Prevalence of frailty and pre-frailty in patients with rheumatoid arthritis: a systematic literature review and meta-analysis

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Abstract

Objective

Frailty is a common geriatric syndrome and is characterised by a decreased physiological reserve and increased vulnerability to stressors. Pre-frailty is a risk-state before frailty. A systematic literature review (SLR) and meta-analysis was conducted to: (1) estimate the prevalence of (pre-)frailty in RA patients; (2) explore whether variation in instruments influences (pre-)frailty prevalence.

Methods

An SLR for the period 2001-2021 was undertaken. All studies (including conference abstracts) that reported on the prevalence of (pre)-frailty in patients with RA were included. Assessment of risk of bias, data extraction and data synthesis were performed by two reviewers independently. A meta-analysis was conducted for studies that used the most commonly accepted frailty instrument (Fried criteria), by obtaining pooled estimates of (pre-) frailty prevalences by random effects models.

Results

25/1,363 studies were included in the SLR. Weighted average age was 58.0 years. Pre-frailty prevalence rates ranged between 20.4%-71% (median: 35.8%); for frailty, rates between 1.2%–75.1% (median: 23.1%) were found. The meta-analysis (Fried criteria), showed a pooled prevalence of 52.8% (95%-CI=42.7–62.8; I^2=99%) for pre-frailty and 24.0% (95%-CI= 19.4–28.6; I^2=96%) for frailty. (Pre-)frailty was highly prevalent in all age groups. Prevalence was generally higher when the frailty instrument also included psychological and social domains, as compared to instruments that solely focused on the physical domain.

Conclusion

(Pre-)frailty is common in RA patients. Large part of the variation is explained by clinical and methodological heterogeneity. High-quality studies with validated frailty instruments specifically for RA patients are needed.

Key words

rheumatoid arthritis, prevalence study, adult, frail, older

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Introduction

The concept of frailty is gaining increasing attention as the population of older persons is rising globally. Frailty is a geriatric syndrome that is characterised by a decreased reserve and function across multiple physiological systems, which may ultimately lead to increased vulnerability to stressors (1). There is no agreed upon definition and measurement approach for identifying older persons as frail. Most commonly, the criteria set of Fried et al. is used to define a frail person. The five items included in this criteria set are: poor hand grip strength, unintentional weight loss, self-reported exhaustion, low physical activity and slow walking pace (2). When at least three of these five criteria are present, the person is classified as being frail. Pre-frailty is defined as the presence of one or two Fried criteria (2). Another commonly used instrument is the Frailty Index (FI) of Rockwood and Mitnitski, which is based on scoring and counting common age-related deficits, such as mobility impairment, aphasia and difficulty with cooking (3). The FI score ranges from 0–1. Cut-off points have not been clearly defined, but a FI ≥0.25 is generally considered as the cut-off for frailty (4).

Frailty is an important independent risk factor for a wide array of negative outcomes such as loneliness, progressive disability, nursing home admission and mortality (1). In addition, frailty often goes hand in hand with other geriatric syndromes such as sarcopenia, delirium and falls. The pooled prevalence of frailty was 11% in a systematic review based on 21 cohorts involving 61.500 older community-dwelling adults. The prevalence however highly varied across studies included in this review (range 4–59%) (5). It seems that in persons with rheumatoid arthritis (RA), frailty is generally more prevalent than in persons without RA. In a study by our group, about half of 80 patients with RA and 65 years or older who visited our outpatient clinic, were classified as frail on the Groningen Frailty Indicator (GFI), another commonly used frailty measurement instrument (6). Measurement of 'true' frailty in RA patients, however, is complicated, since several frailty characteristics are also part of the RA disease symptomatology, for instance lower grip strength and slower walking speed due to sarcopenia (7). Until now, no systematic literature review (SLR) is available to establish the prevalence of (pre-)frailty in patients with RA. More information about frailty in RA is important, as frailty is potentially reversible and patient-centred interventions might preserve or improve independence, functional and cognitive status of an individual (7).

The overall objective of this SLR and meta-analysis is therefore to examine the prevalence of (pre-)frailty in patients with RA. In addition, we aimed to identify what frailty measurement instruments were used by studies, characterise them according to their components and assess how the different instruments may influence (pre-)frailty prevalence.

Materials and methods

Systematic review protocol

The SLR was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations (8). The SLR protocol is registered in PROSPERO (Prospero Record Registration no.: CRD42021242139). The primary research question was: "What is the prevalence of (pre-)frailty, as defined by an explicit definition / frailty criteria / expert opinion, in patients with rheumatoid arthritis?

Search strategy

We searched PubMed, Embase (embase.com), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Epistemonikos from 2001 to 8 June 2021 and updated our search on 1 November 2021. This time frame was chosen in order to focus on studies where the concept of frailty was more clearly defined. Hand-searching and checking reference lists from selected studies were also performed. Letters to the editor, case reports, reviews and editorials were excluded.

Study selection

All studies (including conference abstracts) that reported on the prevalence

of (pre)-frailty in patients with RA were included. Two authors (SG and SM) independently assessed eligibility of the studies. Studies were excluded if they were published in a language other than English, French, German, Dutch or Spanish. Studies were also excluded when they included patients younger than 18 years, did not provide a clear operational definition of frailty or when frailty was only assessed with a single symptom (*e.g.* weight loss). The reason for exclusion of ineligible studies was recorded. Disagreements between the first two assessors were resolved through consensus or involvement of an adjudicator (MO). A PRISMA flow diagram of the literature screening process was developed.

Data extraction

Data were extracted on study characteristics including author, year of publication, country, setting (*e.g.* primary care, outpatient clinic), study design, method of data collection, population type, number of persons included, mean age of the sample, proportion of females, RA disease duration and disease characteristics (*e.g.* mean Disease Activity Score of 28-joints (DAS28) and mean Health Assessment Questionnaire (HAQ)), number of comorbidities, polypharmacy, used frailty instruments and prevalence of frailty or mean frailty score. Authors involved in data extraction (SG and SM) independently extracted data from all the included articles and discussed their findings to ensure consistency.

Risk of bias

The quality of the included original studies was assessed by the Newcastle Ottawa Scale (NOS) adapted for cross-sectional studies (9). Two authors (SG and SM) independently rated each study and disagreements were resolved through consensus or involvement of an adjudicator (MO). The NOS consists of 3 items with 7 subscales, and the total maximum score is 10 (9). Cut-off points are not clearly defined, but based on previous studies, the following cut-off points were used: >7 was considered low risk, 5–7 moderate risk and <5 high risk of bias (9).

Data synthesis

First, all included studies were qualitatively assessed. As there is constant debate about how to measure frailty, each instrument used to assess frailty in the primary studies was further characterised. This was done to understand whether variation in frailty prevalence between the studies might (in part) be explained by the study methodology (such as choice of measurement instrument) or patient characteristics.

Next, a meta-analysis (using RevMan 5, Cochrane Library) was performed for prevalence studies that used (a modified version of) the Fried criteria. The pooled prevalence estimates of frailty were obtained through random effect models. Heterogeneity within the pooled studies was assessed through the I^2 statistics (significant if ≥50%).

Results

The database search yielded 1,363 non-duplicated records (search strategy shown in the online Supplementary file: Supplementary data). After screening the titles and abstracts, 61 studies remained for full paper review. Five records were included after handsearching and checking reference lists, including 4 studies that were published in the period 9 June 2021 to 1 November 2021. After full-text reading, 21 fully published studies and 4 conference abstracts were retained (Suppl. Fig. S1 and Table I) (6, 10-33).

General description of studies

Of the 25 studies included, 12 were performed in Europe, 6 in Japan, 5 in North America, 1 in India and 1 in Brazil (Table I). All included studies were published in 2016 or later.

The number of participants per study ranged from 80 to 50,744. The mean age varied between 50.8±12.4 and 74.6±5.9 years; weighted average age was 58.0 years (information on mean age available in 23 studies). In all 25 studies, predominantly female participants were included (between 65.3% and 100%) (Table I).

Twenty-four studies were cross-sectional observational studies in an outor inpatient setting [n=18 (6, 10-13, 16, 19, 22-31, 33)] or derived cross-sectional data from established RA cohorts or population-based registries [n=6 (14, 15, 18, 20, 21, 32)]. The remaining study calculated frailty on baseline data from eight industry-sponsored clinical trials (17).

Twelve different frailty instruments were used (Suppl. Table S1). All instruments were questionnaires or checklists (*e.g.* FI). The most often applied instruments were (modified versions of) the Fried criteria (nine studies, Table I) (10, 12, 14, 15, 27, 28, 31-33). Twelve studies also reported on the prevalence of pre-frailty (10, 14-16, 22, 24, 27-30, 32, 33). In four studies, frailty was subdivided in several categories, from mild to severe frailty. These four studies did not assess pre-frailty (18, 25, 26, 30).

Prevalence of (pre-)frailty in persons with rheumatoid arthritis

The overall pre-frailty prevalence ranged between studies from 20.4% (30) to 71% (10). For frailty, prevalence rates between 1.2% (21) and 75.1% were found (18).

Two cross-sectional analyses of cohort studies also included a control population (14, 23). In the study of Cook *et al.*, the frailty prevalence according to a modified version of the Fried criteria in population controls was 3.4%, in patients with osteoarthritis 10.0% and in patients with RA 18.6% (14). In the study of Ozeki *et al.*, frailty prevalence was 37.6% in RA patients and 15.7% in controls (23).

Three studies defined frailty according to the FI (14, 17, 20). In these studies, the mean FI ranged from 0.18–0.22 (no cut-off applied; no prevalence available).

Variation in (pre-)frailty prevalence and study methodology

In general, studies that found high (>50%) prevalence rates of frailty (53.1–75.1%), used an instrument that distinguished several frailty levels (mild to severe frailty) and did not include the pre-frailty stage [18, 25, 26, 30]. One study that used a modified version of the Fried criteria, found a relatively high frailty prevalence of 72.8% (27). In this Brazilian study

Table I. Characteristics included studies.

Author, publication year	Country, N, study design and setting	Mean age ± SD / range (years)	Women (%)	Population	RA disease duration ± SD / range (years)	Frailty instrument used	Prevalence of (pre-) frailty or frailty score	Comorbidity, polypharmacy, risks and other results
Andrews, 2019 (10)	USA, 124, cross-sectional observational study, random sample RA patients	58.0 ± 10.8	87	RA patients (2010 ACR/EULAR criteria), >18 years	19.1 ± 10.7	Fried criteria (modified)	Robust: 19% Pre-frail: 71% Frail: 10%	
Bąk, 2020 (11)	Poland, 106, cross-sectional observational study, hospitalised RA patients	65.8 ± 5.0	77.4	RA patients (2010 ACR/EULAR criteria), >60 years	11.9	Tilburg Frailty Indicator	Robust: 65.1% Frail: 34.9%	Charlson Comorbidity Index: 2.1 ± 1.0.
Barile, 2016 (12)	Mexico, 500, cross-sectional observational study, tertiary RA outpatient clinic	51.3 (range 21-90)	90.6	RA patients (2010 ACR/EULAR criteria), >18 years	13.2 (range 11 months –53)	Cardiovascular Health Study frailty index (modified version Fried criteria)	Frail 23.4%	Polypharmacy (≥5 medications): 69.6%.
Cleutjens, 2021 (13)	The Netherlands, 90, cross-sectional observational study, RA outpatient clinics of two hospitals	69.7 ±7.9	66.7	RA patients (rheumatologist diagnosed), >55 years, divided in 3 groups (55-64; 65-74; ≥75)	9.0 (IQR 4.0–20.5)	Groningen Frailty Indicator	Overall prevalence frailty: 42.2% 43.3% aged 55-64, 40.0% aged 65-74, 43.3% aged ≥75	
Cook, 2021 (14)	UK, 4,894, population-based prospective cohort, cross-sectional data derived from UK biobank	59.2 ± 7.1	69.2	RA patients aged 40-69 years.		Frailty index and Fried criteria (modified)	Frailty Index: 0.18 Fried criteria: Robust: 28.7% Pre-frail: 52.7% Frail: 18.6%	Hypertension 35.8%, coronary heart disease 8.0%, DM 7.7%, cerebrovascular disease 3.0%, COPD 4.6%, depression 6.9%)
Furuya, 2021	Japan, 3,290, cross-sectional, observational monocenter IORRA cohort	65.1	86.7	RA patients (rheumatologist diagnosed)	15.0	Frailty screening index (modified version Fried criteria)	Robust: 20.6% Pre-frail: 62.7 % Frail: 16.7%	DAS28 correlated with frailty (OR 1.3 per 1 point increase in DAS28), J-HAQ correlated with frailty (OR 1.3 per 1 point)
Haider, 2019 (16)	Austria, 100, cross-sectional monocenter cohort, outpatient clinic	50.9 ± 9.7	66.0	RA patients (rheumatologist diagnosed) aged 18–65 years	6.0 (IQR 3.0–11.8)	SHARE-FI	Robust: 55% Pre-frail: 30% Frail: 15%	(Pre-)frail participants had higher median CDAI *scores vs*. robust participants (4.0 (IQR: 0–10) *vs*. 11 (IQR: 6–18)).
Hanlon, 2020 (17)	UK, 6100, 8 clinical trials, industry sponsored pharmaceutical trials	50.8 ± 12.4	79.4	7 trials: RA patients aged ≥18 years. 1 trial: 18–75 years		Frailty index	Mean Frailty index: 0.22	
Hippisley, 2017 (18)	UK, two prospective open cohorts including 40,940 RA patients in total, routine collected data, derived from 1436 general practices	NA	NA	RA patients (GP diagnosis)		Qfrailty categories	Robust: 24.9% Mild frailty: 52.8% Moderate frailty: 15.7% Severe frailty: 6.6%	
Kojima, 2020 (19)	Japan, 375, cross-sectional observational prospective study, outpatient clinic of a University Hospital	65.2 ± 9.7	86.1	RA patients (2010 ACR/EULAR criteria), aged 40–79 years	16.6 (11.9)	Kihon Checklist	Overall prevalence frailty: 26.1% 18.5% aged 40–64, 28.8% aged 65–74, 36.6% aged ≥75 .	HAQ-DI ≥0.5 (OR 5.4 for frailty) and DAS-28 ≥2.6 (OR 2.3 for frailty) 76.3% ≥1 comorbidity
Li, 2019 (20)	Canada, 2,923, cross-sectional, participants recruited from clinical OBRI registry	57.7 ± 12.7	78	RA patients (rheumatologist diagnosed)		Frailty index	Mean FI 0.20	
Lieber, 2019 (21) Abstract	USA, 50,744, cross-sectional study, medicare beneficiaries		78.4	RA patients (ICD-9-CM code) aged <65		Frailty scale	1.2% frail	
Minamino, 2021 (22)	Japan, 306, cross-sectional monocenter study, KURAMA cohort, University Hospital	63.5 (IQR 53-71)	100	Female RA patients aged >18 years	9.0 (3-21)	Study of Osteoporotic fracture (SOF) criteria	Robust: 44.1% Pre-frail: 32.7% Frail: 23.2%	Higher DAS28-ESR associated with higher levels of pre-frailty / pre-frailty
Oetsma, 2020 (6)	The Netherlands, 80, cross-sectional study, 1 academic and 1 non-academic hospital outpatient clinic	74.6 ± 5.9	66	RA patients (rheumatologist diagnosed), ≥65 years	16.4	Groningen Frailty Indicator (GFI) and Geriatric 8 (G8)	GFI: 54% frail G8: 55% frail Combined: 41% frail	RDCI: 2.8 (1.6) HAQ-DI: moderate strength correlation coefficient with G8 (r=0.56) or GFI (r=0.54) DAS-28-ESR: weak strength correlation coefficient with G8 (r=0.36) or GFI (r=0.24)

Author, publication year	Country, N, study design and setting	Mean age ± SD / range (years)	Women (%)	Population	RA disease duration ± SD / range (years)	Frailty instrument used	Prevalence of (pre-) frailty or frailty score	Comorbidity, polypharmacy, risks and other results
Ozeki, 2021 (23)	Japan, 210, prospective observational cross-sectional study, outpatient clinic, 2 University Hospitals	71.8 ± 3.7	82.4	RA patients (2010 ACR/EULAR criteria), aged 65–79 years	14.3 (IQR 7.5–27.7)	Kihon Checklist	Frail: 37.6%	Higher levels of DAS28 and HAQ-DI are associated with presence of frailty
Salaffi, 2019 (24)	Italy, 210, cross-sectional study, outpatient clinic, University Hospital	60.4 ± 13.5	65.7	Adult-onset RA (2010 ACR/EULAR criteria	7.5 ± 2.7	SHARE-FI	Robust: 51% Pre-frail: 32.4% Frail: 16.6%	SDAI robust: 24.4 SDAI pre-frail: 32.9 SDAI frail: 40.6 HAQ-DI robust: 1.1 HAQ-DI pre-frail: 1.3 HAQ-DI frail: 1.41 48.1% participants ≥1 comorbidity.
Salaffi, 2020 (25)	Italy, 219, cross-sectional study, outpatient clinic, University Hospital	58.5 ± 13.3	76.3	Adult-onset RA patients (2010 ACR/EULAR criteria)	7.4 ±2.8	CRAF, SHARE-FI	CRAF: Robust: 36.1% Mild frailty: 28.8% Moderate frailty: 15.5% Severe frailty: 19.6% SHARE-FI 2.03	Mean number of medications 5.8 ±3.3 Frail patients had higher SDAI and HAQ-DI scores
Salaffi, 2021 (26)	Italy, 214, cross-sectional observational study, outpatient clinic, University Hospital	60.3 ± 12.7	75.7	Adult RA patients requiring a bDMARD (2010 ACR/EULAR criteria),	7.3 ± 2.6	CRAF	Robust: 39.3% Mild frailty: 26.6% Moderate frailty: 6.5% Severe frailty: 27.6%	Comorbidity: RDCI 1.9 ± 2.0. 67.8% ≥1 comorbidity Polypharmacy: 57% 5–8 medications, 13.1% ≥10 medications
Santo, 2018 (27) Abstract	Brazil, 81, cross-sectional, University Hospital	56.8 ±7.3	88.9	RA patients (2010 ACR/EULAR criteria), aged 40–70 years	11.9 ± 9.6	Fried criteria (modified)	Robust: 3.7% Pre-frail: 23.5% Frail: 72.8%	DAS28 and HAQ higher in frail patients
Sundaram, 2020 (28) Abstract	India, 235, cross-sectional, outpatient clinic	53.8 ± 8.9	84.3	RA patients aged >40 years	>1 year	Fried criteria	Robust: 14.9%, Pre-frail: 61.7% Frail: 23.4%	The frailty phenotype correlated moderately with DAS28-ESR (r=0.48), HAQ (r=0.77)
Tada, 2019 (29)	Japan, 95, prospective observational cross-sectional study, outpatient clinic, general hospital	68.0	78	RA patients ≥20 years (2010 ACR/EULAR criteria	5.5	Kihon checklist	Robust: 42.2% Pre-frail: 38.9% Frail: 18.9%	Frail patients had higher DAS28-ESR (robust: 2.8 ± 1.0, frail: 3.6 ± 1.0) and mHAQ (robust: 0.1±0.1, frail: 0.9±0.7) scores
Tanski, 2021 (30)	Poland, 98, cross-sectional observational study, hospitalised RA patients	72.6 ± 6.5	65.3	RA patients (ARA criteria) >60 years, MMSE ≥23		Edmonton Frail Scale	Robust: 46.9% Pre-frail: 20.4% Mild frailty: 18.4% Moderate frailty 13.3%, Severe frailty 1.0%	Malnutrition 6.1%
Trujillo, 2017 (31) Abstract	Spain, 231, cross-sectional observational study, outpatient clinic, University Hospital	55.4	83.2	RA patients (2010 ACR/EULAR criteria)	11.4	Fried criteria	Frail: 21.5%	Polypharmacy (≥5 medications): 64.7%
Wysham, 2020 (32)	USA, 138, cross-sectional study, observational cohort	58 ± 10.8	84.8	RA patients (2010 ACR/EULAR criteria) >18 years	19 ± 10.9	Fried criteria (modified)	Robust: 20% Pre-frail: 70% Frail: 10%	
Yoshii, 2020 (33)	Japan, 739, cross-sectional study, several outpatient clinics	71.3	79.3	RA patients (2010 ACR/EULAR criteria) >40 years	10.6	Fried criteria (modified)	Robust: 42.6% Pre-frail: 27.5% Frail: 29.9%	Mean number comorbidities 3.1 Higher levels of HAQ-DI associated with presence of frailty

RA: rheumatoid arthritis; NOS: Newcastle-Ottawa Scale; ACR: American College Of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; IQR: interquartile range; DM: Diabetes Mellitus; COPD: chronic obstructive pulmonary disease; DAS28: Disease Activity Score of 28 joints; J-HAQ: Japanese version of Health Assessment Questionnaire; OR: odds ratio; SHARE-FI: Survey of Health, Ageing and Retirement in Europe Frailty Instrument; CDAI: Clinical Disease Activity Index; FI: Frailty Index; HAQ-DI: Health Assessment Questionnaire Disability Index; ESR: erythrocyte sedimentation rate; RDCI: Rheumatic Disease Comorbidity Index; GFI: Groningen Frailty Indicator; G8: Geriatric 8; SDAI: Simple Disease Activity Index; CRAF: Comprehensive Rheumatologic Assessment of Frailty; bDMARD: biological disease-modifying anti-rheumatic drug; ARA: American Rheumatism Association; MMSE: Mini-Mental State Evaluation.

with 81 participants (mean age 56.8 ±7.3 years), all criteria to define frailty corresponded to the original Fried criteria, but the criteria were self-reported instead of physician assessed and grip strength and walking speed were not adjusted for gender, BMI and height in the final score. Overall, the mean prevalence of (pre-)frailty did not seem to increase with age.

Studies that used a frailty instrument that also included psychological and social domains (for example: GFI), found in general higher prevalence rates compared to studies that solely re-

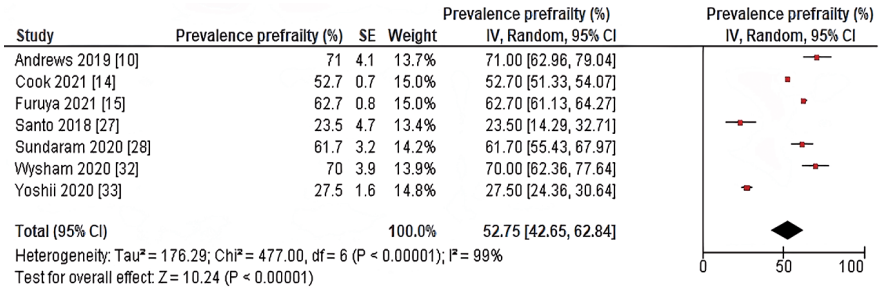

Fig. 1. Prevalence of pre-frailty in patients with rheumatoid arthritis.

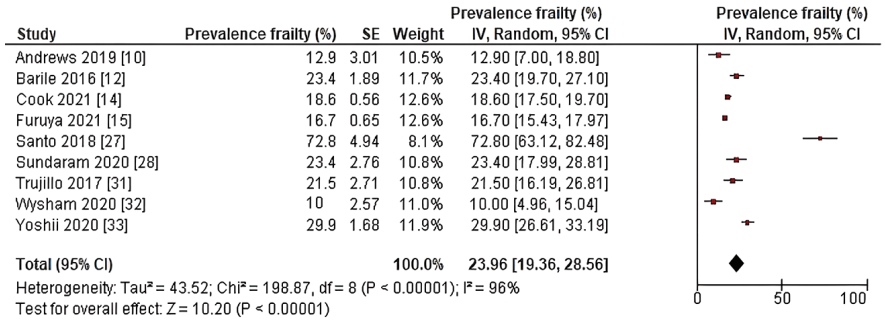

Fig. 2. Prevalence of frailty in patients with rheumatoid arthritis.

lied on the physical domain (for example: Fried criteria). The study with the lowest prevalence rate (1.2%), was an administrative claims database study, assessing frailty with a 12-item scale addressing domains such as nutrition and functioning (≥2 cut-off for frailty) in patients <65 years (21).

Association between disease activity measures, HAQ and prevalence of (pre-)frailty

All nine studies that examined the relation between disease activity measures (for example DAS28) and the prevalence of (pre-)frailty concluded that (pre-)frail participants had on average higher disease activity levels (15, 16, 19, 22-25, 27, 29). Two studies found a low (6) or moderate (28) correlation between the frailty scores and DAS28. All eight studies that examined the relation between the HAQ and prevalence of (pre-)frailty found that HAQ scores were on average higher in (pre-)frail participants (15, 19, 23-25, 27, 29, 33).

Meta-analysis

The meta-analysis showed that, the pooled prevalence of pre-frailty was of 52.8% (95%-CI=42.7–62.8; I^2=99%; weighted average age 61.0 years), in 7 studies who used (modified versions of) the Fried criteria (Fig. 1) [10, 14, 15, 27, 28, 32, 33]. The pooled prevalence of frailty in 9 studies was 24.0% (95%-CI=19.4–28.6; I^2=96%; weighted average age 61.3 years) (Fig. 2) [10, 12, 14, 15, 27, 28, 31-33].

Assessment of bias

The NOS scores for the 21 fully published studies are shown in Supplementary Table S2. Nineteen studies had a moderate risk of bias; two studies had a high risk of bias. In all studies, the sample size was not justified and/or satisfactory. Except for one study with a moderate risk of bias (19), no other study described the characteristics of the RA patients who were excluded from participation or who refused participation.

Discussion

In this SLR, prevalence rates of pre-frailty in patients with RA ranged between 20.4% and 71% and for frailty between 1.2% and 75.1%. The meta-analysis of studies that used (a modified version of) the Fried criteria, showed a pooled prevalence of 52.8% (95%-CI=42.7– 62.8) for pre-frailty. It was 24.0% (95%-CI=19.4–28.6) for frailty. Clinical and methodological heterogeneity contributed to the large range in (pre-)frailty prevalence.

Our results are in line with frailty prevalence studies for other chronic diseases, such as Chronic Obstructive Pulmonary Disease (COPD), cerebrovascular disease and heart failure (34-36). As an example, in patients with COPD, the pooled prevalence of pre-frailty was 56% (95%-CI, 52–60%) and 19% (95%-CI, 14–24%) for frailty (34). This finding suggests that frailty is strongly linked, although not synonymous with, co-existing chronic diseases such as RA. Frailty should therefore be seen as a separate clinical entity worthy of identification, as frailty might require adaptations in management and is possibly reversible (37).

In the 25 studies that were included in our SLR, twelve different frailty instruments were used. To date, there is still no consensus on a single definition of frailty for clinical use and more than 60 frailty instruments have been described in the literature (38). These instruments measure different aspects of the 'construct' frailty, which may in part explain the large heterogeneity between studies found in our SLR. In a study by Aguayo *et al*., it was concluded that only 10.4% of the possible 595 paired comparisons among 35 frailty instruments resulted in better than 'fair' agreement by kappa statistics (39). In addition, several studies in our SLR used modified versions of the Fried criteria, since for instance grip strength is likely to be affected by RA disease activity and damage. These modified versions are however not validated in the RA population and should therefore be used with caution. The only frailty instrument that is developed specifically in RA patients, is the Comprehensive Rheumatologic Assessment of Frailty (CRAF) (25). Although the CRAF demonstrated robust validity and good discriminant accuracy in the developmental phase, validation of the CRAF in other RA populations is needed (25).

In total, about 40% of the studies evaluated the association between frailty, disease activity measures and/or HAQ. All studies concluded that disease activity levels and HAQ scores were higher in frail patients. This finding therefore points to the difficulty of outcome assessment in older patients, as the result of these disease-specific instruments

might be distorted by the presence of frailty or patients might seem frail due to high levels of disease activity (40).

Importantly, about half of the studies in our SLR, included patients with a long RA disease duration. Data about presence of (pre-)frailty in early in the RA disease course and longitudinal data are currently scarce or not available. Such information is however important, as there is current consensus that frailty is potentially reversible with appropriate nutritional, physical and cognitive interventions (1) Immediate tight control of RA disease activity might also be a window of opportunity to prevent the development of frailty later on (41).

Some limitations of the present study should be addressed. First, we applied a language restriction, language bias can therefore not be excluded. Second, the majority of studies came from Europe and North America; geographical bias could have occurred. This is important, as socio-economic inequality is also responsible for part of the variation in frailty prevalence. In a study by Hoogendijk *et al*., income gradients for frailty among older persons were found over a 10-year follow-up period (lowest income group OR 1.8 (95%-CI 1.1–3.0) for development frailty *versus* highest income group) (42). Third, only a few studies were representative of the RA population as a whole, since many studies applied age restrictions. This may hamper the generalisation of the results, as frailty can occur in all age groups.

In conclusion, this SLR with meta-analysis summarised the prevalence of (pre)-frailty in patients with RA. Large part of the observed variation prevalence rates between studies can be explained by differences in applied frailty instruments and difficulties to disentangle frailty from symptoms that inherently belong to RA and *vice versa*. High quality studies with validated frailty instruments specifically for RA patients are needed to estimate the prevalence of (pre)-frailty in this population.

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