Singapore Med J 2019; 60(6): 270-280
https://doi.org/10.11622/smedj.2019057

A systematic review of the association of obesity with the outcomes of inflammatory rheumatic diseases

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ABSTRACT This was a systematic review of the literature on the association between obesity and the outcome of inflammatory rheumatic diseases. We conducted a literature search using PubMed®, Embase and PsycINFO®. Articles were classified into three categories based on the effects of obesity on the outcomes of inflammatory rheumatic diseases. The subject population, country, type of studies, number of patients, measurement of obesity and outcomes assessed were presented. Quality was appraised using Kmet et al's criteria. 4,331 articles were screened and 60 were relevant to the objective. Obesity had a negative, positive and neutral association with outcomes of inflammatory rheumatic diseases in 38 (63.3%) studies with 57,612 subjects, 11 (18.3%) studies with 3,866 subjects, and 11 (18.3%) studies with 3,834 subjects, respectively. In most studies, the disease population had been diagnosed with rheumatoid arthritis (RA). Tumour necrosis factor-α inhibitors were mostly associated with negative outcomes. More studies examining subjects outside Europe and North America and diseases other than RA are warranted.

Keywords: association, obesity, outcomes, rheumatology

INTRODUCTION

Inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA), are usually progressive and associated with pain. Comorbidities may occur in association with rheumatic diseases.[1] If inflammatory rheumatic diseases are not treated appropriately, daily activities will be affected. Disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs and biologic DMARDs (bDMARDs), have been used to decrease pain and inflammation, reduce or prevent joint damage, and preserve joint structure and function.

Outcomes of inflammatory rheumatic diseases can be assessed mainly by two ways – patient-reported outcomes (PROs) and clinical outcomes. Most clinical outcomes involve clinical assessment or laboratory investigations by the healthcare provider. On the other hand, PROs are directly reported by the patient, without requiring interpretation by others. PROs add valuable and unique information on treatment efficacy and quality of life that is immediately relevant to the management of disease activity. Examples of PROs include the Health Assessment Questionnaire (HAQ) for RA and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for SpA.[2,3] In terms of clinical use, a predictive factor is any measurable attribute of an individual that can be used to infer a health-related outcome.

Obesity is increasing in prevalence, with over 600 million adults worldwide being obese. Overweight is defined as a body mass index (BMI) greater than or equal to 25 kg/m^2, while obesity refers to a BMI greater than or equal to 30 kg/m^2.[4] As Asian populations have different associations among BMI, percentage of body fat, and health risks compared to European populations, a lower BMI cut-off is often used. Asians with a BMI above 23 kg/m^2 are considered to be overweight, while a BMI of above or equal to 25 kg/m^2 is considered to be obese. Non-communicable comorbidities such as cardiovascular diseases, diabetes mellitus and musculoskeletal disorders have been associated with obesity.[4]

Overall, the prevalence of obesity in many inflammatory rheumatic diseases seems to be similar or slightly higher than in the general population.[5] The excessive fats in adipose tissues cause the release of inflammatory mediators such as tumour necrosis factor-α (TNF-α) and interleukin,[6] predisposing the body to a pro-inflammatory state.[7] Obesity may impair mobility of the thoracic spine, and an increase in adipose tissue is associated with the increased of production pro-inflammatory cytokines,[6] which may lead to worsening of the inflammatory rheumatic diseases. Furthermore, patients with RA tend to have high rates of cardiovascular morbidity and mortality;[8] obesity further increases this risk.

Several recent studies found an increased risk of RA occurrence related to obesity, while no longitudinal studies were found for other inflammatory rheumatic disease.[9] RA patients have an altered body composition, with decreased lean mass and increased fat mass. This may adversely affect the reliability of conventional BMI cut-offs used to define obesity. Although lower thresholds of BMI have been proposed, these thresholds are not applied in published clinical studies.[9]

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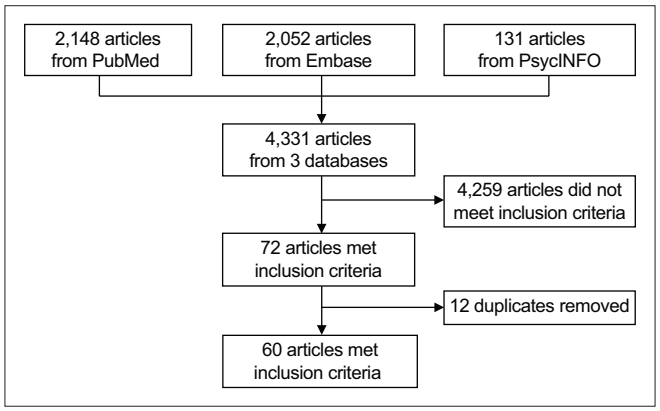

Fig. 1 Flowchart shows selection of articles for review.

To date, there have been numerous conflicting studies regarding the effects of obesity on the outcomes of RA.[10,11] In addition, studies reporting the effects of obesity on the outcomes of other inflammatory rheumatic diseases such as SpA are lacking. However, to the best of our knowledge, there has been no systematic review on the association of obesity with the outcomes of inflammatory rheumatic diseases. Therefore, this article aimed to provide a systematic review of the current literature on how obesity is associated with the outcomes of RA, SpA, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE) and PsA. This systematic review can provide clinicians and researchers with a clearer understanding of the impact of obesity on inflammatory rheumatic diseases.

METHODS

We conducted a systematic review in accordance with the Preferred Reporting Items for Systemic reviews and Meta-Analysis (PRISMA) checklist, but we did not lodge a protocol. We searched the literature using the electronic databases Embase®, PubMed® and PsycINFO®. Hand searches were carried out using the references of the related articles. The databases were searched from their inception to September 2018. The keywords used were: ((obes* OR (body mass index) OR weight)) AND ((clinical outcomes) OR (treatment outcomes) OR (patient-reported outcomes) OR outcomes)) AND ((spondyloarthritis) OR (systemic lupus erythematosus) OR (psoriatic arthritis) OR (Sjogren's syndrome) OR (ankylosing spondylitis) OR (inflammatory bowel disease related to arthritis) OR rheum*)).

Two independent reviewers reviewed both the article inclusion and data extraction process. The inclusion criteria were English peer-reviewed journals that studied adults aged ≥ 18 years with all autoimmune rheumatic diseases and sought to determine the effect of obesity on outcomes. Systematic reviews, meta-analyses, case series, case reports, grey articles and unpublished articles were excluded from the review. Non-English studies as well as studies that investigated autoimmune or rheumatic disease in subjects aged < 18 years were also excluded.

Articles were then classified into three main categories based on the effect of obesity on the outcomes of the autoimmune rheumatic diseases. Studies that showed positive associations that were statistically significant were classified as positive, those that showed negative associations that were statistically significant were classified as negative, and studies that showed no statistical significance were classified as neutral. Data such as subject population, country of study, type of study, number of patients, measurement of obesity and outcomes assessed was extracted, tabulated and presented accordingly. We also rated the quality of the studies found using the standard quality assessment criteria detailed by Kmet et al in 2004.[12] Although no threshold was set for this systematic review, a score of above 0.75 was considered good, with a higher score representing better quality.

RESULTS

A total of 4,331 articles were retrieved from the three databases, consisting of 2,148, 2,052 and 131 articles from PubMed®, Embase and PsycINFO®, respectively. Fig. 1 shows the selection process. Out of these 4,331 articles, only 72 articles met the inclusion criteria outlined in our study. The other 4,259 articles did not meet our inclusion criteria, were not related to obesity or were not about autoimmune rheumatic diseases. After removing 12 duplicates, 60 articles were included in our review. Out of these 60 articles, 26 (43.3%) were cohort studies and 34 (56.7%) were cross-sectional studies.

Positive association with outcome

From the search, it was found that a total of 11 studies with 3,866 subjects showed that obesity is significantly associated with better outcome (Table I).[2,10,13-21] All of the 11 studies were focused on the RA disease population. Most of these studies were conducted in Western populations based in America and Europe, with only three investigating Asian subjects. Van der Heijde–Sharp (vdHS) erosion scores were the most commonly used clinical outcome. Other clinical outcomes included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), simplified erosion narrowing score, tender joint count (TJC), disease activity score in 28 joints (DAS28), disease activity score in 44 joints, Larsen score and swollen joint count (SJC). PROs were assessed using the HAQ. Out of the 11 studies, 8 (72.7%) were cross-sectional studies, while 3 (27.3%) were cohort studies.

Neutral association with outcome

A total of 11 studies with 3,834 subjects showed that obesity was neither associated with better nor worse outcomes, with insignificant associations reported (Table II).[6,8,22-30] Most of the studies investigated the RA disease population. For PsA and axial SpA (AxSpA), one study was found for each disease population. Again, most of the studies were conducted on subjects from Western populations, and only one study was conducted in Asia. For the RA studies, clinical outcome DAS28 was the most commonly used. PROs used included the visual analogue scale for pain (VAS) and HAQ. Clinical outcomes included CRP, ESR, simple disease activity index (SDAI), TJC and SJC. For the PsA study, SDAI, DAS28 or HAQ was used. For the AxSpA study, the AS disease activity score was used. Out of the 11 studies,

Table I. Studies that show a positive association between obesity and outcome (n = 3,866).

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcome	Quality; COI
RA[19]	Holland; CS; 236	Age > 18 yr with early RA 60% female	BMI (linear)	NA	DAS28	0.91; included
RA[2]	Asia, Europe, Australia, Latin America and North America; CS; 499	Age > 18 yr MTX vs. golimumab vs. combination therapy MTX dose 20 mg/wk	BMI (categorical): U < 20 kg/m^2 N 20–24.9 kg/m^2 OW 25–29.9 kg/m^2 O ≥ 30 kg/m^2	HAQ	DAS28, CRP, vdHS erosion score	0.95; included
RA[13]	Germany; cohort; 54	Age 56 (range 30–83) yr 83% female Use of conventional DMARDs	BMI (categorical): low < 27 kg/m^2 high ≥ 27 kg/m^2	NA	Larsen score, CRP, ESR	0.95; not included
RA[16]	Holland; CS; 579	Age > 18 yr DMARD naive Sequential therapy vs. step-up combination therapy	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS44, vdHS	0.95; none declared
RA[10]	United States; CS; 1,068	Age > 18 yr 82% female MTX and biologic-naive subjects or subjects who previously failed MTX	BMI (categorical): N < 25 kg/m^2 OW > 25 to < 30 kg/m^2 O ≥ 30 kg/m^2	NA	vdHS erosion score	0.95; included
RA[14]	United States; cohort; 123	Age > 18 yr 71% female	BMI (categorical): U ≤ 20 kg/m^2 N 20–25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	ESR	1.00; none declared
RA[17]	United Kingdom; CS; 197	Age 59.4 ± 8.7 yr 60% female No prior cardiovascular events or procedures Use of MTX, infliximab, adalimumab or rituximab	BMI (linear)	NA	vdHS erosion score	0.95; included
RA[15]	Japan; cohort; 145	Age 53.1 ± 12.5 yr 82% female Use of MTX (7.1 ± 1.9) vs. tocilizumab (6.9 ± 2.0)	BMI (linear)	NA	vdHS erosion score	0.86; included
RA[20]	United States; CS; 97	Age > 18 yr 63% female	BMI (linear)	HAQ	CRP, ESR	0.75; not included
RA[21]	India; CS; 101	Age 41.9 ± 11.9 yr 80% female	BMI (categorical): U < 18.5 kg/m^2 N 18.5–23 kg/m^2 OW 23–27.5 kg/m^2 O > 27.5 kg/m^2	NA	SENS, ESR, TJC, SJC, DAS28	0.80; not included
RA[18]	Germany; CS; 767	Age 57.2 ± 13.0 yr 72% female Recent onset, disease duration < 24 mth	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28	0.95; included

BMI: body mass index; COI: conflict of interest; CRP: C-reactive protein; CS: cross-sectional; DAS28: disease activity score in 28 joints; DAS44: disease activity score in 44 joints; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; MTX: methotrexate; N: normal weight; NA: not applicable; O: obese; OW: overweight; PRO: patient-reported outcome; RA: rheumatoid arthritis; SENS: simplified erosion narrowing score; SJC: swollen joint count; TJC: tender joint count; vdHS: van der Heijde–Sharp; U: underweight

5 (45.5%) studies were cross-sectional studies, while 6 (54.5%) were cohort studies.

Negative association with outcome

A total of 38 studies with 57,612 subjects showed that obesity is significantly associated with worse outcomes (Table III).[1,3,11,31-65] 21 studies were focused on the RA disease population, while five studies assessed PsA patients, and another four studies examined the AS disease population. There were three studies on AxSpA, four studies on SLE and one study on polyarthritis. Most of the studies were conducted on Western populations with limited studies based on Asian populations. For RA studies, the clinical

Table II. Studies that show a neutral association between obesity and outcome (n = 3,834).

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcomes	Quality; COI
RA[22]	France; cohort; 115	84% female Patients receiving tocilizumab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS	DAS28, ESR, CRP, TJC, SJC	0.91; none declared
RA[23]	France; cohort; 114	82% female Patients receiving rituximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS	DAS28, ESR, CRP, TJC, SJC	0.91; included
RA[27]	France; CS; 222	Age 56 (IQR 47–166) yr 82% female Patients receiving tocilizumab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28, ESR	0.91; not included
RA[8]	Iran; cohort; 106	Age 48.5 ± 13.9 yr 88% female Treated with conventional DMARDs	BMI (categorical): U < 18.5 kg/m^2 N 18.5–25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28, ESR	0.95; none declared
RA[24]	United States; cohort; 79	Age 53.2 ± 13.6 yr 76% female	BMI (linear)	NA	ESR, SJC, TJC	0.86; included
RA[26]	Korea; CS; 568	Age 56.6 ± 38.7 yr 89% female Use of conventional DMARDs and biologic infliximab, etanercept, adalimumab or abatacept	BMI (categorical): U < 18.5 kg/m^2 N 18.5–23 kg/m^2 OW 23–25 kg/m^2 O ≥ 25 kg/m^2	NA	SDAI, ESR, CRP, SJC, TJC	0.91; none declared
RA[28]	United States; CS; 1,456	Mean age 50.0 yr 82% female Abatacept plus MTX (≥ 15 mg/wk)	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28, SDAI, CDAI	0.89; included
RA[29]	United States; CS; 470	Mean age 49.1 yr 83% female Golimumab with MTX vs. MTX monotherapy vs. golimumab monotherapy	BMI (categorical): U < 20 kg/m^2 N 20 to < 25 kg/m^2 OW 25 to < 30 kg/m^2 O ≥ 30 kg/m^2	HAQ	DAS28, CRP, TJC, SJC, magnetic resonance imaging activity	0.86; included
RA[30]	France; CS; 141	82% female Abatacept use	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS	DAS28, ESR, CRP	0.75; none declared
PsA[25]	Italy; cohort; 135	50% female Use of adalimumab, etanercept or infliximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ	DAS28, SDAI	0.91; not included
AxSpA[6]	Holland, Norway, Italy; cohort; 428	Age > 16 yr 63% female	BMI (categorical): N ≤ 24.9 kg/m^2 OW ≥ 25 kg/m^2	NA	ASDAS	0.95; none declared

ASDAS: ankylosing spondylitis disease activity score; AxSpA: axial spondyloarthritis; BMI: body mass index; CDAI: clinical disease activity index; COI: conflict of interest; CRP: C-reactive protein; CS: cross-sectional; DAS28: disease activity score in 28 joints; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; MTX: methotrexate; N: normal weight; NA: not applicable; O: obese; OW: overweight; PRO: patient-reported outcome; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SDAI: simple disease activity index; SJC: swollen joint count; TJC: tender joint count; U: underweight; VAS: visual analogue scale for pain

outcome DAS28 was also the most commonly used. PROs used included VAS and HAQ. Clinical outcomes included CRP, ESR, TJC, SJC and vdHS erosion score. For PsA studies, TJC, SJC, Psoriasis Area and Severity Index score, HAQ, VAS, patient global assessment, ESR, CRP and tender entheseal count were used. For AS studies, BASDAI was the most commonly used PRO; other instruments used included the Bath AS Functional Index, AS disease activity score, VAS and the 36-Item Short Form Health Survey (i.e. SF-36). For the AxSpA studies, BASDAI was used, and for the polyarthritis study, HAQ was used. For the SLE studies, employment, International Physical Activity Questionnaire, SLICC/ACR-DI (Systemic Lupus International Collaborating

Clinics/American College of Rheumatology Damage Index) and Valued Life Activities disability questionnaire were used. Out of the 38 studies, 21 (55.3%) were cross-sectional studies and 17 (44.7%) were cohort studies.

Rheumatoid arthritis studies

Out of the 60 studies, 41 (68.3%) studies were conducted in the RA population. Among these 41 studies, 11 (26.8%) found that obesity was associated with a positive outcome in the RA population. In another 9 (22.0%) RA studies, obesity was associated with a neutral outcome, while 21 (51.2%) RA studies found that it was associated with a negative outcome. Only 4 (9.8%) of the 41 RA studies were conducted in Asian populations.

Quality assessment

All studies achieved a score of at least 0.75. 41 (68.3%) of the studies achieved a score of more than 0.90, showing that all studies included were of good quality.

DISCUSSION

This study comprehensively reviewed the available literature on the association of obesity with the outcomes of inflammatory rheumatic diseases. We also closely followed the PRISMA checklist for reporting systematic reviews. As far as we know, there is no systematic review regarding the association between obesity and the outcomes of inflammatory rheumatic diseases. Our study gives an overview of the studies that provided evidence that obesity could have a positive, neutral or negative association with the outcomes of autoimmune rheumatic disease. We also found the number of studies done on various types of inflammatory rheumatic diseases.

Out of the 60 studies, 38 (63.3%), 11 (18.3%) and 11 (18.3%) studies showed that obesity is negatively associated, not associated and positively associated, respectively, with the outcomes of autoimmune rheumatic disease. No studies on PsA, AS, AxSpA, SLE and polyarthritis showed that obesity had a positive association with outcomes. However, given that the number of studies in these areas is limited and that the populations studied are not very varied, with different outcomes used for evaluation, this information may not be sufficient to draw the conclusion that obesity only has a negative association with these diseases.

Most of the studies were completed in countries in the West, including America and European countries. Only four out of 41 RA studies were conducted in Asia. The body composition of Asians is different from that of Caucasians. Asians may have higher body fat at a specific BMI as compared to Caucasians;[4] as such, the definition of obesity in various studies may not be applicable to Asians. The various BMI categories for Asians have been defined as: < 18.5 kg/m^2 for underweight, 18.5–22.9 kg/m^2 for normal weight, 23.0–24.9 kg/m^2 for overweight and ≥ 25 kg/m^2 for obese,[4] which is different from the international definitions. Furthermore, as ethnicity may result in variability in responses to drug therapy, Asians and Caucasians may respond differently to medications. Therefore, we may not be able to conclude from this study that obesity is negatively associated with the outcome of RA in an Asian setting.

Although some of the included RA studies had a methotrexate arm, the dosing of methotrexate varied from study to study. Methotrexate dosing is usually based on a balance of efficacy and tolerability. The dose in one of the studies conducted in the Japanese population was 7.1 ± 1.9 mg/week,[15] while the dose in an Italian study was 15–25 mg/week.[32] As Asians are likely to have a smaller body surface area compared to the Western population, a lower methotrexate dose may be tolerated, thus possibly favouring the study drug in those studies conducted in Asian populations.

bDMARDs that were used in the included studies can be categorised into three classes: TNF-α inhibitors, B-cell targeted therapies and interleukin-6 (IL-6) inhibitors. TNF-α is a cytokine that results in inflammation and bone degradation, and TNF-α inhibitors include adalimumab, etanercept, infliximab and golimumab. The effects of a TNF-α inhibitor may be dependent on TNF-α expression in synovial joints and infiltration by inflammatory cells that produce TNF-α.[66] B-cell targeted therapy includes rituximab, a chimeric monoclonal antibody that targets the CD20 surface molecule of some B cells. Its mechanism of action in RA is not completely understood.[67] IL-6 inhibitors, comprising the relatively new agent tocilizumab, inhibit IL-6-mediated signalling and induce B-regulatory cells, decreasing pro-inflammatory cytokines.[68]

We found that the studies involving TNF-α inhibitors were associated with different outcomes: four studies[2,10,16,17] were associated with positive outcomes, three studies[25,26,29] with neutral outcomes and ten studies[11,32-34,40,55,56,61,62,65] with negative outcomes. Rituximab was associated with positive,[17] neutral[23] and negative[11,56] outcomes, while tocilizumab was similarly associated with positive,[15] neutral[22,27] and negative[11,56] outcomes. Due to the limited number of studies for tocilizumab, we conducted an additional literature search on it and found that tocilizumab is unlikely to be affected by obesity.[69] An alternative modality for RA is abatacept, a selective modulator that targets the CD80/CD86:CD28 pathway that is needed for complete activation of T cells. The relevant studies showed neutral[26,28,30] or negative[11,56] outcomes. However, the two studies in which rituximab, tocilizumab and abatacept were associated with negative outcomes[11,56] were conducted in populations with refractory disease, and thus obesity was unlikely to be the only reason for the lack of response. Further studies are needed to determine if obesity is indeed associated with negative outcomes for patients on rituximab, tocilizumab or abatacept.

A relatively new drug, tofacitinib, is a potent selective Janus kinase (JAK) inhibitor that preferentially inhibits JAK1 and JAK3. Tofacitinib was found to be non-inferior to adalimumab, although more studies are needed to determine its place in therapy.[70] As tofacitinib is oral therapy, it may be more acceptable than bDMARDs. To our knowledge, there are currently no studies to determine if tofacitinib efficacy is affected by obesity, and more studies are needed in this area.

Apart from having a direct impact on inflammation, obesity may modify the pharmacokinetics of bDMARDs. Studies have identified high body weight as a risk factor associated with increased clearance of TNF-α inhibitors, leading to lower serum trough concentration and shorter half-life,[71] which may explain the greater number of studies that associate RA with negative outcomes.

It is interesting to note that cross-sectional studies made up 73%, 46% and 55% of the studies, respectively, that showed positive outcomes, neutral outcomes and negative outcomes associated with obesity. As cross-sectional studies are generally regarded as weaker study designs than cohort studies,[72] this should be taken into consideration when interpreting the results that linked obesity to positive outcomes.

Using the quality assessment criteria, we found that the included studies were generally of good quality, with all studies achieving a score more than 0.75.[12] However, some studies did not include a conflict of interest section and we could not evaluate potential bias arising from it.

A limitation of the present study is that it is a systematic review and not a meta-analysis of the effect of obesity on the outcomes of inflammatory rheumatic diseases; hence, we do not know the aggregate level of the effect of obesity on the outcome. However, we have summarised the literature as much as possible. Another weakness is that non-English articles have been excluded. Nevertheless, the number of non-English articles in this area is limited. Although we sought to carry out a systematic review on inflammatory rheumatic diseases using thorough and comprehensive keywords, the search results only yielded the particular diseases we have listed.

In conclusion, a systematic review was conducted and 60 articles that met the inclusion criteria were selected. Further studies focused on examining Asian populations suffering from RA as well as other inflammatory rheumatic diseases are warranted.

Table III. Studies that show a negative association between obesity and outcome (n = 57,612).

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcomes	Quality; COI
RA[11]	Italy; cohort; 292	85% female Began treatment with biologic after inadequate response to ≥1 DMARDs (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, tocilizumab, rituximab)	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28, ESR	0.95; none declared
RA[31]	Sweden; cohort; 495	71% female DMARD naive	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS, HAQ	DAS28	0.95; none declared
RA[32]	Italy; cohort; 641	Age 52.1 ± 13.5 yr 81% female MTX at the usual dosage of 15–25 mg/wk, use of adalimumab, etanercept, infliximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS, HAQ	DAS28, ESR	0.95; included
RA[1]	Sweden; cohort; 1,391	Age 55.6 ± 14.6 yr 68% female	BMI (categorical): N 20–25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ, VAS	DAS28	0.91; included
RA[33]	Holland; cohort; 89	74% female MTX (5–30 mg/wk), biologic naive, use of infliximab	BMI (categorical): U < 20 kg/m^2 N and OW 20–30 kg/m^2 O > 30 kg/m^2	NA	DAS28	0.95; included
RA[34]	France; cohort; 76	Age 49.1 (IQR 42.3–55.8) yr 83% female Use of infliximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS	DAS28, ESR, CRP, TJC, SJC	0.86; none declared
RA[35]	United States; cohort; 24,535	Age 58.9 ± 13.2 yr 78% female	BMI (categorical): U < 18.5 kg/m^2 N 18.5–25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ, SF36	NA	0.95; not included

(Contd...)

Table III. *(Contd...)*

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcomes	Quality; COI
RA[55]	Holland; CS; 508	68% female 1. Sequential monotherapy starts with MTX 2. Step-up combination therapy starting with MTX 3. Initial combination therapy scheme: MTX, sulfasalazine 4. A combination of MTX and IFX	BMI (categorical): < 25 kg/m^2 ≥ 25 kg/m^2	NA	DAS	0.95; included
RA[42]	Morocco; CS; 250	Age 46.3 ± 12.6 yr 79% female	BMI (categorical) U < 18.5 kg/m^2 N 18.5–23 kg/m^2 OW 23–28 kg/m^2 O ≥ 28 kg/m^2	HAQ	DAS28, ESR, CRP, vdHS erosion score	0.91; none declared
RA[44]	United Kingdom; CS; 294	74% female	BMI (linear)	HAQ	DAS28, ESR, CRP	0.91; none declared
RA[45]	Peru; CS; 359	Age 58 ± 14 yr 87% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	SF-36	NA	0.91; included
RA[46]	Canada; CS; 200	Age > 18 yr 76% female	BMI (categorical): Male O ≥ 24.7 kg/m^2 Female O ≥ 26.1 kg/m^2	HAQ, VAS	ESR, CRP, SJC, TJC	0.81; included
RA[47]	Finland; CS; 200	Age > 18 yr 77% female	WC (categorical): Male AO ≥ 102 cm Female AO ≥ 88 cm	HAQ, SF-36	DAS28	0.86; not included
RA[48]	Argentina, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, Holland, Poland, Russia, Serbia, Spain, Sweden, Turkey, United Arab Emirates, United Kingdom and United States; CS; 5,161	Age 56.2 ± 13.7 yr 79% female	BMI (categorical): U < 18.5 kg/m^2 N 18.5–25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	NA	DAS28	0.91; none declared
RA[49]	United States; CS; 197	Age 59.4 ± 8.7 yr 60% female	Fat, lean and bone mass BMI (linear)	NA	DAS28	0.95; included
RA[50]	United States; CS; 196	60% female	Fat, lean and bone mass BMI (linear)	NA	CRP	0.95; included
RA[51]	United States; CS; 980	Age: 67.4 ± 11.0 yr 9% female	BMI (categorical): < 24 kg/m^2 24–27.3 kg/m^2 27.3–31.4 kg/m^2 ≥ 31.4 kg/m^2	NA	SJC, ESR, CRP	0.95; included

(Contd...)

Table III. *(Contd...)*

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcomes	Quality; COI
RA[56]	United Kingdom; CS; 13,502	Median age 57 yr 76% female Adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab or ocrelizumab, anakinra, tocilizumab, abatacept	BMI (categorical): Not O < 30 kg/m^2 O ≥ 30 kg/m^2	HAQ, SF-36	DAS28, ESR, TJC, SJC, physician global assessment	0.91; included
RA[58]	United States; cohort; 174	Age 60.4 ± 13.2 yr 85% female	BMI (categorical): N < 25 kg/m^2 OW ≥ 25 kg/m^2	NA	CDAI	0.82; included
RA[60]	Canada; CS; 982	Age 53 ± 15 yr 72% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ, VAS	TJC, SJC, DAS28, ESR, CRP, physician global assessment	0.86; included
RA[61]	Sweden; CS; 260	Median age 56 yr 71% female MTX, sulfasalazine, hydroxychloroquine or MTX and infliximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ, VAS	DAS28, ESR	0.86; included
PsA[36]	Canada; cohort; 557	Age 48.6 ± 13.1 yr 41% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	VAS, PGA	Skin, enthesitis, TJC, SJC	0.95; none declared
PsA[37]	Italy; cohort; 126	Age 45.1 ± 11.5 yr 63% female	BMI (categorical): OW 25–30 kg/m^2 O ≥ 30 kg/m^2 WC (categorical): Men AO ≥ 102 cm Women AO ≥ 88 cm	PASI, HAQ, VAS	TJC, SJC, tender entheseal count, ESR, CRP	0.95; none declared
PsA[38]	Italy; cohort; 270	Age > 18 yr 50% female	BMI (categorical): N < 30 kg/m^2 1st degree O 30–35 kg/m^2 2nd degree O 35–40 kg/m^2	PASI, HAQ, VAS	TJC, SJC, ESR, CRP, tender entheseal count	0.95; not included
PsA[39]	Italy; cohort; 144	Treated with an anti-TNF drug for ≥ 12 mth	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	PASI	NA	0.77; none declared
PsA[65]	Denmark and Iceland; cohort; 1,943	Obese group age 43.7 ± 12.5 yr Non-obese group age 49.4 ± 11.9 yr Use of etanercept, adalimumab, infliximab, certulizumab, golimumab	BMI (categorical): Not O < 30 kg/m^2 O ≥ 30 kg/m^2	HAQ, VAS	TJC, CRP, DAS28	0.91; included
AxSpA[40]	Italy; cohort; 170	Age 39.5 ± 11.8 yr 31% female Patients who have received or are receiving infliximab	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	BASDAI	NA	0.95; none declared

(Contd...)

Table III. *(Contd...)*

Disease	Country; study type; no. of patients	Patient characteristics	Independent variable (obesity)	PRO	Clinical outcomes	Quality; COI
AxSpA[62]	Switzerland; cohort; 624	Age 39.4 ± 11.6 yr 37.8% female Adalimumab, certolizumab, etanercept, golimumab, infliximab	BMI (categorical): N 18.5 to < 25 kg/m^2 OW 25–30 kg/m^2 O > 30 kg/m^2	BASDAI, BASMI	ASDAS, CRP, ASAS40	0.91; included
AxSpA[63]	Singapore; CS; 194	Age 38.72 ± 13.73 yr 22.7% female	BMI (categorical): N < 23 kg/m^2 OW 23 to < 27.5 kg/m^2 O ≥ 27.5 kg/m^2	BASDAI, BASFI, BAS-G, HAQ, VAS, SF-36	ESR, CRP	0.86; none declared
AS[3]	France; cohort; 155	Age 43.1 (IQR 35.0–51.8) yr 37% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	BASDAI, VAS	CRP	0.91; none declared
AS [52]	Holland; CS; 135	Age 51 ± 13 yr 40% female	BMI (linear)	BASDAI, BASFI, SF-36	NA	0.91; included
AS[53]	Ireland; CS; 46	Age 45.1 (range 24–69) yr 24% female	BMI (categorical): N < 25 kg/m^2 OW and O > 25 kg/m^2	BASDAI, BASFI, HAQ, SF-36	NA	0.77; not included
AS[64]	Spain; CS; 57	Age 47.14 ± 10.38 yr 35% female Adalimumab use	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	BASDAI, BASFI, ASDAS	Adalimumab levels	0.82; included
Polyarthritis[54]	United Kingdom; CS; 1,246	Age 57 (IQR 46–69) yr 63% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	HAQ	NA	0.95; included
SLE[41]	United States; cohort; 716	Age 48.1 ± 12.6 yr 100% female	BMI (categorical): Women O ≥ 30 kg/m^2 Revised female O ≥ 26.8 kg/m^2	VLA, employment, SF-36	NA	0.95; included
SLE[43]	Brazil; CS; 170	Age 18–60 yr 100% female	BMI (categorical): N 18–24.9 kg/m^2 OW ≥ 25 kg/m^2	IPAQ	SLICC/ACR-DI	0.91; none declared
SLE[57]	United States; CS; 148	Age 48 ± 12.3 yr 100% female	BMI (categorical): Not O < 30 kg/m^2 O ≥ 30 kg/m^2	VAS, SLAQ, CES-D	NA	0.86; included
SLE[59]	United States; CS; 129	Age 45.5 ± 10.9 yr 94% female	BMI (categorical): N < 25 kg/m^2 OW 25–30 kg/m^2 O ≥ 30 kg/m^2	FSS, PROMIS® fatigue score, SELENA-SLEDAI	Leptin, adiponectin, resistin	0.86; included

AO: abdominal obesity; ASAS40: Assessment in SpondyloArthritis International Society 40% response; ASDAS: ankylosing spondylitis disease activity score; AxSpA: axial spondyloarthritis; BAS-G: Bath Ankylosing Spondylitis Patient Global Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; CDAI: clinical disease activity index; CES-D: Center for Epidemiologic Studies Depression Scale; COI: conflict of interest; CRP: C-reactive protein; CS: cross-sectional; DAS: disease activity score; DAS28: disease activity score in 28 joints; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; FSS: fatigue severity score; HAQ: health assessment questionnaire; IFX: infliximab; IPAQ: International Physical Activity Questionnaire; IQR: interquartile range; MTX: methotrexate; N: normal weight; NA: not applicable; O: obese; OW: overweight; PASI: psoriasis area and severity index; PGA: patient global assessment; PRO: patient-reported outcome; PROMIS®: Patient-Reported Outcomes Measurement Information System; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SELENA-SLEDAI: Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36: Medical Outcomes Study 36-item short form survey; SJC: swollen joint count; SLAQ: Systemic Lupus Activity Questionnaire; SLE: systemic lupus erythematosus; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; TJC: tender joint count; TNF: tumour necrosis factor; U: underweight; vdHS: van der Heijde–Sharp; VLA: Valued Life Activities disability questionnaire; W: waist circumference

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