Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Background Low muscle mass occurs in patients with rheumatoid arthritis without weight loss; this condition is referred as rheumatoid cachexia. The aim of the current study was to perform a systematic review with meta-analysis to determine the rheumatoid cachexia prevalence.
Methods A systematic review with meta-analysis of observational studies published in English, between 1994 and 2016, was conducted using MEDLINE (via PubMed) and other relevant sources. Search strategies were based on pre-defined keywords and medical subject headings. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale. Meta-analysis was used to estimate the prevalence, and because studies reported different methods and criteria to estimate body composition and prevalence of rheumatoid cachexia, subgroup analyses were performed. Meta-regression adjusted for the 28-joint disease activity score and disease duration (years) was performed (significance level at $P \leq 0.05$).
Results Of 136 full articles (one duplicate publication) screened for inclusion in the study, eight were included. The estimated overall prevalence of rheumatoid cachexia was 19% [95% confidence interval (CI) 07–33%]. This prevalence was 29% (95% CI 15–46%) when body composition was measured by dual-energy X-ray absorptiometry. When the diagnostic criteria were fat-free mass index below the 10th percentile and fat mass index above the 25th percentile, rheumatoid cachexia prevalence was 32% (95% CI 14–52%). The 28-joint disease activity score and disease duration had no influence on the estimated prevalence of rheumatoid cachexia ($P > 0.05$). Most studies were rated as having moderate methodological quality.
Conclusions Meta-analysis showed a prevalence of rheumatoid cachexia of 15-32%, according to different criteria, demonstrating that this condition is a frequent comorbidity of rheumatoid arthritis. To better understand its clinical impact, more studies using standardized definitions and prospective evaluations are urgently needed.

Keywords Cachexia; Rheumatoid cachexia; Sarcopenia; Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic, symmetric, and erosive synovitis that may lead to severe disability and premature death.[1–3] In addition to joint damage, changes in body composition have been observed in patients with RA, including reduced fat-free mass (FFM), of which muscle mass is the major component, with or without loss of fat mass (FM), resulting in no or limited changes in body mass index.[4,5] This condition has been referred to as rheumatoid cachexia (RC).[6–8]

The definition of 'cachexia' (classic cachexia), 'sarcopenia', 'sarcopenic obesity', and 'RC' is diverse in the available literature. Sarcopenia (Greek 'sarx' or flesh and 'penia' or loss) is currently used to characterize the combination of low muscle mass and function (strength and performance),[9,10] while sarcopenic obesity refers to the copresence of both sarcopenia and obesity. Classic cachexia (Greek 'kako's' or bad and 'he'xis'

or condition) is a term used to characterize the condition involving severe loss of weight, fat, and muscle mass and increased protein catabolism due to underlying disease(s).[11,12] Roubenoff et al.[5,13] described a common reduction in total body cell mass (BCM) in patients with RA and referred to this condition as RC. BCM consists primarily of muscle mass, with visceral mass (serum proteins, erythrocytes, granulocytes, lymphocytes, liver, kidneys, pancreas, and heart) and immune cell mass contributing lesser amounts. Also, this author considers FM, extracellular water, connective tissue (cartilage, fibrous tissues, and skeletal tissues), and bone, components not included in BCM. However, recently, Engvall et al. described RC as adverse changes in body composition (reduced FFM with or without loss of FM) in patients with RA.[14,15]

Excess of pro-inflammatory cytokines as IL-1 beta and TNF-alpha is considered to be the central feature in RC.[5] In addition, as for clinical outcomes, RC has been associated with an increased risk of physical disability, morbidity, and mortality.[16,17]

Despite several publications on RC, there is no consensus on the clinical criteria for its diagnosis,[18] leading to considerable variability in reports of RC prevalence. Attempts have been made to diagnose RC based on body composition measured by different methods, including computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and anthropometric methods. In addition to different methods to evaluate body composition, different criteria have been used to diagnose RC.[11,14,19] Therefore, the diagnostic criteria used for RC and the method used to measure body composition can greatly impact the estimation of RC prevalence, but this has not been systematically studied. The aim of the current study was to systematically review the literature and estimate the RC prevalence.

Methods

We conducted this systematic review with meta-analysis in accordance with PRISMA guidelines[20] after registering the protocol with PROSPERO (CRD42017073495).

Data sources

An electronic search was performed using MEDLINE (via PubMed) and other relevant sources. We used a comprehensive search strategy tailored to each database.

Search terms

Keywords and medical subject headings for the terms 'rheumatoid arthritis', 'arthritis', 'arthritis rheumatoid' AND 'cachexia' AND 'sarcopenia' were selected.

Inclusion/exclusion criteria

Cross-sectional and cohort studies were included in the systematic review and meta-analysis. Studies on experimental models, randomized controlled trials, and reviews; studies on other diseases or topics; and studies without prevalence data of RC were excluded. In addition, studies that evaluated only muscle mass, without providing data on FM, were excluded.

Data extraction

Title, abstract, and full-text screening were performed in duplicate by two independent reviewers (Santo, R. C. E. and Fernandes, K. Z.). The reviewers independently extracted data from the studies using a pre-established data extraction form, which is available upon request. All study data were recorded using a bibliographic management program (Mendeley®, version 1.17.9). Disagreements about data abstraction were resolved by discussion between the two reviewers. If no agreement could be reached, a third and fourth reviewers (Filippin, L. and Lora, P.) provided the final decision. Information extracted during data abstraction included author names, date of publication, journal of publication, number of study participants, age range of population, type of population, definition of RC [with method(s) of body composition assessment, cut-off points, and reference population], and RC prevalence (percentage or number of participants with and without RC).

Strategy for data synthesis

The Newcastle-Ottawa Scale, adapted for cross-sectional studies, was used to assess methodological quality of sampling, selection, exposure, and clinical outcomes of the studies selected. Using the Newcastle-Ottawa Scale, each study was judged on seven items categorized into three groups: selection of study groups; comparability of groups; and ascertainment of either the exposure or outcome of interest. The maximum possible score was 10 stars, which represented the highest methodological quality.[21] Studies awarded 7–10 stars were rated as having high quality; 5–6 stars, as having moderate quality; and <5 stars, as having low quality.[22] Studies include independently of the methodological quality calculated. Meta-analysis was performed using Stata® 11.0. The prevalence of RC [with 95% confidence intervals (CI)] was estimated using random effect adjust and Freeman–Tukey double arcsine transformation (FFT). The I^2 statistic was used to assess heterogeneity among studies. Meta-regression adjusted for the 28-joint disease activity score (DAS28) and disease duration (years) was performed, and

the significance level was set $P \leq 0.05$. All analyses were performed using the metaprop command in Stata.

Results

Search strategy

We identified 136 potentially relevant full articles (one duplicate publication) based on the search strategy described at the initial search stage. *Figure* 1 shows the flow diagram of study selection. After title, abstract, and full-text screening, 127 articles were excluded (25 experimental model; 40 reviews; 10 clinical trials; 10 other populations; 26 other topics; and 16 without prevalence of RC) in accordance with inclusion/exclusion criteria. Therefore, eight relevant full articles were included in the review and incorporated into the meta-analysis.

Characteristics of the studies

All included studies were published between 2008 and 2016. Sample sizes ranged from 50 to 400 patients, with a female

predominance. Mean age ranged from 54.1 to 65.0 years. DAS28 ranged from 3.1 to 5.2. The characteristics of the included studies are summarized in *Table* 1. All studies had a cross-sectional design. Most studies were conducted in European populations, while one was from Morocco, and another was from South Africa.

Diagnostic criteria for rheumatoid cachexia

Most studies used only body composition parameters as diagnostic criteria for RC. Fat-free mass index (FFMI) below the 10th percentile and fat mass index (FMI) above the 25th percentile, as proposed by Engvall *et al.*,[14] were used as diagnostic criteria for RC in six (75.0%) of eight included studies.[14,19,23–28] Of the remaining two studies, one used the diagnostic criteria proposed by Elkan *et al.* of FFMI below the 25th percentile and FMI above the 50th percentile,[19] and the other used the diagnostic criteria proposed by Evans *et al.* that includes another parameters besides body composition {body weight loss of 5% or more within 12 months [or a body mass index $\leq$20 kg/m^2] and at least three of the following factors: decreased muscle strength; fatigue; anorexia; low FMI; and abnormal biochemistry [increased inflammatory

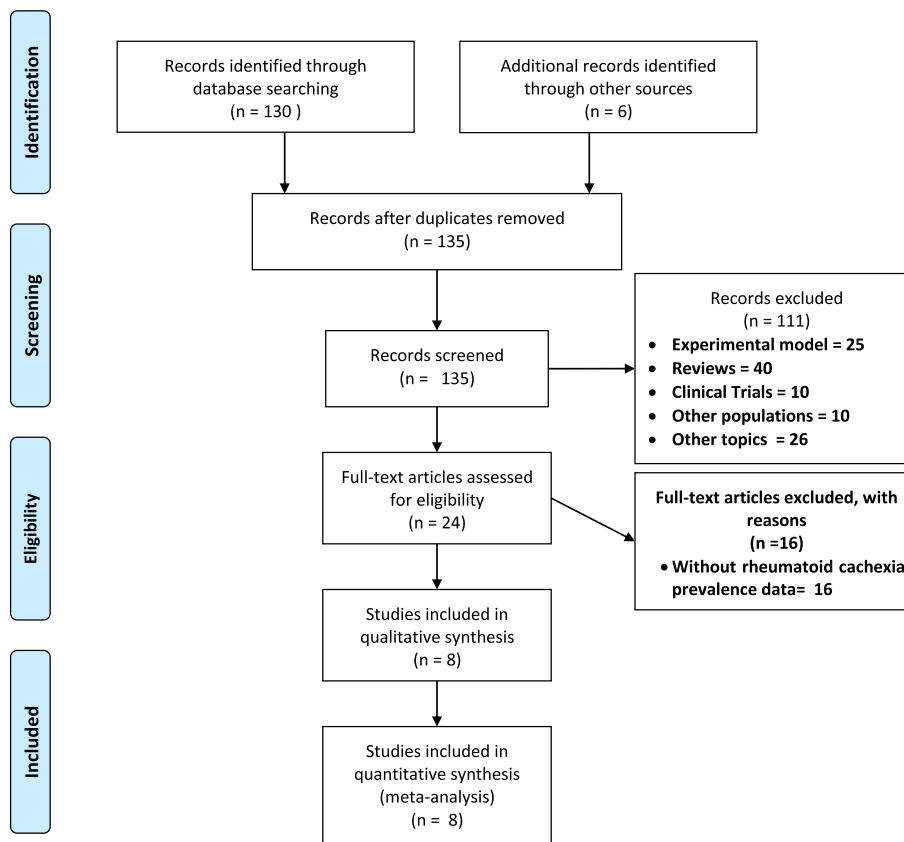**Figure 1** Flow diagram of search results and study selection.

Table 1 Characteristics of included studies

First author name	Country	Sample size	Mean age (years)	Disease duration (years)	Mean DAS28	Diagnostic criteria	Methods of body composition	Prevalence of cachexia (%)
Hugo et al.[28]	France	(n = 57) W: 41 M: 16	57.0 ± 13.0	3.8 (3.0)	4.4 ± 1.1	Engvall et al.[14]	DEXA	18.0
El Maghraoui et al.[27]	Morocco	(n = 178) W: 147 M: 31	T: 54.1 ± 11.5 W: 51.8 ± 10.3 M: 53.3 ± 10.7	8.9 (7.4)	T: 4.3 ± 1.6 W: 4.7 ± 1.5 M: 4.1 ± 0 1.4	Engvall et al.[14]	DEXA	T: 53.9 W: 53.7 M: 54.8
Lombard et al.[26]	South Africa	(n = 246) W: 204 M: 42	54.7 ± 13.6		NP	Engvall et al.[14]	AM	10.3
Bokhorst et al.[25]	Netherlands	(n = 103) W: 79 M: 24	T: 60.0 (26.0–90.0)[a]	8.0[a]	3.32	Evans et al.[11]	BIA; handgrip strength; FAACT; VAS fatigue and pain; CRP; ESR; Hb	1.0
Elkan et al.[24]	Sweden	(n = 80) W: 61 M: 19	W: 60.8 (57.3–64.4)[a] M: 63.4 (59.8–66.9)[a]	6.0	W: 3.3 (3.0–3.6)[a] M: 2.6 (2.1–3.0)[a]	Engvall et al.[14]	DEXA	W: 18.0
Elkan et al.[19]	Sweden	(n = 80) W: 61 M: 19	W: 60.8 (57.3–64.4)[a] M: 63.4 (59.8–66.9)[a]	6.0	W: 3.3 (3.0–3.6)[a] M: 2.6 (2.1–3.0)[a]	FFMI below the 25th percentile and FMI above the 50th percentile.	DEXA	M: 21.0 W: 18.0 M: 26.0
Metsios et al.[23]	UK	(n = 400) W: 292 M: 108	+RC: 68.3 (64.7–73.0)[a] −RC: 62.7 (54.0–69.4)[a]	+RC: 11.0[a] −RC: 10.0[a]	RA + RC: 4.3 ± 1.8 RA − RC: 4.2 ± 1.4	Engvall et al.[14]	BIA	8.5
Engvall et al.[14]	Sweden	(n = 60) W: 50 M: 10	W: 66.0 (63.0–69.0)[a] M: 60.0 (51.0–70.0)[a]	W: 13.0[a] M: 16.0[a]	W: 5.7 (5.3–6.1)[a] M: 4.6 (3.7–5.5)[a]	Engvall et al.[14]	DEXA	38.0

+RC, patients with rheumatoid arthritis and rheumatoid cachexia; −RC, patients without rheumatoid cachexia; AM, anthropometric measurements; BIA, bioelectrical impedance analysis; CRP, C-reactive protein; DAS28, 28-joint disease activity score; DEXA, total-body dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; FAACT, the Functional Assessment of Anorexia/Cachexia Therapy questionnaire; FFMI, fat-free mass index; FMI, fat mass index; Hb, haemoglobin; M, men; NP, not published; T, total; VAS, visual analogue scale; W, women.
[a]Median; ±standard deviation; Engvall et al.[14] diagnostic criteria, FFMI below the 10th percentile and FMI above the 25th percentile.

markers (CRP, IL-6), anaemia (Hb <12 g/dL), low serum albumin (<3.2 g/dL)]}.[11]

Methods of body composition assessment for rheumatoid cachexia

Of eight included articles, five (62.5%) used total-body DEXA, two (25.0%) used BIA,[23,25] and one (12.5%) used anthropometric measurements.[26]

Rheumatoid cachexia prevalence

Rheumatoid cachexia prevalence ranged from 1.0% to 53.9% (*Table* 1). El Maghraoui *et al.*[27] found the highest prevalence using the diagnostic criteria for RC proposed by Engvall *et al.*,[14] while Bokhorst *et al.*[25] found the lowest prevalence using the diagnostic criteria for cachexia proposed by Evans *et al.*[11]

Meta-analysis

In the overall meta-analysis (body composition as the only criterion), RC prevalence estimated was 19% (95% CI 07–33%) with I^2 = 96.74%, P = 0.00 (*Figure* 2). Two subgroup analyses were performed. When body composition determine by DEXA, RC prevalence was estimated at 29% (95% CI 15–46%) with I^2 = 92.63%, P = 0.00 (*Figure* 3), and when FFMI below the 10th percentile and FMI above the 25th percentile were used as diagnostic criteria, RC prevalence estimated was 32% (95% CI 14–52%) with I^2 = 93.24%, P = 0.00 (*Figure* 4). In the meta-regression model, neither DAS28 nor age had an influence on the RC estimated prevalence (P = 0.545, SEM = 0.04; and P = 0.614, SEM = 0.02, respectively).

This prevalence was when body composition was measured by DEXA.

Methodological quality of the studies

The methodological quality of included studies is described in *Table* 2. Most studies were rated as having moderate quality.

Discussion

Rheumatoid cachexia is a term used to characterize adverse changes in body composition that involve reduction in FFM and maintenance or increase in FM in patients with RA. These

Figure 2 Forest plot of the prevalence of rheumatoid cachexia using body composition (assessed by dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or anthropometric measurements) as a diagnostic criterion; ES, estimated; I^2, heterogeneity among studies.
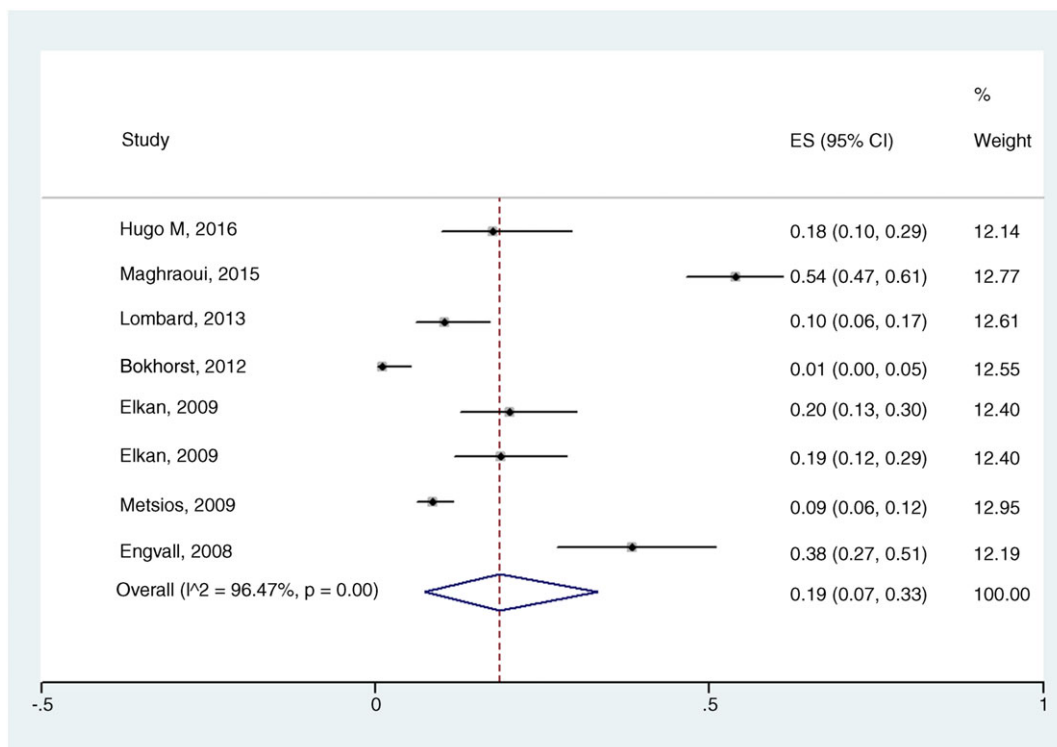
Figure 3 Forest plot of the prevalence of rheumatoid cachexia using dual-energy X-ray absorptiometry. ES, estimated; I^2, heterogeneity among studies.
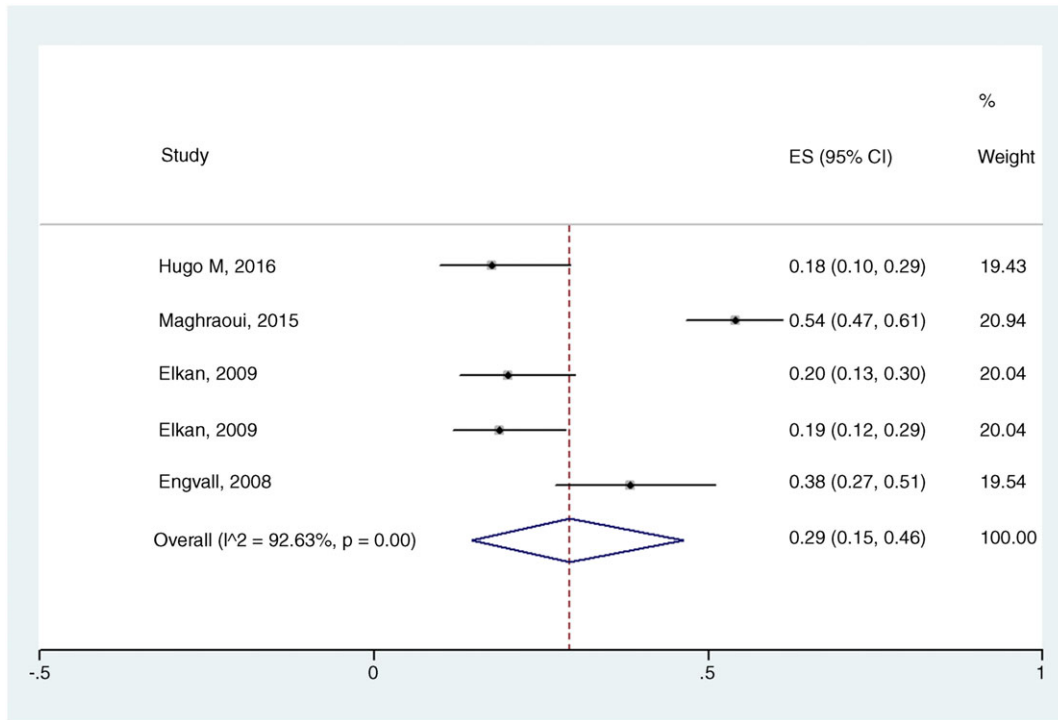

Figure 4 Forest plot of the prevalence of rheumatoid cachexia using dual-energy X-ray absorptiometry and fat-free mass index below the 10th percentile and fat mass index above the 25th percentile as diagnostic criteria. ES, estimated; I^2, heterogeneity among studies.
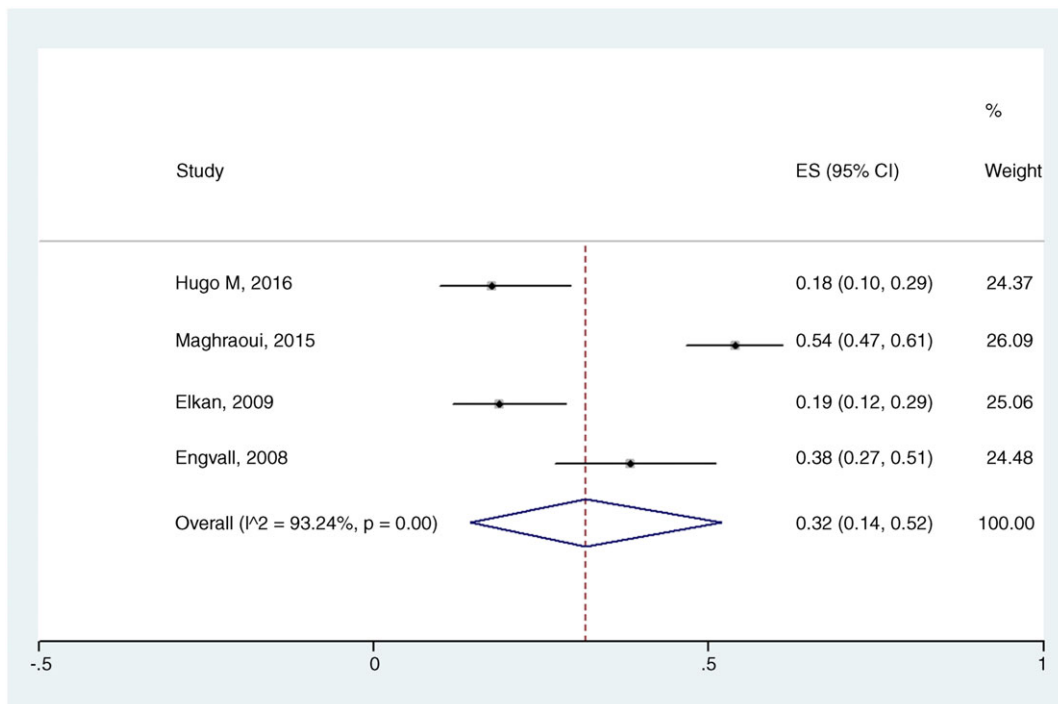
Table 2 Description of quality assessment using the Newcastle-Ottawa Scale (NOS)

First author name	Country	Selection (1–5 stars)	Comparability (1–2 stars)	Outcome (0–3 stars)	Overall NOS (1–10 stars)
Hugo et al.[28]	France	**	*	**	5
El Maghraoui et al.[27]	Morocco	**	*	**	5
Lombard et al.[26]	South Africa	****	*	**	7
Bokhorst et al.[25]	Netherlands	**	*		3
Elkan et al.[24]	Sweden	**	*	**	5
Elkan et al.[19]	Sweden	**	*	**	5
Metsios et al.[23]	UK	**	*	***	6
Engvall et al.[14]	Sweden	**	*	**	5

Asterisks (*) Represents the number of "stars" of quality Newcastle-Ottawa Scale (NOS).

changes may be related to pro-inflammatory cytokine-induced hypermetabolism.[13–15] To our knowledge, this is the first systematic review with meta-analysis to estimate the prevalence of RC in patients with RA. Of the eight articles included in our study, seven studies used diagnostic criteria developed specifically for RC—six used the criteria proposed by Engvall et al.,[14] and one used the criteria proposed by Elkan et al.,[19] while one study used the criteria for classic cachexia proposed by Evans et al.[11]

The estimated RC prevalence was 19% (95% CI 07–33%). However, estimated prevalence varied when studies with different methods of body composition assessment or different cut-off points were included in the analysis. In the analysis using specific diagnostic criteria for RC and DEXA, the estimated prevalence of RC was 29%. Nevertheless, in the analysis using specific criteria for RC, DEXA, and the cut-off points proposed by Engvall et al.[14] (i.e. FFMI below the 10th percentile and FMI above the 25th percentile), the estimated prevalence of RC was 32% (95% CI 14–52%). Therefore, we can state that RC is influenced by the method of body composition assessment and criteria used for diagnosis.

Body composition analysis refers to the quantification of the main structural components of the human body, divided into specific tissues that compose the total body mass.[29,30] Methods of body composition assessment such as DEXA, BIA, and anthropometric measurements have been used in the clinical and research settings. Using BIA, Bokhorst et al.[25] found a very low prevalence of RC (1%). Metsios et al.,[23] also using BIA, found a prevalence of RC of 8.5%. Elkan et al.[24] compared BIA and DEXA and found good agreement between the two methods, but BIA showed higher lean mass values and lower FM values. Although BIA has lower cost, greater ease of use, and higher measurement speed, the use of this technique requires that the person undergo a set of previous procedures, without which there may be loss of information quality obtained from FM when compared with DEXA.

In addition to these precautions, equipment characteristics and calibration, body position, individual hydration level and food intake, ambient and cutaneous temperature, and use of heavier garments and metal parts may have some influence on the quality of measurements.[31,32] Using anthropometric measurements to assess body composition in patients with RA, Lombard et al.[26] found a prevalence of RC of 10.3%. Anthropometric measurement is considered a double indirect method of body composition assessment, and the instruments used, the evaluator's ability, intra-rater and inter-rater errors, individual factors (hydration level, physical exercise, and menstrual cycle), and the choice of the anthropometric prediction equation, among other factors, may be a source of error.[33–36]

Using DEXA as the method of body composition assessment in patients with RA, Hugo et al.[28] found an RC prevalence of 18%, while El Maghraoui et al.[27] found a prevalence of 53.9%. A number of techniques are being used to assess body composition as water dilution, anthropometry, DEXA, analysis of computerized tomography and magnetic resonance imaging, and BIA.[37] However, DEXA represents a reliable alternative method, non-invasive, improved feasibility, lower cost, minimal radiation exposure, high accuracy, sensitive and reproducibility for measuring FM and FFM.[38,39] In addition, DEXA is a clinically accessible method that is widely used in bone mineral density measurement for the evaluation of osteoporosis; therefore, it is also suitable for the analysis of body composition.

Rheumatoid cachexia prevalence also varied according to the criteria used for diagnosis, because the diagnostic criteria for RC are not well established. Engvall et al.[14] and Elkan et al.[19] proposed a RC diagnostic criteria that include changes in FFM and FM. Engvall et al.[14] used data from a Swiss population sample of healthy adults (2986 men and 2649 women) to found body composition index that determine RC. Therefore, RC was classified as FFMI below the 10th percentile and FMI below the 25th percentile. Using these cut-off points, they found an RC prevalence of 38%. Other studies conducted using the same diagnostic criteria (and cut-off points) found an RC prevalence ranged from 8.5% to 53.9%.

Elkan et al.[19] proposed a variation in the same parameters but different cut-off point and the same Swiss population database used by Engvall et al.[14] for RC in order to test the association of RC with dyslipidaemia and risk of cardiovascular disease. Patients with RA were classified as having RC if they

had FFMI below the 25th percentile and FMI above the 50th percentile.[19] Using these cut-off points, they found an RC prevalence of 21% for women and 26% for men. Despite the difference between the RC criteria proposed by Engvall *et al.*[14] and by Elkan *et al.*,[19] no apparent difference was observed between prevalence rates.

Evans *et al.*,[11] however, proposed a diagnosis of cachexia to be used in several diseases, including RA. Based on these criteria, Bokhorst *et al.*[25] found a prevalence of RC of 1%. Physical inactivity[40] and treatment effects,[41–43] due to the effective reversal of the systemic inflammatory process, seem to affect the gain or maintenance of body weight in patients with RA. Therefore, patients with controlled RA do not lose body weight, and, for this reason, the prevalence of RC using the diagnostic criteria proposed by Evans *et al.*[11] is lower than that reported in the studies that used the diagnostic criteria proposed by Engvall *et al.*[14] or by Elkan *et al.*[19,24]

In fact, no study evaluated the impact of RC on patient outcomes, and no study prospectively validated these criteria. To define the best criterion, such studies are required. Despite the lack of body weight loss, patients with RA lose muscle mass compared with healthy individuals. Loss of muscle mass is commonly evaluated in classic cachexia, RC, and sarcopenia; therefore, these syndromes are often confused with one another.

Using loss of muscle mass as a diagnostic criterion for sarcopenia in patients with RA, studies have reported prevalence rates of sarcopenic patients ranging from 11.0% to 57.1%. However, studies that evaluated only loss of muscle mass were not included in our systematic review with meta-analysis, because the objective was to specifically evaluate RC according to currently used RC diagnostic criteria. Considering that patients with RA have a decrease in lean mass, maintenance or increase in adipose tissue, and changes in functionality, Weber *et al.*[44,45] proposed a new parameter of adiposity-adjusted muscle mass ($ALMI_{FMI}$). This parameter was defined as appendicular lean mass divided by height squared adjusted for age and body fat (adjZ-score), and low lean mass was defined as adjZ-score less than -1.0, leading to stronger positive associations with functional results compared with unadjusted estimates in patients with RA.[44,45] Thus, it is suggested that this new parameter be used in future sarcopenia and cachexia studies of patients with RA.

The systemic inflammatory process of RA has been associated with altered body composition and RC.[14] Elkan *et al.* assessed patients with mild to moderate disease activity and found an RC prevalence of 18.0%[19,24] for women and 21.0%[24]–26.0%[19] for men. Conversely, studies evaluating patients with moderate to high disease activity found an RC prevalence of 18–53.9%.[14,19,24,27,28] In our meta-analysis, no association between disease activity and RC was demonstrated, probably because most patients had moderate to high disease activity (DAS28 between 3.1 and 5.2) and because all studies had a cross-sectional design, thereby

preventing the evaluation of changes in body composition and disease activity over time.

Regardless of whether there is agreement between the diagnostic criteria and methods used for body composition assessment, there is common agreement that RC affects the clinical outcome of patients. Patients with RA have increased IL-6 and TNF within the muscle. These muscle inflammatory markers correlate with physical inactivity and disability.[46] Engvall *et al.*[14] demonstrated that patients with RA who had RC and high disease activity had lower physical activity and IGF-1 levels. In addition to muscle alterations, patients with RA also have endothelial dysfunction and increased risk of atherosclerosis and cardiovascular disease.[47–49] However, the effects of RC on the risk of cardiovascular disease are still controversial.[50] Elkan *et al.*,[19] in patients with RA who had RC and moderate disease activity, found high levels of total cholesterol and low-density lipoprotein, low levels of IgM against phosphorylcholine (anti-PC IgM), and high frequency of hypertension. However, in patients with RA and moderate RC, disease activity does not appear to be associated with worse cardiovascular disease profile[23] or metabolic syndrome.[28] Impaired bone metabolism may also be present, because patients with RA and RC have lower hip bone mineral density than patients without RC.[27] Considering that RC affects the clinical outcome of patients, longitudinal studies are needed to fill the gaps in the literature regarding the effects of RC on patients with RA.

The main limitation of this study is the small number of RC studies included, making meaningful meta-analysis difficult. In conclusion, the results of this systematic review with meta-analysis indicate that the estimated prevalence of RC ranges from 19% to 32% and that there is variability in the prevalence rates according to the diagnostic criteria used for RC. Therefore, there is a need for greater standardization of terms such as RC, cachexia, and sarcopenia, as well as for further prospective studies aiming to clarify the impact of this comorbidity on clinical outcomes.

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Conflict of interest

None declared.

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