SYSTEMATIC REVIEW

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

Peter Hanlon¹, Holly Morrison¹, Fraser Morton², Bhautesh D Jani¹, Stefan Siebert², Jim Lewsey¹, David McAllister¹, Frances S Mair¹

¹Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
²Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK

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 the prevalence of frailty in people with rheumatoid arthritis, and the relationship between frailty and clinical outcomes.

Methods: We searched three electronic databases (January 2001 to April 2021) for observational studies assessing the prevalence of frailty in adults (≥18 years) with rheumatoid arthritis, or analysing the relationship between frailty and clinical outcomes in the context of rheumatoid arthritis. Titles, abstracts and full texts were assessed independently by two reviewers. Study quality was assessed using an adapted Newcastle-Ottawa Scale.

Results: We identified 17 analyses, from 14 different sample populations. 15/17 were cross-sectional. These 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 associated with higher disease activity (10/10 studies), lower physical function (7/7 studies), longer disease duration (2/5 studies), hospitalization (1/1 study) and osteoporotic fractures (1/1 study).

Conclusion: Our review found that frailty is common in adults with rheumatoid arthritis, including those aged <65 years, and is associated with a range of adverse features. However, these is substantial heterogeneity in how frailty is measured in rheumatoid arthritis. We found a lack of 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
Introduction
Rheumatoid arthritis is the most common chronic inflammatory arthropathy, the incidence of which increases with age. 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. Frailty has been highlighted as an emerging concept in our understanding of the impact of musculoskeletal disorders. Frailty is an age-related state of increased vulnerability leading to decompensation in response to physiological stress. While most studies have focused on people aged over 65 years, frailty is also prevalent and associated with adverse health outcomes in younger populations. Many measures exist to quantify frailty, of which the most widely used are the frailty phenotype (a physical measure assessed by grip strength, walking speed, exhaustion, weight loss, and low physical activity) and the frailty index (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, research on frailty in the context of inflammatory diseases in general, and rheumatoid arthritis in particular, is relatively recent. Frailty has been reported to be prevalent in people with rheumatoid arthritis, including relatively young individuals (i.e. <65 years). Others have explored associations between frailty and functional limitations in rheumatoid arthritis. 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 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) if frailty is associated with adverse health outcomes in the context of 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.

Eligibility criteria
Criteria for inclusion, defined according to PECOS (Population, Exposure, Comparator, Outcome, Setting and Study design) 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. We included studies in any setting (community, outpatient, or inpatient). Observational studies with cross-sectional or cohort designs

Table 1. Inclusion Criteria.

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

**Box 1. Search Strategy**

1. Exp Arthritis, Rheumatoid/
2. (fei$t adj2 syndrome).tw
3. (caplan$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$).tw
9. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumat$c or reummatic or reuma$t or reumat$ or revmarthrit$) adj3 (arthritis$ 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. 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), 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. We used a version of the Newcastle-Ottawa tool, previously adapted to assess observational studies of frailty, to quantify risk of bias (criteria shown in Box 2).

**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. 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. Findings related to other outcomes (characteristics of rheumatoid arthritis or clinical outcomes) were summarised using a Harvest plot\(^\text{[8,10]}\). Harvest plots can be used to display heterogeneous 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.

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). Eleven studies identified rheumatoid arthritis according to the 2010 ACR/EULAR criteria\(^\text{[11]}\), while others used either ‘clinician diagnosed’ rheumatoid arthritis (three studies), diagnostic codes from primary care records (one study) or did not specify (two studies). Mean age of the study samples ranged from 50.9 to 74.6 years. Only one study presented data on ethnicity\(^\text{[20]}\), and none commented on socioeconomic status.

The quality assessment of the included studies is summarised in Table 4. Most samples were recruited from rheumatology clinics, with most judged to be representative based on subsequent exclusion criteria and sampling methods. 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).

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 heterogeneous 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 associations between frailty and baseline measures of disease activity or physical function. These are discussed in greater detail below.

Rheumatoid arthritis disease activity. Ten studies, using seven different frailty measures and four different markers of rheumatoid arthritis disease activity (four using Disease Activity...
Figure 1. PRISMA diagram of study selection.
Table 2. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Setting</th>
<th>Frailty measure</th>
<th>Rheumatoid arthritis definition</th>
<th>Total n</th>
<th>Age, years – mean (sd)</th>
<th>N (%) women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews 2017, Andrews 2019</td>
<td>USA</td>
<td>Outpatient</td>
<td>Frailty phenotype</td>
<td>ACR</td>
<td>124</td>
<td>58 (10.8)</td>
<td>59 (47.6%)</td>
</tr>
<tr>
<td>Bak 2020</td>
<td>Poland</td>
<td>Inpatient</td>
<td>Tilburg frailty indicator</td>
<td>ACR/EULAR 2010</td>
<td>106</td>
<td>65.8 (5)</td>
<td>82 (77.4%)</td>
</tr>
<tr>
<td>Chang 2010</td>
<td>USA</td>
<td>Community</td>
<td>Frailty phenotype</td>
<td>NA</td>
<td>11</td>
<td>74.1 (2.8)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Haider 2019</td>
<td>Austria</td>
<td>Outpatient</td>
<td>SHARE-FI</td>
<td>ACR/EULAR 2010</td>
<td>100</td>
<td>50.9 (9.7)</td>
<td>66 (66%)</td>
</tr>
<tr>
<td>Hippisley-Cox 2017</td>
<td>UK</td>
<td>Community</td>
<td>Qfrailty</td>
<td>Primary Care clinical coding</td>
<td>10312</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kojima 2020</td>
<td>Japan</td>
<td>Outpatient</td>
<td>Kihon checklist</td>
<td>ACR 2010</td>
<td>375</td>
<td>65.2 (9.7)</td>
<td>323 (86.1%)</td>
</tr>
<tr>
<td>Li 2019</td>
<td>Canada</td>
<td>Outpatient (registry)</td>
<td>Frailty index</td>
<td>“Active RA”</td>
<td>2923</td>
<td>57.7 (12.7)</td>
<td>2290 (78.3%)</td>
</tr>
<tr>
<td>Minamino 2021</td>
<td>Japan</td>
<td>Outpatient</td>
<td>Study of Osteoporotic Fracture frailty indicator</td>
<td>NA</td>
<td>306</td>
<td>63.5</td>
<td>306 (100%)</td>
</tr>
<tr>
<td>Oetsma 2020</td>
<td>Netherlands</td>
<td>Outpatient</td>
<td>Groningen frailty indicator, Geriatric 8</td>
<td>Rheumatologist diagnosed RA</td>
<td>80</td>
<td>74.6 (5.9)</td>
<td>53 (66.2%)</td>
</tr>
<tr>
<td>Salaffi 2019</td>
<td>Italy</td>
<td>Outpatient</td>
<td>SHARE-FI</td>
<td>ACR/EULAR</td>
<td>210</td>
<td>60.4 (13.5)</td>
<td>138 (65.7%)</td>
</tr>
<tr>
<td>Salaffi 2020</td>
<td>Italy</td>
<td>Outpatient</td>
<td>Comprehensive Rheumatologic Assessment of Frailty</td>
<td>ACR/EULAR</td>
<td>219</td>
<td>60.4 (13.5)</td>
<td>138 (63%)</td>
</tr>
<tr>
<td>Tada 2019, Tada 2021</td>
<td>Japan</td>
<td>Outpatient</td>
<td>Kihon checklist</td>
<td>ACR/EULAR</td>
<td>95</td>
<td>68 (5.5)</td>
<td>78 (82.1%)</td>
</tr>
<tr>
<td>Wysham 2020</td>
<td>USA</td>
<td>Outpatient</td>
<td>Frailty phenotype</td>
<td>Rheumatologist diagnosed RA</td>
<td>138</td>
<td>58 (10.8)</td>
<td>117 (84.8%)</td>
</tr>
<tr>
<td>Yoshii 2019</td>
<td>Japan</td>
<td>Outpatient</td>
<td>Frailty phenotype</td>
<td>ACR/EULAR</td>
<td>441</td>
<td>64.5 (13.5)</td>
<td>337 (76.4%)</td>
</tr>
<tr>
<td>Yoshii 2020</td>
<td>Japan</td>
<td>Outpatient</td>
<td>5-item frailty score</td>
<td>ACR/EULAR</td>
<td>739</td>
<td>71.3</td>
<td>-</td>
</tr>
</tbody>
</table>

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


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. One study, using CDAI, found that this relationship was no longer evident after adjusting for age. 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))10,27.

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 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 group10. 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-up10.

Taken together these data show a consistent relationship between frailty and disease activity, assessed by a diverse...
<table>
<thead>
<tr>
<th>Frailty measure</th>
<th>Components</th>
<th>Range and categorisation</th>
<th>Outcomes reported in included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty phenotype</td>
<td>5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)</td>
<td>1-2 criteria: Pre-frail ≥ 3 criteria: Frail</td>
<td>Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI</td>
</tr>
<tr>
<td>Kihon checklist</td>
<td>Self-administered checklist (components: activities of daily living, exercise, falling, nutrition, oral health, cognition, depression)</td>
<td>Unweighted sum of components.</td>
<td>Frailty prevalence, Duration of rheumatoid arthritis, Disease activity, HAQ-DI</td>
</tr>
<tr>
<td>Survey for Health, Aging and Retirement in Europe Frailty Instrument (SHARE-FI)</td>
<td>5 components (unintentional weight loss, exhaustion, low grip strength, slow walking pace, low physical activity)</td>
<td>Weighted score calculated and then categorised into robust, pre-frail, frail.</td>
<td>Frailty prevalence, Disease activity, HAQ-DI</td>
</tr>
<tr>
<td>Frailty index</td>
<td>Count of health-related deficits (≥ 30, type and number of chosen deficits may vary between studies)</td>
<td>Range 0-1, sometimes categorised (threshold for frailty varies (e.g. 0.2, 0.24))</td>
<td>Hospitalisation, Fractures</td>
</tr>
<tr>
<td>Comprehensive Geriatric Assessment of Frailty (CRAF)</td>
<td>10 domains identified as relevant to the assessment of frailty in the context of a rheumatological condition.</td>
<td>Conceptually similar to the frailty index, cumulative deficit model (but with fewer deficits than the frailty index).</td>
<td>Frailty prevalence, Disease activity, HAQ-DI</td>
</tr>
<tr>
<td>5-item frailty risk score</td>
<td>15 questions across 3 domains (physical, psychological and social)</td>
<td>Range 0-15, &lt; 14 indicates frail</td>
<td>Frailty prevalence</td>
</tr>
<tr>
<td>Tilburg frailty indicator</td>
<td>8 domains scored and summed (nutritional status, weight loss, body mass index, motor skills, psychological, number of medications, self-rated health, age)</td>
<td>Range 0-17, &lt; 14 indicates frail</td>
<td>Frailty prevalence</td>
</tr>
<tr>
<td>Groningen frailty indicator</td>
<td>15 items across 4 domains (physical, cognitive, social and psychological)</td>
<td>Range 0-15, &lt; 14 indicates frail</td>
<td>Frailty prevalence</td>
</tr>
<tr>
<td>Study of Osteoporotic Fracture Frailty indicator</td>
<td>3 components (weight loss, chair stand, exhaustion)</td>
<td>Range 0-15, &lt; 14 indicates frail</td>
<td>Frailty prevalence</td>
</tr>
<tr>
<td>QFrailty</td>
<td>Algorithm based on electronic medical records (e.g. Mortality score) and hospital admission (QAdmission score)</td>
<td>Categorised as mild, moderate and severe frailty</td>
<td>Frailty prevalence</td>
</tr>
</tbody>
</table>

Table 3. Frailty measures used in included studies.

Table adapted from Hanlon et al. [2020].
Table 4. Quality assessment of included studies (based on adapted Newcastle Ottawa Scale).

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Representative</th>
<th>Selection of non frail comparison</th>
<th>Ascertainment of exposure frailty</th>
<th>Non respondents</th>
<th>Outcome not present at start</th>
<th>Controls for age and sex</th>
<th>Controls for other factors</th>
<th>Outcome assessment</th>
<th>Length of follow up</th>
<th>Adequacy of follow up</th>
<th>Cross-sectional score</th>
<th>Longitudinal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews 2017, Andrews 2019</td>
<td>1 1 2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4/5</td>
<td>10/11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bak 2020</td>
<td>0 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang 2019</td>
<td>1 1 1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haider 2019</td>
<td>1 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippisley-Cox 2017</td>
<td>1 1 1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kojima 2020</td>
<td>0 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2019</td>
<td>1 1 2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4/5</td>
<td>10/11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minamino 2021</td>
<td>1 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oetsma 2020</td>
<td>1 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salaffi 2019</td>
<td>1 1 2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salaffi 2020</td>
<td>1 1 1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tada 2019, Tada 2021</td>
<td>1 1 2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wysham 2020</td>
<td>1 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshii 2019</td>
<td>1 1 2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshii 2020</td>
<td>1 1 1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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 more likely to experience deterioration in physical function than robust participants. 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. Findings were mixed, with three studies showing no association between frailty and disease duration. By contrast, two studies showed that frailty was associated with greater duration of rheumatoid arthritis at the time of assessment, however only one of these studies additionally adjusted for age in the analysis.

**Other outcomes.** One study, using the frailty index approach to quantifying frailty in 2923 participants, assessed the relationship between frailty and all-cause hospitalisations.
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. 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. 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. 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. 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. 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. 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. 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 along-side 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, and the prevalence of multimorbidity among people with rheumatoid arthritis, it is important to better understand the whether incorporating frailty assessment into the management of rheumatoid arthritis would be 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’.

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. 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 upper-middle income of LMICs. 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 upper-middle-income countries or LMICs 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

**Reporting guidelines**

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Author contributions**
Peter Hanlon: Conceptualisation, Investigation, Methodology, Visualisation, Writing – Original Draft Preparation, 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**

Open Peer Review

Current Peer Review Status: ️

Version 1

Reviewer Report 08 November 2021

https://doi.org/10.21956/wellcomeopenres.19016.r46327

© 2021 Siriwardhana D. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 bars 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.