailty status), with the height of the bar indicating the sample size of the study and the colour indicating the frailty measure used. Harvest plots were generated using Microsoft Powerpoint.

Results

Databases searches identified 367 titles and abstracts, after removal of duplicates, of which 91 were retained for full-text screening. From these, 17 eligible full texts were identified, describing 14 separate cohorts (three samples were analysed in two separate papers each). Numbers screened along with reasons for exclusion are shown in Figure 1.

Baseline data for each of the included studies is shown in Table 2. Studies were from Japan (five studies), USA (three studies), Italy, Austria, Canada, Netherlands, Poland and UK (1 study each). Twelve studies identified rheumatoid arthritis according to the 2010 ACR/EULAR criteria[17], while others used either 'clinician diagnosed' rheumatoid arthritis (three studies), diagnostic codes from primary care records (one study) or other medical records (one study). Mean age of the study samples ranged from 50.9 to 74.6 years. Only one study presented data on ethnicity[20], and none commented on socioeconomic status.

The quality assessment of the included studies is summarized in Table 4. Most samples were recruited from rheumatology clinics. We judged most of these to be representative of people with rheumatoid arthritis as most people with the condition will be managed within specialist outpatient clinics and the sampling techniques of these studies were generally inclusive without applying further, restrictive exclusion criteria. Frailty measures used were generally validated or well-described. Few studies presented data on non-responders.

Frailty measurement

Across the 14 included studies, 11 different frailty measures were used. These are summarised in Table 3. The most commonly used measure was the frailty phenotype described by Fried *et al.* (five studies, six papers), followed by the Kihon frailty checklist (two studies, three papers) and the SHARE frailty instrument (an adaptation of the frailty phenotype developed from the Survey for Health, Aging and Retirement in Europe, reported in two studies).

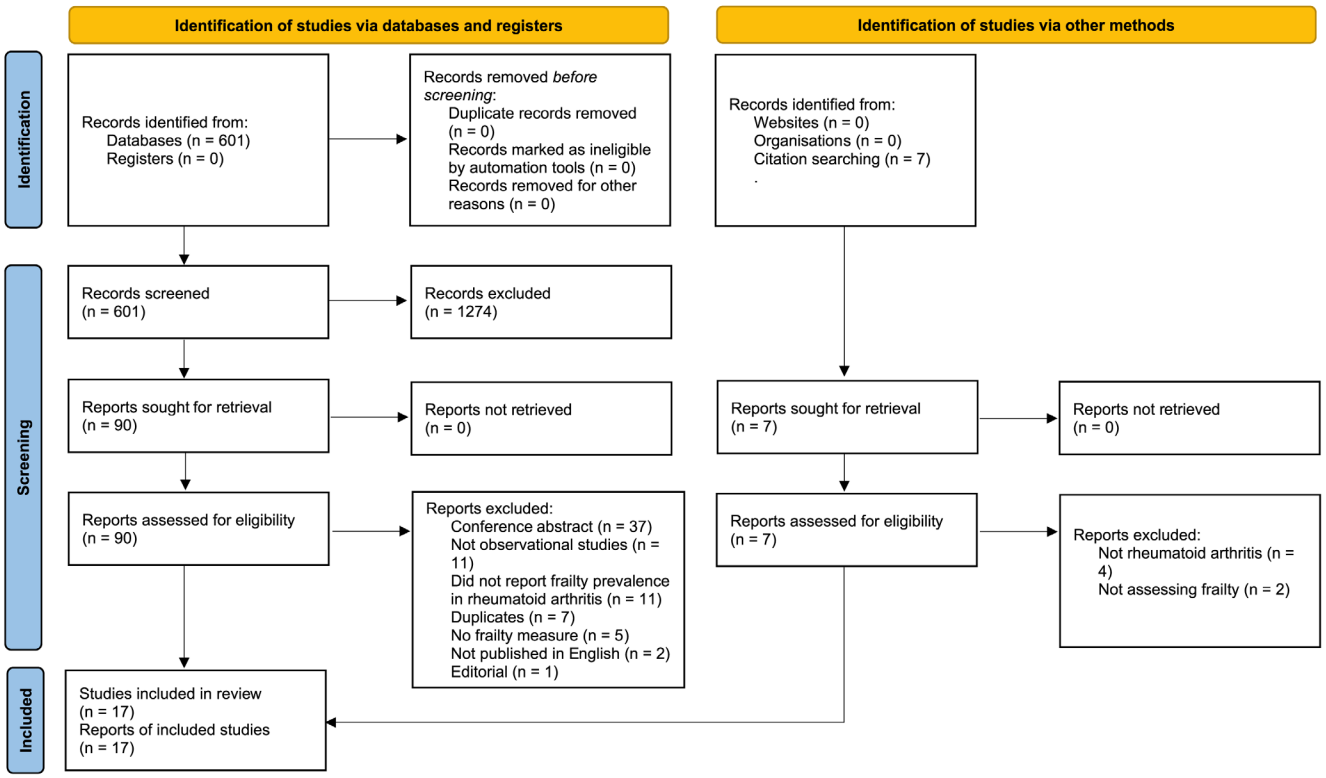

Figure 1. PRISMA diagram of study identification and screening.

Of the five studies that used the frailty phenotype (based on grip strength, weight loss, physical activity, exhaustion, and walking speed), two also explored alternatives to grip strength, given the potential for the measurement of grip strength to be impacted by rheumatoid arthritis affecting the hands. Both used lower extremity strength as an alternative to grip strength to capture 'weakness'.

Frailty prevalence

The prevalence of frailty in each of the studies identified is shown in Figure 2, stratified by age group. The prevalence in general adult populations with rheumatoid arthritis ranged from 10.1% (using the frailty phenotype) to 36% (using the Comprehensive Rheumatologic Assessment of Frailty (CRAF), taking 'moderate frailty' as the cut-off). Studies (or subsets of studies) with populations aged under 60 or 65 years had a frailty prevalence ranging from 2.4% (frailty phenotype) to 19.9% (Kihon checklist). In older populations, estimates ranged from 31.2% (Kihon checklist) to 55% (Geriatric 8 tool).

While frailty prevalence is recognised to vary depending on the measure used, and therefore heterogeneity in these estimates is expected, the prevalence of frailty varied widely even among similar frailty definitions. For example, three studies applied the frailty phenotype to general adult populations with prevalence estimates of 10.1%, 12.9% and 28.5%, respectively. Two studies applied the SHARE-FI to populations aged under 65 years and found a prevalence of 2.5% and 15%, respectively. Therefore, estimates of frailty prevalence in rheumatoid arthritis appear to vary widely even between samples of similar ages applying similar measures of frailty.

One study assessed frailty using the standard frailty phenotype definition, and then using an alternative measure of weakness based on lower extremity strength rather than grip. This was to limit the impact of rheumatoid arthritis affecting the hands on the assessment of frailty. The prevalence of frailty using this alternative strength assessment was lower than the standard grip strength assessment (3.6% and 12.9%, respectively).

We did not attempt to meta-analyse any estimates of frailty prevalence as it is not valid to directly compare frailty prevalence assessed by different measures, and, even for those studies using similar measures, population demographics and exclusion criteria were too heterogenous to allow for a meaningful estimate.

Relationship between frailty and clinical characteristics and outcomes

Associations between frailty and clinical characteristics or outcomes in rheumatoid arthritis are summarised in Figure 3. Most (8/10) of these studies were cross-sectional, showing

Table 2. Characteristics of included studies.

Author, Year	Country	Setting	Frailty measure	Rheumatoid arthritis definition	Total n	Age, years – mean (sd)	Eligible age range	N (%) women
Andrews 2017, Andrews 2019[12,21]	USA	Outpatient	Frailty phenotype	ACR	124	58 (10.8)	>18	59 (47.6%)
Bak 2020[22]	Poland	Inpatient	Tilburg frailty indicator	ACR/EULAR 2010	106	65.8 (5)	≥60	82 (77.4%)
Chang 2010[23]	USA	Community	Frailty phenotype	Medical record review	11	74.1 (2.8)	≥65	11 (100%)
Haider 2019[11]	Austria	Outpatient	SHARE-FI	ACR/EULAR 2010	100	50.9 (9.7)	18-65	66 (66%)
Hippisley-Cox 2017[24]	UK	Community	Qfrailty	Primary Care clinical coding	10312	-	≥18	-
Kojima 2020[25]	Japan	Outpatient	Kihon checklist	ACR 2010	375	65.2 (9.7)	40-79	323 (86.1%)
Li 2019[26]	Canada	Outpatient (registry)	Frailty index	"Active RA"	2923	57.7 (12.7)	≥65	2290 (78.3%)
Minamino 2021[27]	Japan	Outpatient	Study of Osteoporotic Fracture frailty indicator	ACR/EULAR 2010	306	63.5	≥18	306 (100%)
Oetsma 2020[28]	Netherlands	Outpatient	Gronigen frailty indicator, Geriatric 8	rheumatologist diagnosed RA	80	74.6 (5.9)	≥65	53 (66.2%)
Salaffi 2019[29*]	Italy	Outpatient	SHARE-FI	ACR/EULAR	210	60.4 (13.5)	≥18	138 (65.7%)
Salaffi 2020[10*]	Italy	Outpatient	Comprehensive Rheumatologic Assessment of Frailty	ACR/EULAR	219	60.4 (13.5)	≥18	138 (63%)
Tada 2019, Tada 2021[30,31]	Japan	Outpatient	Kihon checklist	ACR/EULAR	95	68 (5.5)	≥18	78 (82.1%)
Wysham 2020[20]	USA	Outpatient	Frailty phenotype	rheumatologist diagnosed RA	138	58 (10.8)	≥18	117 (84.8%)
Yoshii 2019[32]	Japan	Outpatient	Frailty phenotype	ACR/EULAR	441	64.5 (13.5)	≥18	337 (76.4%)
Yoshii 2020[33]	Japan	Outpatient	5-item frailty score	ACR/EULAR	739	71.3	≥18	-

*Based on same sample, presented on separate lines as report different frailty measure.

ACR: American College of Rheumatology, EULAR: European Alliance of Associations of Rheumatology, RA: rheumatoid arthritis SHARE-FI: Survey for Health, Aging and Retirement in Europe Frailty Instrument. UK: United Kingdom, USA: United States of America

associations between frailty and baseline measures of disease activity or physical function. These are discussed in greater detail below. The studies assessing outcomes were judged to be representative of people with rheumatoid arthritis as most recruited consecutive or non-selected patients from rheumatology outpatient departments (where most patients with rheumatoid arthritis undergoing treatment are managed). Frailty measures were either validated or well-described. Cross sectional characteristics were assessed similarly in people with and without frailty. As such these were judged to be a high quality assessment of the cross-sectional associations between frailty and features of rheumatoid arthritis but with limited assessment of the longitudinal impact of frailty or the causal role of frailty in the development of outcomes and complications.

Rheumatoid arthritis disease activity. Ten studies, using seven different frailty measures and four different markers of rheumatoid arthritis disease activity (four using Disease Activity Score in 28 joints, two using the Rheumatoid Arthritis Disease Activity Index, two using Simple Disease Activity Index and two using Clinical Disease Activity Index) all showed a significant cross-sectional association between frailty status and activity of rheumatoid arthritis before adjustment for additional factors[10,11,20,21,25,27–30,33]. One study, using CDAI, found that this relationship was no longer evident after adjusting for age[33]. In contrast, two other studies, showed that frailty remained associated with a higher baseline DAS-28 score after adjustment for age, sex, duration of rheumatoid arthritis and physical impairment (quantified using the Health Assessment Questionnaire – Disability Index (HAQ-DI))[25,27].

Two studies presented data on prevalence or degree of frailty, stratified by disease activity (remission, low, medium or high). Tada and colleagues assessed frailty using the Kihon checklist

Table 3. Frailty measures used in included studies.

Frailty measure	Components	Range and categorisation	Outcomes reported in included studies	Included studies
Frailty phenotype[6]	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)	1-2 criteria: Pre-frail ≥3 criteria: Frail	Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI	Andrews 2017[12], Andrew 2019[21], Chang 2010[23], Wysham 2020[20], Yoshii 2019[32]
Kihon checklist[34]	Self-administered checklist (components: activities of daily living, exercise, falling, nutrition, oral health, cognition, depression)	Unweighted sum of components. Range 0–25. Pre-frail (4–7), Frail (≥8).	Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI	Kojima 2020[25], Tada 2019[30], Tada 2021[31]
Survey for Health, Aging and Retirement in Europe Frailty Instrument (SHARE-FI)[35]	5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity). Conceptually based on the frailty phenotype with an alternative calculation for the final categorisation of frailty.	Weighted score calculated and then categorised into robust, pre-frail, frail.	Frailty prevalence, Disease activity, HAQ-DI	Haider 2019[11], Salaffi 2019[29]
Frailty index[7,8]	Count of health-related deficits (≥30, type and number of chosen deficits may vary between studies). Total present divided by number of possible deficits	Range 0-1 Sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24)	Hospitalisation, Fractures	Li 2019[26]
Comprehensive Rheumatologic Assessment of Frailty (CRAF)[10]	10 domains identified as relevant to the assessment of frailty in the context of rheumatological condition. Conceptually similar to the frailty index, cumulative deficit model (but with fewer deficits than the frailty index).	Range 0-1 Authors propose to categorise as robust (0–0.12), mild (0.12–0.24), moderate (0.24–0.36) and severe (>0.36) frailty.	Frailty prevalence, disease activity	Salaffi 2020[10]
5-Item frailty risk score[36]	5 components (weight loss, fatigue, short term memory decline, slow walking pace, low physical activity). Conceptually based on the frailty phenotype, with alteration of variables included.	1-2 criteria: Pre-frail ≥3 criteria: Frail	Frailty prevalence, Disease activity, HAQ-DI	Yoshii 2020[33]
Tilburg frailty indicator[37]	15 questions across 3 domains (physical, psychological and social) Responses combined into unweighted sum.	Range 0–15 ≥5 indicates frailty	Frailty prevalence	Bak 2020[22]
Geriatric 8 score[38]	8 domains scored and summed (nutritional status, weight loss, body mass index, motor skills, psychological, number of medications, self-rated health, age)	Range 0–17 <14 indicates frailty	Frailty prevalence	Oetsma 2020[28]
Groningen frailty indicator[39]	15 items across 4 domains (physical, cognitive, social and psychological).	Range 0–15 ≥4 indicates frailty	Frailty prevalence, HAQ-DI	Oetsma 2020[28]
Study of Osteoporotic Fracture frailty indicator	3 components (weight loss, chair stand, exhaustion)	1 component: prefrail 2-3 components: frail	Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI	Minamino 2021[27]
QFrailty[24]	Algorithm based on electronic medical records combining mortality (QMortality score) and hospital admission (QAdmission score) risk.	Categorised as mild, moderate and severe frailty.	Frailty prevalence	Hippisley-Cox 2017[24]

Table adapted from Hanlon *et al.* 2020[15]

Table 4. Quality assessment of included studies (based on adapted Newcastle Ottawa Scale).

Author, Year	Representative	Selection of non frail comparison	Ascertainment of exposure frailty	Non respondents	Outcome not present at start	Controls for age and sex	Control for other factors	Outcome assessment	Length of follow up	Adequacy of follow up	Cross-sectional score	Longitudinal score
Andrews 2017, Andrews 2019[12,21]	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Bak 2020[22]	0	1	2	0	-	-	-	-	-	-	3/5	-
Chang 2010[23]	1	1	1	0	-	-	-	-	-	-	3/5	-
Haider 2019[11]	1	1	2	0	-	-	-	-	-	-	3/5	-
Hippisley-Cox 2017[24]	1	1	1	0	-	-	-	-	-	-	3/5	-
Kojima 2020[25]	0	1	2	0	-	-	-	-	-	-	3/5	-
Li 2019[26]	1	1	2	0	1	1	1	1	1	1	4/5	10/11
Minamino 2021[27]	1	1	2	0	-	-	-	-	-	-	4/5	-
Oetsma 2020[28]	1	1	2	0	-	-	-	-	-	-	4/5	-
Salaffi 2019[29]	1	1	2	1	-	-	-	-	-	-	5/5	-
Salaffi 2020[10]	1	1	1	1	-	-	-	-	-	-	4/5	-
Tada 2019, Tada 2021[30,31]	1	1	2	1	-	-	-	-	-	-	4/5	-
Wysham 2020[20]	1	1	2	0	-	-	-	-	-	-	4/5	-
Yoshii 2019[32]	1	1	2	0	-	-	-	-	-	-	4/5	-
Yoshii 2020[33]	1	1	1	0	-	-	-	-	-	-	3/5	-

and reported a prevalence of 6.7% in the remission group, 18% in people with low disease activity, and 47% in the medium or high disease activity group[30]. Salaffi and colleagues, analysing the CRAF, showed that none of the participants in remission or with low disease activity groups had scores above the threshold for 'moderate frailty', whereas among participants with high disease activity the median CRAF score was 0.34 (close to the threshold for 'severe frailty' of 0.36)[10].

One cohort study assessed the relationship between frailty and change in disease activity over time, reporting no significant association between frailty and change in RADAI over 3.7 years follow-up[21].

Taken together these data show a consistent relationship between frailty and disease activity assessed using DAS28, however there was some inconsistency in this relationship when disease activity was assessed by different measures. The prevalence of frailty appears considerably higher in people with active disease. However, these were cross sectional assessments and no studies assessed whether frailty prevalence or severity is sensitive to changes in disease severity over time.

Physical function. Seven studies assessed the relationship between frailty and physical function using the HAQ-DI[11,12,21,22,25,27,28,30,33]. Each of these studies demonstrates an association between frailty and higher baseline HAQ scores (indicating a greater degree of physical impairment). One of these studies also included a longitudinal analysis in which frailty at baseline (assessed using the frailty phenotype) was associated with worsening of HAQ scores over two-years follow-up, indicating that participants with frailty at baseline were

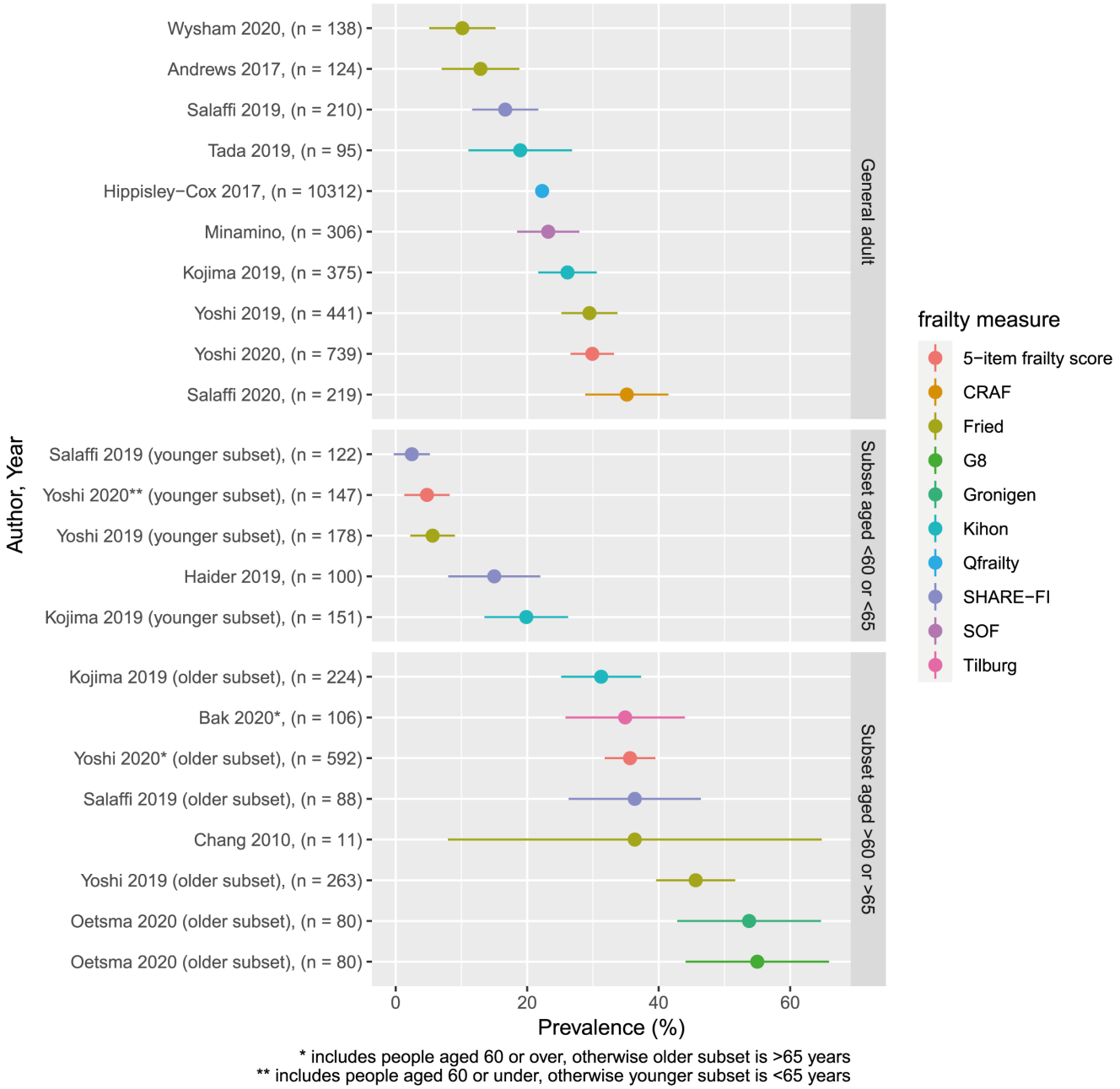

Figure 2. Prevalence of frailty. Colours indicate frailty measure. Points indicate point estimate of for frailty prevalence, with bars indicating 95% confidence intervals. Ordered by frailty prevalence for ease of comparison.

more likely to experience deterioration in physical function than robust participants[21]. This analysis was also adjusted for rheumatoid arthritis disease activity. Together these findings show a consistent relationship between frailty status, assessed through a range of measures, and greater physical impairment assessed using HAQ.

Duration of rheumatoid arthritis. Five studies assessed the relationship between frailty and the duration of rheumatoid arthritis at baseline[10,20,25,27,29]. Findings were mixed, with three studies showing no association between frailty and disease duration[10,20,27]. By contrast, two studies showed that frailty was associated with greater duration of rheumatoid arthritis at the time of assessment[25,29], however only one of these studies additionally adjusted for age in the analysis[25].

Other outcomes. One study, using the frailty index approach to quantifying frailty in 2923 participants, assessed the

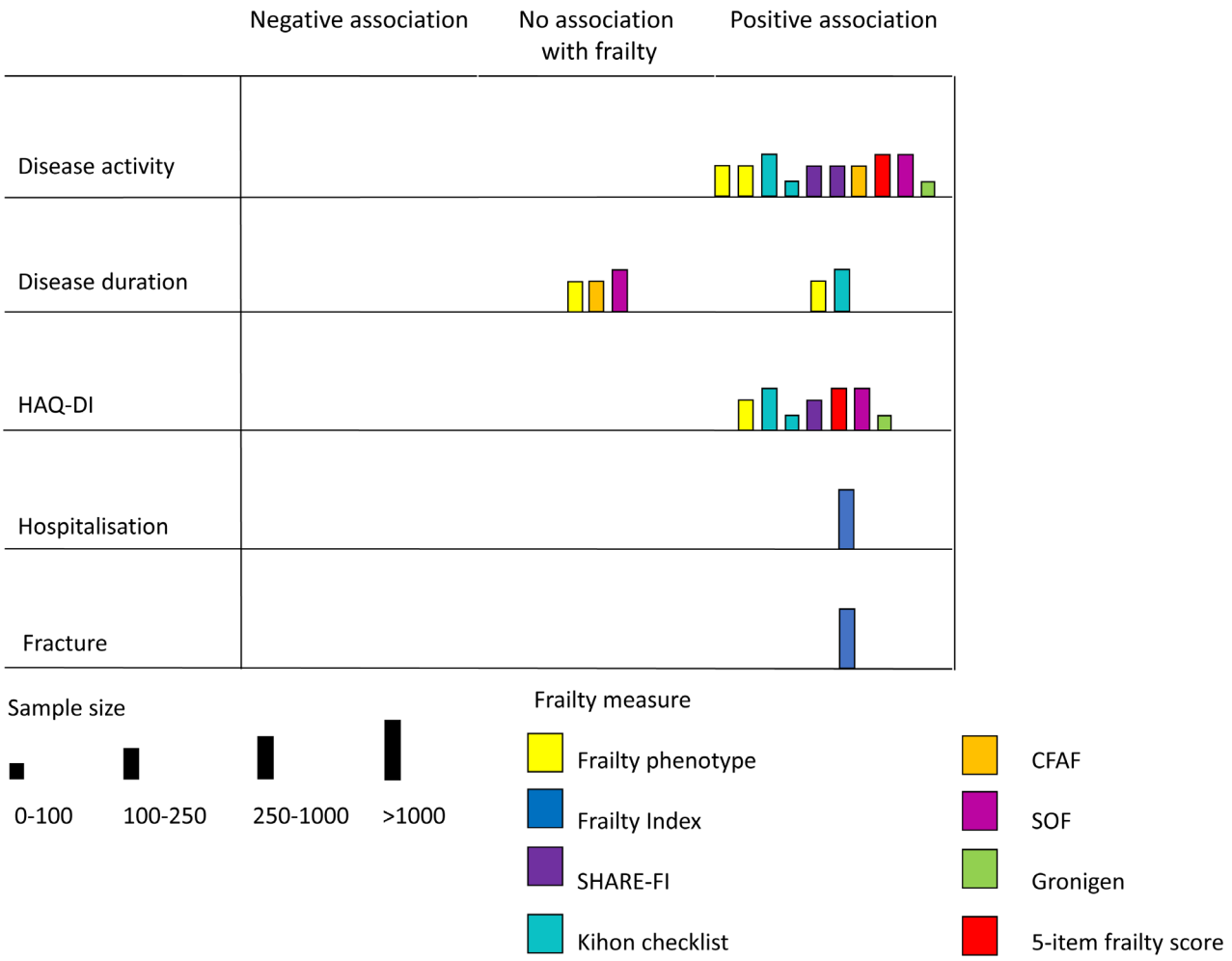

Figure 3. Association between frailty and clinical outcomes. Each bar represents a study. The position of the bar on the matrix indicates the association between frailty and the outcome in question (positive association, negative associaton or neutral assocaiton). Colour indicates the frailty measure used in the study. The weight of the bar indicates the study sample size.

relationship between frailty and all-cause hospitalisations[26]. Higher frailty index values were associated with a greater risk of hospitalisation during a mean follow-up of 3.7 years. This same study also showed that a higher frailty index was associated with a greater risk of osteoporotic fractures over the same follow-up period.

No studies assessed the relationship between frailty and mortality, cardiovascular events, or outcomes in response to treatment. Also, no studies assessed frailty at any other time-points following baseline, and therefore no analyses were identified of frailty trajectories in rheumatoid arthritis or of factors associated with worsening or amelioration of frailty.

Discussion

Summary of findings

In this systematic review we identified 17 papers, based on 14 different populations, reporting the prevalence of frailty in people with rheumatoid arthritis. Frailty was common in all studies, ranging from 10% to 36% among adult populations with rheumatoid arthritis, however there was considerable heterogeneity in both the measures used to identify frailty and the demographics of the populations studied (most notably age). There were 11 different measures used to identify frailty across the 14 cohorts, which limits the comparability of prevalence estimates. However, even among studies using similar measures, estimates of the frailty prevalence were variable. This may reflect differences in the underlying population (e.g. ethnicity, socioeconomic status, disease activity), inclusion criteria, or the application of frailty measures. All these factors may influence prevalence estimates of frailty. It is notable, therefore, that few studies reported data on ethnicity or socioeconomic status.

Nonetheless, frailty (however measured) was consistently associated with greater disease activity assessed through scores such as DAS-28, and with greater physical impairment indicated by HAQ-DI. The relationship with duration of rheumatoid

arthritis was inconsistent, with some studies reporting an association between frailty and greater duration of rheumatoid arthritis. None assessed the prevalence of frailty in new-onset rheumatoid arthritis. Most studies were cross sectional, with only two reporting longitudinal follow-up (showing frailty to be associated with hospitalisations and fractures, and worsening physical function, respectively). Therefore, the prognostic significance of frailty in rheumatoid arthritis remains unclear, nor do we know anything about the likely trajectory of frailty over time or the sensitivity of frailty to changes in disease activity as a result of treatment with disease-modifying antirheumatic drugs.

Findings in context of previous literature

Estimates of frailty prevalence are understood to be limited by variability in how frailty is measured. Different frailty measures are based on different characteristics, are underpinned by different theoretical constructs, and identify different populations. A recent systematic review estimated a pooled global prevalence of frailty in the general population at 7% (95% CI 5-9%) using a physical frailty model and 24% (22-26%) using a cumulative deficit model, however estimates vary widely depending on the underlying population demographics[40]. Despite these limitations in comparing frailty prevalence between studies, the estimates reported in this review indicate that frailty is common in people with rheumatoid arthritis compared to the general population. This is consistent with previous observations that frailty, identified using a frailty index, was common in phase 3-4 randomised controlled trials of people with rheumatoid arthritis[41]. As in this review, frailty in these trials was strongly associated with greater disease activity.

The cross-sectional nature of the included studies makes determining the extent to which the frailty is caused by rheumatoid arthritis difficult. The development of frailty is understood to be multifactorial. Furthermore, different approaches to identifying frailty (such as a frailty phenotype versus a cumulative deficit model, or a physical model versus one including psychological and social vulnerability) may have different causal pathways and mechanisms underlying them[42,43]. However, rheumatoid arthritis may lead to a range of states or complications (such as fatigue, sarcopenia, weight loss, and functional limitation) which may all contribute to the identification of frailty. Fatigue in rheumatoid arthritis may result from the underlying inflammatory process as well as symptoms, functional, emotional and psychological impact of the condition and treatments[44]. Weight loss and low body mass index, thought partly to be mediated through excess pro-inflammatory mediators such as IL-1 and TNF-alpha, are associated with greater erosive disease in rheumatoid arthritis as well as greater cardiovascular risk, physical disability, and mortality[45–47]. Rheumatoid arthritis, through a combination of systemic inflammation and reduced physical activity, may also result in sarcopenia which in turn contributes to the development of frailty[48–52]. These observations, along with the consistent association between frailty and greater disease activity, mean it is likely that rheumatoid arthritis – particularly if highly active or severe – leads to the development of features of frailty.

Conversely, frailty has a wide range of potential causes and associations, and it is unlikely that there is a single common pathway or mechanism underlying the development of frailty in people with rheumatoid arthritis. Co-existing frailty alongside rheumatoid arthritis may lead or contribute to functional limitations not exclusively attributable to rheumatoid arthritis itself. The rationale for frailty identification and assessment is to facilitate a broad and multidimensional evaluation of a person's needs and priorities. Given increasing rheumatoid arthritis in older age[1], and the prevalence of multimorbidity among people with rheumatoid arthritis[53], it is important to better understand whether incorporating frailty assessment into the management of rheumatoid arthritis would being additional benefits beyond those measures already commonly used.

Implications

These findings highlight several important gaps in our understanding of frailty in the context of rheumatoid arthritis. The first is the prognostic significance of frailty in people with rheumatoid arthritis. Only one study, using a frailty index model, assessed the association between frailty and hospitalisations and none explored whether frailty is associated with mortality, cardiovascular events, or long-term care needs in people with rheumatoid arthritis. The association between frailty and these outcomes in the general population is well established. However, given the overlap between features of active or severe rheumatoid arthritis and frailty, it is not clear if assessment of frailty in the context of rheumatoid arthritis improves prediction of these outcomes.

The second gap is to disentangle the relationship between frailty and rheumatoid arthritis disease activity. Active rheumatoid arthritis may give rise to a range of features which may indicate frailty (fatigue, weakness, pain, functional limitation, etc.). Frailty may, therefore, be amenable to intervention. Frailty is recognised to be a dynamic state which changes over time. However, the degree to which frailty in rheumatoid arthritis is reversible is not clear. This question, like the association between frailty and clinical outcomes, would require longitudinal studies ideally with serial assessments of both frailty and disease activity.

A final, more nuanced, gap in our understanding is how these epidemiological measures of frailty translate to the experience and understanding of people living with rheumatoid arthritis and to the clinical impression of professionals involved in their care. While a range of physical, functional, and psychological features common in rheumatoid arthritis may be consistent with current definitions of frailty, this may not be how people living with rheumatoid arthritis would choose to characterise their experience. It is also not clear if frailty identified in such a way, particularly when it results from active rheumatoid arthritis, is equivalent to frailty as it would be understood by clinicians. Understanding the implications of frailty in rheumatoid arthritis therefore not only requires a fuller understanding of its epidemiology, but also the broader clinical implications and the utility of a frailty 'label'. For clinicians, understanding that there is uncertainty around the prognostic significance of frailty in people with rheumatoid

arthritis is important. Recommendations for frailty based, for example, on limited life expectancy or the likelihood of functional decline may not be relevant for all individuals with rheumatoid arthritis who meet the criteria for frailty. For this reason, future research assessing the relationship between frailty and outcomes such as mortality and the development of disability in people with rheumatoid arthritis, as disentangling this from the impact of rheumatoid arthritis disease activity, is important to inform clinical decisions.

Strengths and limitations

Strengths of this review include a comprehensive search strategy with duplicate screening and data extraction. However, the search was limited to English language only and we excluded Grey literature. This could potentially lead to language or publication bias, respectively. We used an adapted version of the Newcastle-Ottawa scale (prespecified in our protocol) to maximise the comparability of assessment of cross-sectional and longitudinal studies (e.g., where both assessed prevalence). However, most studies identified and included were cross sectional, and this tool is not specific to the assessment of cross-sectional studies. It was not possible to conduct a meta-analysis of frailty prevalence due to the degree of heterogeneity. This was particularly evident in the measurement of frailty, as a range of different measures were used and prevalence estimates are therefore not directly comparable. Studies were also heterogenous in terms of their inclusion criteria, demographics, and definitions of rheumatoid arthritis. Studies were all from high-income countries with no data from low-and middle-income countries. Also only one study presented data on the ethnicity of participants, and none assessed socioeconomic status, factors which may impact the prevalence of frailty. Finally, the studies included in this review were observational and mostly cross-sectional. It is therefore not possible to assess causal relationships.

Conclusion

Frailty in people with rheumatoid arthritis has been quantified in high income countries using a wide range of different approaches and is consistently demonstrated to be common, particularly among people with more active disease. Assessment of frailty among people with rheumatoid arthritis, including those aged under 65 years, is likely to identify people at greater risk of functional limitation. However, a relative lack of longitudinal studies and heterogeneity in the methods used to assess frailty mean that the clinical implications, prognostic significance, and potential reversibility remain unclear. There is a need for studies in low- and middle-income countries as well as studies with serial follow-up and repeated measures to understand the trajectories and outcomes of frailty in rheumatoid arthritis, as well as greater exploration of the implications of frailty from the perspective of patients and clinicians. Understanding these relationships in greater detail may reveal potential for interventions to ameliorate frailty in rheumatoid arthritis, limit its impact, and support people living with frailty.

Data availability

Underlying data

Zenodo: Data underlying Frailty in people with rheumatoid arthritis – A systematic review of observational studies, https://doi.org/10.5281/zenodo.6966157[54].

This project contains the following underlying data:

- Abstract_screening_RA_frailty_complete.xlsx
- Abstract_screening_RA_frailty_full_texts.xlsx
- Data_extraction.xlsx
- MOOSE checklist.doc

Reporting guidelines

PRISMA checklist available at Zenodo: Data underlying Frailty in people with rheumatoid arthritis – A systematic review of observational studies, https://doi.org/10.5281/zenodo.6966157[54].

Author contributions

Peter Hanlon: Conceptualisation, Investigation, Methodology, Visualisation, Writing – Original Draft Perparation, Writing – Review & Editing

Holly Morrison: Investigation, Writing – Review & Editing

Fraser Morton: Writing – Review & Editing

Bhautesh D Jani: Writing – Review & Editing

Stefan Siebert: Writing – Review & Editing

Jim Lewsey: Investigation, Methodology, Supervision, Writing – Review & Editing

David McAllister: Investigation, Methodology, Supervision, Writing – Review & Editing

Frances S Mair: Investigation, Methodology, Supervision, Writing – Review & Editing

References

1. Salaffi F, Di Carlo M, Carotti M, *et al.*: **The impact of different rheumatic diseases on health-related quality of life: a comparison with a selected sample of healthy individuals using SF-36 questionnaire, EQ-5D and SF-6D utility values.** *Acta Biomed.* 2019; **89**(4): 541–57.
PubMed Abstract | Publisher Full Text | Free Full Text

2. Salaffi F, Farah S, Di Carlo M: **Frailty syndrome in rheumatoid arthritis and symptomatic osteoarthritis: an emerging concept in rheumatology.** *Acta Biomed.* 2020; **91**(2): 274–96.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Espinoza G, Maldonado G, Narvaez J, *et al.*: **Beyond Rheumatoid Arthritis Evaluation: What are We Missing?** *Open Access Rheumatol.* 2021; **13**: 45–55.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Clegg A, Young J, Iliffe S, *et al.*: **Frailty in elderly people.** *Lancet.* 2013; **381**(9868): 752–62.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Hanlon P, Nicholl BI, Jani BD, *et al.*: **Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants.** *Lancet Public Health.* 2018; **3**(7): e323–e332.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Fried LP, Tangen CM, Walston J, *et al.*: **Frailty in older adults: evidence for a phenotype.** *J Gerontol A Biol Sci Med Sci.* 2001; **56**(3): M146–M56.
PubMed Abstract | Publisher Full Text

7. Mitnitski AB, Mogilner AJ, Rockwood K: **Accumulation of deficits as a proxy measure of aging.** *ScientificWorldJournal.* 2001; **1**: 323–36.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Rockwood K, Mitnitski A: **Frailty in relation to the accumulation of deficits.** *J Gerontol A Biol Sci Med Sci.* 2007; **62**(7): 722–7.
PubMed Abstract | Publisher Full Text

9. Hoogendijk EO, Afilalo J, Ensrud KE, *et al.*: **Frailty: implications for clinical practice and public health.** *Lancet.* 2019; **394**(10206): 1365–1375.
PubMed Abstract | Publisher Full Text

10. Salaffi F, Di Carlo M, Farah S, *et al.*: **The Comprehensive Rheumatologic Assessment of Frailty (CRAF): development and validation of a multidimensional frailty screening tool in patients with rheumatoid arthritis.** *Clin Exp Rheumatol.* 2020; **38**(3): 488–499.
PubMed Abstract

11. Haider S, Grabovac I, Berner C, *et al.*: **Frailty in seropositive rheumatoid arthritis patients of working age: a cross-sectional study.** *Clin Exp Rheumatol.* 2019; **37**(4): 585–92.
PubMed Abstract

12. Andrews JS, Trupin L, Yelin EH, *et al.*: **Frailty and reduced physical function go hand in hand in adults with rheumatoid arthritis: a US observational cohort study.** *Clin Rheumatol.* 2017; **36**(5): 1031–9.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Moher D, Liberati A, Tetzlaff J, *et al.*: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med.* 2009; **6**(7): e1000097.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Morgan RL, Whaley P, Thayer KA, *et al.*: **Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes.** *Environ Int.* 2018; **121**(Pt 1): 1027–1031.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Hanlon P, Fauré I, Corcoran N, *et al.*: **Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis.** *Lancet Healthy Longev.* 2020; **1**(3): e106–e116.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Hanlon P, Fauré I, Corcoran N, *et al.*: **Identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: a systematic review protocol.** *BMJ Open.* 2020; **10**(9): e037476.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Aletaha D, Neogi T, Silman AJ, *et al.*: **2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.** *Arthritis Rheum.* 2010; **62**(9): 2569–81.
PubMed Abstract | Publisher Full Text

18. Crowther M, Avenell A, MacLennan G, *et al.*: **A further use for the Harvest plot: a novel method for the presentation of data synthesis.** *Res Synth Methods.* 2011; **2**(2): 79–83.
PubMed Abstract | Publisher Full Text

19. Ogilvie D, Fayter D, Petticrew M, *et al.*: **The harvest plot: a method for synthesising evidence about the differential effects of interventions.** *BMC Med Res Methodol.* 2008; **8**(1): 8.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Wysham KD, Shoback DM, Andrews JS, *et al.*: **Sex differences in frailty and its association with low bone mineral density in rheumatoid arthritis.** *Bone Rep.* 2020; **12**: 100284.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Andrews JS, Trupin L, Wysham KD, *et al.*: **The Impact of Frailty on Changes in Physical Function and Disease Activity Among Adults With Rheumatoid Arthritis.** *ACR Open Rheumatol.* 2019; **1**(6): 366–72.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Bak E, Mlynarska A, Marcisz C, *et al.*: **Factors that affect the assessment of the quality of life of rheumatoid arthritis patients depending on the prevalence of frailty syndrome.** *Health Qual Life Outcomes.* 2020; **18**(1): 216.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Chang SS, Weiss CO, Xue QL, *et al.*: **Patterns of comorbid inflammatory diseases in frail older women: the Women's Health and Aging Studies I and II.** *J Gerontol A Biol Sci Med Sci.* 2010; **65**(4): 407–13.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Hippisley-Cox J, Coupland C: **Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study.** *BMJ.* 2017; **358**: j4208.
PubMed Abstract | Publisher Full Text | Free Full Text

25. Kojima M, Kojima T, Waguri-Nagaya Y, *et al.*: **Depression, physical function, and disease activity associated with frailty in patients with rheumatoid arthritis.** *Mod Rheumatol.* 2020; **31**(5): 979–986.
PubMed Abstract | Publisher Full Text

26. Li G, Chen M, Li X, *et al.*: **Frailty and risk of osteoporotic fractures in patients with rheumatoid arthritis: Data from the Ontario Best Practices Research Initiative.** *Bone.* 2019; **127**: 129–34.
PubMed Abstract | Publisher Full Text

27. Minamino H, Katsushima M, Torii M, *et al.*: **Habitual fish intake negatively correlates with prevalence of frailty among patients with rheumatoid arthritis.** *Sci Rep.* 2021; **11**(1): 5104.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Oetsma S, Boonen A, Starmans M, *et al.*: **Validation of two frailty questionnaires in older patients with rheumatoid arthritis: a cross-sectional study.** *Clin Exp Rheumatol.* 2020; **38**(3): 523–8.
PubMed Abstract

29. Salaffi F, Di Carlo M, Farah S, *et al.*: **Prevalence of frailty and its associated factors in patients with rheumatoid arthritis: a cross-sectional analysis.** *Clin Rheumatol.* 2019; **38**(7): 1823–30.
PubMed Abstract | Publisher Full Text

30. Tada M, Yamada Y, Mandai K, *et al.*: **Correlation between frailty and disease activity in patients with rheumatoid arthritis: Data from the CHIKARA study.** *Geriatr Gerontol Int.* 2019; **19**(12): 1220–5.
PubMed Abstract | Publisher Full Text

31. Tada M, Yamada Y, Mandai K, *et al.*: **Relationships of the stand-up time to falls and fractures in patients with rheumatoid arthritis: Results from the CHIKARA study.** *Int J Rheum Dis.* 2021; **24**(2): 246–53.
PubMed Abstract | Publisher Full Text

32. Yoshii I, Chijiwa T, Sawada N: **Validity of adopting a Health Assessment Questionnaire Disability Index less than 0.5 as a target in elderly rheumatoid arthritis patients.** *Clin Rheumatol.* 2019; **38**(12): 3351–60.
PubMed Abstract | Publisher Full Text

33. Yoshii I, Kondo M: **Clinical Characteristics of frailty in Japanese Rheumatoid Arthritis Patients.** *J Frailty Aging.* 2020; **9**(3): 158–64.
PubMed Abstract | Publisher Full Text

34. Satake S, Senda K, Hong YJ, *et al.*: **Validity of the Kihon Checklist for assessing frailty status.** *Geriatr Gerontol Int.* 2016; **16**(6): 709–15.
PubMed Abstract | Publisher Full Text

35. Romero-Ortuño R, Walsh C, Lawlor BA, *et al.*: **A frailty instrument for primary care: Findings from the Survey of Health, Ageing and Retirement in Europe (SHARE).** *BMC Geriatrics.* 2010; **10**: 57.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Yamada M, Arai H: **Predictive value of frailty scores for healthy life expectancy in community-dwelling older Japanese adults.** *J Am Med Dir Assoc.* 2015; **16**(11): 1002.e7–e11.
PubMed Abstract | Publisher Full Text

37. Gobbens RJ, Schols JM, van Assen MA: **Exploring the efficiency of the Tilburg Frailty Indicator: a review.** *Clin Interv Aging.* 2017; **12**: 1739–1752.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Bellera CA, Rainfray M, Mathoulin-Pelissier S, *et al.*: **Screening older cancer patients: first evaluation of the G-8 geriatric screening tool.** *Ann Oncol.* 2012; **23**(8): 2166–72.
PubMed Abstract | Publisher Full Text

39. Steverink N: **Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator).** *The gerontologist.* 2001; **41**: 236.
Reference Source

40. O'Caoimh R, Sezgin D, O'Donovan MR, *et al.*: **Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies.** *Age Ageing.* 2021; **50**(1): 96–104.
PubMed Abstract | Publisher Full Text

41. Hanlon P, Butterly E, Lewsey J, *et al.*: **Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions.** *BMC Med.* 2020; **18**(1): 309.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Fried LP, Cohen AA, Xue QL, *et al.*: **The physical frailty syndrome as a**

transition from homeostatic symphony to cacophony. *Nat Aging.* 2021; **1**(1): 36–46.
PubMed Abstract | Publisher Full Text | Free Full Text

43. Rockwood K, Howlett SE: **Fifteen years of progress in understanding frailty and health in aging.** *BMC Med.* BioMed Central; 2018; **16**(1): 220.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Nikolaus S, Bode C, Taal E, *et al.*: **Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review.** *Arthritis Care Res (Hoboken).* 2013; **65**(7): 1128–46.
PubMed Abstract | Publisher Full Text

45. Santo RC, Fernandes KZ, Lora PS, *et al.*: **Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis.** *J Cachexia Sarcopenia Muscle.* 2018; **9**(5): 816–25.
PubMed Abstract | Publisher Full Text | Free Full Text

46. Kremers HM, Nicola PJ, Crowson CS, *et al.*: **Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis.** *Arthritis Rheum.* 2004; **50**(11): 3450–7.
PubMed Abstract | Publisher Full Text

47. Book C, Karlsson MK, Akesson K, *et al.*: **Early rheumatoid arthritis and body composition.** *Rheumatology (Oxford).* 2009; **48**(9): 1128–32.
PubMed Abstract | Publisher Full Text

48. Mochizuki T, Yano K, Ikari K, *et al.*: **Sarcopenia-associated factors in Japanese patients with rheumatoid arthritis: A cross-sectional study.** *Geriatr Gerontol Int.* 2019; **19**(9): 907–12.
PubMed Abstract | Publisher Full Text

49. Giles JT, Ling SM, Ferrucci L, *et al.*: **Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies.** *Arthritis Rheum.* 2008; **59**(6): 807–15.
PubMed Abstract | Publisher Full Text | Free Full Text

50. Petermann-Rocha F, Chen M, Gray SR, *et al.*: **Factors associated with sarcopenia: A cross-sectional analysis using UK Biobank.** *Maturitas.* 2020; **133**: 60–7.
PubMed Abstract | Publisher Full Text

51. Munro R, Capell H: **Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response.** *Ann Rheum Dis.* 1997; **56**(5): 326–9.
PubMed Abstract | Publisher Full Text | Free Full Text

52. Doğan SC, Hizmetli S, Hayta E, *et al.*: **Sarcopenia in women with rheumatoid arthritis.** *Eur J Rheumatol.* 2015; **2**(2): 57–61.
PubMed Abstract | Publisher Full Text | Free Full Text

53. McQueenie R, Nicholl BI, Jani BD, *et al.*: **Patterns of multimorbidity and their effects on adverse outcomes in rheumatoid arthritis: a study of 5658 UK Biobank participants.** *BMJ Open.* 2020; **10**(11): e038829.
PubMed Abstract | Publisher Full Text | Free Full Text

54. Hanlon P: **Data underlying Frailty in people with rheumatoid arthritis – A systematic review of observational studies [Data set].** *Zenodo.* 2021.
http://www.doi.org/10.5281/zenodo.6966157

Open Peer Review

Current Peer Review Status: ✔ ?

Version 2

Reviewer Report 01 November 2022

https://doi.org/10.21956/wellcomeopenres.20165.r52462

✔ **Dhammika Deepani Siriwardhana**
Research Department of Primary Care and Population Health, University College London, London, UK

The authors have addressed my comments adequately. I am happy to approve the manuscript for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 20 June 2022

https://doi.org/10.21956/wellcomeopenres.19016.r50113

? **Rose Galvin**
Ageing Research Centre, Health Research Institute, University of Limerick, Limerick, Ireland

Many thanks for inviting me to review this systematic review of cohort studies exploring the prevalence of frailty and its association with clinical outcomes among people with RA. I have

included some comments that would help in the reading and interpretation of the findings:

Abstract

Background

- State the clinical outcomes that you are interested in. Process outcomes are also reported in the findings.

Methods

- What approach was used to diagnose frailty?
- What approach was used to synthesise the data?
- Was study quality also assessed independently?

Results

- It would be helpful if the timeframe between exposure and outcome was quantified for each outcome.

Introduction

- The introduction quantifies the burden of the problem of RA and associated morbidities. However, the rationale for conducting the SR warrants further consideration. Why is it important to recognise frailty in this population in terms of risk stratification and subsequent allocation of resources?
- The differences between objectives 3 and 4 are unclear. You have also reported findings across other outcomes (e.g. hospitalisaton) other than those reported in objectives. Please correct this inconsistency.

Methods

- How was the PRIMSA statement modified to inform the conduct and reporting of this study? Consider using the MOOSE guidelines and the PRISMA flow diagram.
- What definitions of RA are eligible for inclusion?
- The authors mention that 'Studies were considered regardless of frailty measure, to allow comparison between different methods of identifying frailty'. Were validated measures of frailty considered only or studies where self-reporting or clinical judgment was used to diagnose frailty in the absence of any set criteria?
- Study designs – was the control arm of experimental studies considered for inclusion?
- Was an informational specialist involved in developing the search string?
- Check consistency in reporting the number of databases searched in abstract/methods.
- Insert initials of reviewers involved in screening, full-text selection, data extraction, and quality appraisal.
- Perhaps include a rationale for why the Newcastle-Ottawa tool was chosen as an RoB tool.
- How was the variation in the reporting of adverse outcomes handled (for example, the differences in reporting functional decline across studies). Greater clarity is needed on the

parameters used to extract data.

Results

- Overall, the findings to map the objectives of the review are clearly reported.
- It would be helpful to include more details in the narrative on the impact of the quality appraisal on the interpretation of findings.

Discussion

- Consideration needs to be given to other factors that might influence the prevalence of frailty aside from age and the measure of frailty?
- The results are well contextualised with regard to the current literature. The strengths and weaknesses are well-considered.
- Perhaps insert a few lines on the clinical implications of frailty in this population for a clinical audience.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ageing, quantitative research methods

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 05 Aug 2022

Peter Hanlon, University of Glasgow, Glasgow, UK

Thank you for your detailed review of our manuscript. We have now uploaded a revised version based on your comments and those of the other reviewer. Please find below our response to each of the comments. Thank you again for your time and consideration in reviewing our manuscript.

Review 2:
Many thanks for inviting me to review this systematic review of cohort studies exploring the

prevalence of frailty and its association with clinical outcomes among people with RA. I have included some comments that would help in the reading and interpretation of the findings:

Abstract

Background

- State the clinical outcomes that you are interested in. Process outcomes are also reported in the findings.

We have edited the following sentences: "We undertook a systematic review to assess prevalence of frailty in people with rheumatoid arthritis, and the relationship between frailty and disease activity or clinical outcomes" and "[we searched for studies]... analysing the relationship between frailty and disease activity or clinical outcomes (e.g. quality of life, hospitalisation or mortality) in people with rheumatoid arthritis".

Methods

- What approach was used to diagnose frailty?

Author response: We have added text to the abstract to specify that we would consider "any frailty measure".

- What approach was used to synthesise the data?

Author response: We have now added: "We used narrative synthesis".

- Was study quality also assessed independently?

Author response: Yes, these were. We have added the following text: "Screening, quality assessment and data extraction were performed independently by two reviewers."

Results

- It would be helpful if the timeframe between exposure and outcome was quantified for each outcome.

Author response: We have edited this sentence in the abstract to present this information: "Frailty was cross-sectionally associated with higher disease activity (10/10 studies), lower physical function (7/7 studies) and longer disease duration (2/5 studies), and with hospitalization and osteoporotic fractures (1/1 study, 3.7 years follow-up)."

Introduction

- The introduction quantifies the burden of the problem of RA and associated morbidities. However, the rationale for conducting the SR warrants further consideration. Why is it important to recognise frailty in this population in terms of risk stratification and subsequent allocation of resources?

Author response: We have added the following text: "This is important as frailty measures are increasingly being advocated to aid risk stratification and identification of high-risk populations in a range of clinical contexts. The utility and appropriateness of such an approach in people with rheumatoid arthritis therefore requires careful consideration of the relationship between frailty and this condition."

- The differences between objectives 3 and 4 are unclear. You have also reported findings across other outcomes (e.g. hospitalisaton) other than those reported in objectives. Please correct this inconsistency.

Author response: We have re-worded the final aim in the background section to make specific reference to the types of outcomes we are interested in: "what is the association between frailty and adverse health outcomes (e.g. hospitalisation, mortality or quality of life) in people with rheumatoid arthritis." The full list of outcomes is given in Table 1.

Methods

- How was the PRIMSA statement modified to inform the conduct and reporting of this study? Consider using the MOOSE guidelines and the PRISMA flow diagram.

Author response: Thank you. We have added the MOOSE checklist to the supplementary file.

- What definitions of RA are eligible for inclusion?

Author response. We have added the following to the methods to clarify our inclusion criteria "We did not exclude studies on the basis of the criteria used to define rheumatoid arthritis (i.e. validated criteria, physician diagnosis, medical record/clinical codes or self-reported definitions were all eligible for inclusion)."

- The authors mention that 'Studies were considered regardless of frailty measure, to allow comparison between different methods of identifying frailty'. Were validated measures of frailty considered only or studies where self-reporting or clinical judgment was used to diagnose frailty in the absence of any set criteria?

Author response: We have added the following text to clarify the criteria used to determine eleigibility of a frailty measure: "These could include validated measures of frailty (e.g. frailty phenotype or frailty index), adaptations of these measures where the adaptation was described, or unvalidated measures intended to capture frailty as long as the criteria used to define frailty within the study were fully described."

- Study designs – was the control arm of experimental studies considered for inclusion?

Author response: Experimental studies were not part of our inclusion criteria (although we accept the reviewer's point that the control arm could be a useful source of information should such studies have been identified).

- Was an informational specialist involved in developing the search string?

Author response: For this search strategy we did not involve a specialist, although the search terms for rheumatoid arthritis were taken from previous reviews in which a research librarian informed the development of the search strategy.

- Check consistency in reporting the number of databases searched in abstract/methods.

Author response: Thank you for highlighting this. We have amended the abstract to state four databases were searched.

- Insert initials of reviewers involved in screening, full-text selection, data extraction, and quality appraisal.

Author response: We have added this information to the text.

- Perhaps include a rationale for why the Newcastle-Ottawa tool was chosen as an RoB tool.

Author response: We have added the following text: "The Newcastle-Ottawa scale is frequently used to assess quality of observational studies. Previous reviews have also adapted elements of the scale to reflect the studies of interest to the review itself. For this review, we used an adaptation previously developed for observational studies of frailty. This adaptation altered the 'exposure' component of the was altered to award two points if a study used validated measure of frailty implemented according to its original description. One point was awarded if studies used an alternative measure of frailty (e.g. an adapted or non-validated measure of frailty) but the criteria were described in sufficient detail to allow the assessment to be replicated. This adaptation was to reflect the fact that there is no 'gold-standard' measure of frailty and that frailty is assessed using a diverse range of measures within the literature. The scale was applied to all studies (cross sectional or longitudinal), with only the first 5 elements of the scale being relevant to the cross-sectional studies. This approach was taken to allow an identical approach to quality assessment for prevalence estimates from cross sectional or (baseline of) longitudinal studies."

- How was the variation in the reporting of adverse outcomes handled (for example, the differences in reporting functional decline across studies). Greater clarity is needed on the parameters used to extract data.

Author response: We have added the following text to the methods section to expand on this description along with a supplementary table of the extracted data which underlies the presentation of outcomes in the harvest plot: "For outcomes, we extracted data on the method used to assess the outcome, timeframe or length of follow-up, the magnitude of the association along with measure of uncertainty, and any adjustment for potential confounders. Where there was variation between studies in the assessment of similar outcomes we presented this data in supplementary tables."

Results

- Overall, the findings to map the objectives of the review are clearly reported.

Author response: Thank you.

- It would be helpful to include more details in the narrative on the impact of the quality appraisal on the interpretation of findings.

Author response: Thank you for this suggestion. We have added the following text: "The studies assessing outcomes were judged to be representative of people with rheumatoid arthritis as most recruited consecutive or non-selected patients from rheumatology outpatient departments (where most patients with rheumatoid arthritis undergoing treatment are managed). Frailty measures were either validated or well-described. Cross sectional characteristics were assessed similarly in people with and without frailty. As such these were judged to be a high quality assessment of the cross-sectional associations between frailty and features of rheumatoid arthritis but with limited assessment of the longitudinal impact of frailty or the causal role of frailty in the development of outcomes and complications."

Discussion

- Consideration needs to be given to other factors that might influence the prevalence of frailty aside from age and the measure of frailty?

Author response: We agree with the reviewer. We have added the middle sentence to the section below to emphasise the potential impact of additional factors on the prevalence of frailty: "This may reflect differences in the underlying population (e.g. ethnicity, socioeconomic status, disease activity), inclusion criteria, or the application of frailty measures. All of these factors may influence prevalence estimates of frailty. It is notable, therefore, that few studies reported data on ethnicity or socioeconomic status."

- The results are well contextualised with regard to the current literature. The strengths and weaknesses are well-considered.

Author response: Thank you.

- Perhaps insert a few lines on the clinical implications of frailty in this population for a clinical audience.

Author response: Thank you. We have added the following text: "For clinicians, understanding that there is uncertainty around the prognostic significance of frailty in people with rheumatoid arthritis is important. Recommendations for frailty based, for example, on limited life expectancy or the likelihood of functional decline may not be relevant for all individuals with rheumatoid arthritis who meet the criteria for frailty. For this reason, future research assessing the relationship between frailty and outcomes such as mortality and the development of disability in people with rheumatoid arthritis, as disentangling this from the impact of rheumatoid arthritis disease activity, is important to inform clinical decisions."

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 November 2021

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Dhammika Deepani Siriwardhana
Research Department of Primary Care and Population Health, University College London, London, UK

This review summarizes the available evidence on the prevalence of frailty and associated adverse outcomes in people with rheumatoid arthritis. The manuscript is well written. I have a few comments for the authors to consider.

- In the abstract, the authors have mentioned that they searched in three electronic databases. However, in the methods, they have mentioned four databases (MEDLINE, EMBASE, WoS Core Collection, and Scopus). Suggest correcting the inconsistency.

- The objective (iv) (if frailty is associated with adverse health outcomes in the context of rheumatoid arthritis) is not clear. What was the rationale for this objective (potential clinical and research significance)?
- Authors could consider using the PRISMA 2020 diagram of study selection and checklist.
- Suggest mentioning for which database the search strategy presented in Box 1 was applied to.
- I wonder whether the authors have calculated the inter-rater reliability of the study selection/screening process.
- Was there any particular reason for allocating 2 points for the criteria “Ascertainment of exposure frailty” in the Newcastle-Ottawa tool?
- Are there any cut-offs to interpret the risk of bias assessment results?
- There are a few risks of bias assessment tools specifically developed for cross-sectional studies looking at several aspects of methodology and reporting results, e.g. AXIS, JBI critical appraisal tools for prevalence studies and analytical cross-sectional studies.
- What was the rationale for using a version of the Newcastle-Ottawa tool as a risk of bias assessment tool (only 5 criteria were applied to cross-sectional studies although the majority of the studies in this review are cross-sectional)?
- Suggest providing more information on data analysis, e.g. statistical software used to create figures, the information you fed to the software, etc.
- It is interesting that the authors have used harvest plots to present heterogeneous study findings. Was there any particular reason to annotate the bards of the harvest plots with sample size instead of using other characteristics, e.g. risk of bias assessment score?
- The method of identification of rheumatoid arthritis is not mentioned in the two included studies. I wonder whether the authors of this manuscript contacted the study authors for additional information.
- The following sentence is difficult to comprehend: “Most samples were recruited from rheumatology clinics, with most judged to be representative based on subsequent exclusion criteria and sampling methods.”.
- Table 1: “NA” stands for what? Suggest mentioning it as a footnote.
- Suggest incorporating minimum recruitment age for each study in Table 1.
- Suggest incorporating sample size into Figure 2.
- “Few studies presented data on non-responders.": Suggest presenting relevant references

along with this statement.

- “Taken together these data show a consistent relationship between frailty and disease activity, assessed by a diverse range of measures.”: I wonder about the accuracy of the above claim since the findings are mixed at the moment.

- The authors have mentioned that they have provided the search strategy for different databases as a supplementary file in the PRISMA checklist. Unfortunately, I am not able to find it.

- “no data from upper-middle income of LMICs”: This phrase is not clear. Is it about “no data from upper-middle income countries of low-and middle-income countries” or “no data from low-and middle-income countries”?

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 05 Aug 2022

Peter Hanlon, University of Glasgow, Glasgow, UK

Thank you for this review of our article. We have now uploaded a revised version based on these helpful comments and those of the second reviewer. Please see below for our response to each of the comments and details of changes added to the text. Thank you again for your time and consideration in reviewing our manuscript.

Review 1:
This review summarizes the available evidence on the prevalence of frailty and associated adverse outcomes in people with rheumatoid arthritis. The manuscript is well written. I have a few comments for the authors to consider.

- In the abstract, the authors have mentioned that they searched in three electronic

databases. However, in the methods, they have mentioned four databases (MEDLINE, EMBASE, WoS Core Collection, and Scopus). Suggest correcting the inconsistency.

Author response: Thank you. We have amended the abstract to correct this error.

- The objective (iv) (if frailty is associated with adverse health outcomes in the context of rheumatoid arthritis) is not clear. What was the rationale for this objective (potential clinical and research significance)?

Author response: We have changed the wording of this objective to make it clearer. It now reads: "what is the association between frailty and adverse health outcomes (e.g. hospitalisation or mortality) in people with rheumatoid arthritis."

- Authors could consider using the PRISMA 2020 diagram of study selection and checklist.

Author response: We have updated the PRISMA diagram to the 2020 version.

- Suggest mentioning for which database the search strategy presented in Box 1 was applied to.

Author response: This was the search strategy used for Medline. We have added this to the title along with a note that the strategy was adapted for other databases.

- I wonder whether the authors have calculated the inter-rater reliability of the study selection/screening process.

Author response: We have now added this detail to the text: "Inter-rater agreement was high (kappa statistic 98%)."

- Was there any particular reason for allocating 2 points for the criteria "Ascertainment of exposure frailty" in the Newcastle-Ottawa tool?

- Are there any cut-offs to interpret the risk of bias assessment results?

Author response: We did not apply cut off nor was quality assessment used as an exclusion criteria. We have clarified this in the text. "Studies were not excluded on the basis of the quality assessment."

- There are a few risks of bias assessment tools specifically developed for cross-sectional studies looking at several aspects of methodology and reporting results, e.g. AXIS, JBI critical appraisal tools for prevalence studies and analytical cross-sectional studies.

Author response: See the response to the comment below.

- What was the rationale for using a version of the Newcastle-Ottawa tool as a risk of bias assessment tool (only 5 criteria were applied to cross-sectional studies although the majority of the studies in this review are cross-sectional)?

Author response: This choice of the tool was made *a priori* before the identification of eligible studies. Our rationale was to allow a consistent application of quality assessment across all studies included in the review. This was particularly because among the aims of the review were to assess the prevalence and assess longitudinal outcomes. Where longitudinal studies were identified, we assessed prevalence using the baseline data from

these studies. The Newcastle-Ottawa tool allowed a similar assessment to be made for cross-sectional studies and the baseline data of longitudinal studies (first 5 questions). While we acknowledge that no single quality assessment tool provides a complete or comprehensive assessment of study quality, this tool allowed us to explicitly show our judgments on representativeness, sample selection, frailty assessment, and outcome assessment. The quality of which is particularly central to the study aims and discussed in the accompanying text.

We have added the following text to explain this decision:
"The Newcastle-Ottawa scale is frequently used to assess quality of observational studies. Previous reviews have also adapted elements of the scale to reflect the studies of interest to the review itself. For this review, we used an adaptation previously developed for observational studies of frailty. This adaptation altered the 'exposure' component of the was altered to award two points if a study used validated measure of frailty implemented according to its original description. One point was awarded if studies used an alternative measure of frailty (e.g. an adapted or non-validated measure of frailty) but the criteria were described in sufficient detail to allow the assessment to be replicated. This adaptation was to reflect the fact that there is no 'gold-standard' measure of frailty and that frailty is assessed using a diverse range of measures within the literature. The scale was applied to all studies (cross sectional or longitudinal), with only the first 5 elements of the scale being relevant to the cross-sectional studies. This approach was taken to allow an identical approach to quality assessment for prevalence estimates from cross sectional or (baseline of) longitudinal studies."

And the following text to the limitation section:
"We used an adapted version of the Newcastle-Ottawa scale (prespecified in our protocol) to maximise the comparability of assessment of cross-sectional and longitudinal studies (e.g., where both assessed prevalence). However, most studies identified and included were cross sectional, and this tool is not specific to the assessment of cross-sectional studies."

- Suggest providing more information on data analysis, e.g. statistical software used to create figures, the information you fed to the software, etc.

Author response: We have added the following sentences to the synthesis section of the methods: "Extracted data for each study were collected on .csv files."
"Prevalence estimates were plotted stratified by age-group of the sample and with reference to the frailty measure used for each estimate using the *ggplot2* package in R. Confidence intervals were calculated for each prevalence estimate using the point estimate and sample size."
"Harvest plots were generated using Microsoft Powerpoint."

- It is interesting that the authors have used harvest plots to present heterogeneous study findings. Was there any particular reason to annotate the bards of the harvest plots with sample size instead of using other characteristics, e.g. risk of bias assessment score?

Author response: We intended the harvest plot to provide a visual summary of these data without cluttering the image with too much data. We have now added a supplementary table with the data underlying the harvest plot including the effect estimates themselves

and the quality assessment scores for each study displayed.

- The method of identification of rheumatoid arthritis is not mentioned in the two included studies. I wonder whether the authors of this manuscript contacted the study authors for additional information.

Author response: We have gone back and evaluated these studies further. We were able to identify further detail on the respective cohorts from other publications which have allowed us to update Table 1 with this information.

- The following sentence is difficult to comprehend: “Most samples were recruited from rheumatology clinics, with most judged to be representative based on subsequent exclusion criteria and sampling methods.”.

Author response: Thank you for highlighting this. We have changed the sentence to the following to make it clearer: “We judged most of these to be representative of people with rheumatoid arthritis as most people with the condition will be managed within specialist outpatient clinics and the sampling techniques of these studies were generally inclusive without applying further, restrictive exclusion criteria.”

- Table 1: “NA” stands for what? Suggest mentioning it as a footnote.

Author response: These instances have now been removed from the table having clarified the method of RA definition in the two studies concerned.

- Suggest incorporating minimum recruitment age for each study in Table 1.

Author response: We have added this information.

- Suggest incorporating sample size into Figure 2.

Author response: Thank you, we have added the sample size to the study labels in this figure.

- “Few studies presented data on non-responders.": Suggest presenting relevant references along with this statement.

Author response: We have added references to this statement.

- “Taken together these data show a consistent relationship between frailty and disease activity, assessed by a diverse range of measures.”: I wonder about the accuracy of the above claim since the findings are mixed at the moment.

Author response: Thank you for highlighting this. We agree with the reviewer and have amended the sentence to the following: “Taken together these data show a consistent relationship between frailty and disease activity assessed using DAS28, however there was some inconsistency in this relationship when disease activity was assessed by different measures.”

- The authors have mentioned that they have provided the search strategy for different databases as a supplementary file in the PRISMA checklist. Unfortunately, I am not able to find it.

Author response: Thank you for highlighting. We have uploaded this with the revised

version to the supplementary information available on the Zenodo link at the end of the manuscript.

- “no data from upper-middle income of LMICs”: This phrase is not clear. Is it about “no data from upper-middle income countries of low-and middle-income countries” or “no data from low-and middle-income countries”?

Author response: We have edited to “no data from low- and middle-income countries”

Competing Interests: No competing interests were disclosed.