Association of Body Mass Index Categories with Disease Activity and Radiographic Joint Damage in Rheumatoid Arthritis: A Systematic Review and Metaanalysis

Celine Vidal, Thomas Barnetche, Jacques Morel, Bernard Combe, and Claire Daïen

ABSTRACT. Objective. Obesity and overweight are increasing conditions. Adipose tissue with proinflammatory properties could be involved in rheumatoid arthritis (RA) activity and radiographic progression. This study aims to investigate the influence of overweight and obesity on RA activity and severity.

Methods. We conducted a systematic review and metaanalysis to assess the association of body mass index (BMI) categories with the Disease Activity Score in 28 joints (DAS28), functional disability [Health Assessment Questionnaire (HAQ)], and radiographic joint damage in patients with RA. We searched Medline through PubMed, EMBASE, and the Cochrane Database of Systematic Reviews for all studies assessing DAS28, HAQ, or/and radiographic damage according to predefined BMI groups.

Results. Among the 737 citations retrieved, 58 articles met the inclusion criteria and 7 were included in the metaanalysis. DAS28 was higher in obese (BMI > 30 kg/m^2) than non-obese (BMI ≤ 30 kg/m^2) patients (mean difference 0.14, 95% CI 0.01–0.27, p = 0.04, I^2 = 0%). HAQ score was also higher among obese patients (mean difference 0.10, 95% CI 0.01–0.19, p = 0.03, I^2 = 0%). Radiographic joint damage was negatively associated with obesity (standardized mean difference –0.15, 95% CI –0.29 to –0.02, p = 0.03, I^2 = 38%).

Conclusion. Obesity in RA is associated with increased DAS28 and HAQ score and with lower radiographic joint damage. These associations mainly result from an increase of subjective components of the DAS28 (total joint count and global health assessment) in obese patients. Conflicting results were reported concerning inflammation markers (C-reactive protein and erythrocyte sedimentation rate). (J Rheumatol First Release November 1 2015; doi:10.3899/jrheum.150224)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OBESITY BODY MASS INDEX

About one-third of the world's population is estimated to be overweight [body mass index (BMI) > 25 kg/m^2)] or obese (BMI > 30 kg/m^2)[1]. Among people with rheumatoid arthritis (RA), this proportion is higher by more than 50%[2].

This problem of obesity and the resulting metabolic syndrome in patients with RA has attracted research attention[3]. Indeed, adipose tissue has immunomodulating and proinflammatory properties that could affect inflammatory diseases such as RA[4]. Among the cytokines produced by adipose tissue, tumor necrosis factor (TNF), interleukin 6 (IL-6), leptin, resistin, and visfatin are considered proinflammatory, whereas adiponectin has antiinflammatory and proinflammatory properties, depending on its molecular form[5].

Serum IL-6, visfatin, and adiponectin levels in patients with RA were found to be positively associated with radiographic joint damage in cross-sectional and longitudinal studies[6,7]. Moreover, some studies have found that a high BMI was associated with poor RA disease outcome, whereas others have suggested that increased BMI may be associated with less radiographic joint damage[8,9].

Thus, the effect of obesity among patients with RA has to be clarified.

We performed a systematic review and metaanalysis to assess the cross-sectional association between obesity and disease activity, functional disability, and radiographic joint damage in patients with RA in observational studies.

From the Rheumatology Department, Hôpital Lapeyronie, Montpellier I University; Institut of Molecular Genetic of Montpellier, Unité Mixte de Recherche n. 5535 (UMR5535), Montpellier; Rheumatology Department, Hôpital Pellegrin, Bordeaux, France.

C. Vidal, MD, Rheumatology Department, Hôpital Lapeyronie, Montpellier I University; T. Barnetche, PhD, Rheumatology Department, Hôpital Pellegrin; J. Morel, MD, PhD, Rheumatology Department, Hôpital Lapeyronie, Montpellier I University, and Institut of Molecular Genetic of Montpellier, UMR5535; B. Combe, MD, PhD, Rheumatology Department, Hôpital Lapeyronie, Montpellier I University, and Institut of Molecular Genetic of Montpellier, UMR5535; C. Daïen, MD, PhD, Rheumatology Department, Hôpital Lapeyronie, Montpellier I University, and Institut of Molecular Genetic of Montpellier, UMR5535.

Address correspondence to Dr. C. Daïen, Rheumatology Department, Hôpital Lapeyronie, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France. E-mail: c-daien@chu-montpellier.fr

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MATERIALS AND METHODS

Literature search. We searched Medline through PubMed, EMBASE, and the Cochrane Database of Systematic Reviews for articles published up to June 22, 2015, with the MeSH terms "body mass index" OR "obese" OR "obesity" AND "rheumatoid arthritis", without any limits. We also performed a manual search, but no congress abstracts [European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR)] were retrieved because we needed exhaustive data for our metaanalysis. Using our prespecified inclusion and exclusion criteria, 2 independent rheumatologist reviewers examined titles and abstracts for potential relevance and then chose full-text articles. Any discrepancies were resolved by discussion.

Study selection. Inclusion criteria were patients with a diagnosis of RA according to the 1987 ACR criteria (score ≥ 4/7 with symptoms persisting for more than 6 weeks) and/or the 2010 ACR/EULAR criteria (score ≥ 6/10) and predefined BMI groups, including a group of overweight/obese patients[10,11]. We searched for cohort, longitudinal, and cross-sectional studies. Studies with a group of patients with BMI ≥ 30 kg/m^2 were included in the metaanalysis; studies with other cutoffs were included in the systematic review. Studies with results expressed in means were included in the metaanalysis; studies with results expressed in medians were included in the systematic review.

We excluded reviews and case reports. Articles with data expressed as medians were excluded from the metaanalysis, but were retained for the systematic review. Manual search was performed using references of the selected studies.

Risk of bias assessment. We used the Quality in Prognostic Studies tool to evaluate the quality of studies included in the metaanalysis because they were prospective studies[12].

Data collected. We collected data on the 28-joint count Disease Activity Score (DAS28) and/or its components [tender joint count (TJC), swollen joint count (SJC), global health assessment (GHA; visual analog scale from 0–100), erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP)], Health Assessment Questionnaire (HAQ) score, and patient's global pain assessment (GPA; visual analog scale from 0–100). We collected radiographic joint damage scored by Ratingen, Simple Erosion Narrowing Score (SENS), or modified Sharp/van der Heijde (SvdH) scales[13,14].All these assessments had to be analyzed by BMI categories. For data collected in clinical trials or cohort studies, only baseline information was considered.

Statistical analysis. Results of each selected study were presented as mean differences with their 95% CI. Metaanalyses were carried out using the inverse variance method, pooling estimates of each study using fixed or random-effects model according to the level and significance of heterogeneity. Heterogeneity was tested with the Cochran Q-test and evaluated by the I^2 statistic with the following classification: 0–30% indicating negligible heterogeneity, 30–50% moderate heterogeneity, 50–75% substantial heterogeneity, and considerable heterogeneity for values larger than 75%. For the Q-test, a p value < 0.10 was considered significant and a random-effects model was used. Standardized means were used for the analysis of radiographic joint damage because of the varied radiographic scores used among studies. Funnel plots and the Egger test assessed publication biases. Analysis involved the use of RevMan 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) for the metaanalysis calculations, and STATA 13.1 software (StataCorp) was used to perform publication bias assessment. P values < 0.05 were considered statistically significant.

RESULTS

The literature search yielded 58 articles for the systematic review; 7 articles (3787 patients) were included in the metaanalysis (Figure 1).

Description of studies retrieved. Studies were mainly prospective, conducted in various centers and countries, except for 3 retrospective studies[15,16,17]. The diagnosis of RA was according to the revised 1987 ACR criteria, except for 1 study, in which 63% of patients fulfilled the 2010 ACR/EULAR criteria and 42% fulfilled the revised 1987 ACR criteria[18]. In most of the studies, patients were divided by BMI in accordance with the World Health Organization definition or with a lower boundary of 20 kg/m^2 for normal BMI, except in 5 studies[19]. One study defined obesity as BMI > 25 kg/m^2 because the population was Asian and 1 divided BMI into 3 categories (< 20, 20–30, and > 30 kg/m^2) to have large groups[20,21,22]. One study defined normal BMI as 18.5–22.9 kg/m^2 and obesity as > 28 kg/m^2 because patients with RA may have decreased fat-free mass because of inflammation and increased fat mass secondary to inactivity, thereby suggesting that BMI cutoffs in the RA population may be more appropriate if they were reduced by about 2 kg/m^2[23,24]. In 1 study, obese patients were compared with only non-obese patients (BMI < 30 kg/m^2) and in others, underweight and normal weight patients were included in the same group (BMI < 25 kg/m^2)[15,16,17,25,26].

DAS28 assessment was detailed in 6 studies, with TJC and SJC assessed by experienced rheumatologists or nurses[18,20,27,28,29,30]. Radiographic evaluation was detailed in 3 studies. One study used the mean scores of 2 blinded centralized readers[31]. In another study, physicians who scored the radiographs were unaware of the clinical data, and the BeSt study (Behandel Strategieën, i.e., Treatment Strategies Study) used the mean score from the 2 readers[29]. Another study used the radiograph scores from 1 investigator[30].

Risk of bias assessment. Articles were rated low bias considering the population studied, except for 1 in which patients were not randomized[32]. The evaluation of study attrition was not applicable for 3 studies because they were not designed to evaluate RA activity and severity by BMI[31,32,33]. The remaining 4 studies had low to moderate bias[25,29,30,34]. All studies were rated low bias for prognostic factor measurement and study confounding. The outcome measurement was also rated low bias, except for 2 studies rated as moderate bias because the DAS28 assessment method was not well described[25,33]. Studies were rated as low bias because of the statistical analysis and results reported, except for 1 study rated moderate bias because the statistical analysis was not well explained[25].

Study characteristics. Table 1 shows the characteristics of the 7 studies included in the metaanalysis. Mean age of patients ranged from 47.6 ± 13.6 to 63.5 ± 12.3 years. Patients were mostly women, representing 67% to 100% of the patients. Mean duration of RA ranged from 25 weeks (range 15–45) to 15.5 ± 12.3 years. Smoking was assessed in 3 studies and no clear difference was found between obese and normal BMI patients[29,31,33]. Obese patients more often had seronegative RA [rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies] than patients with normal BMI[29,30,31]. There were no differences for disease-modifying anti-

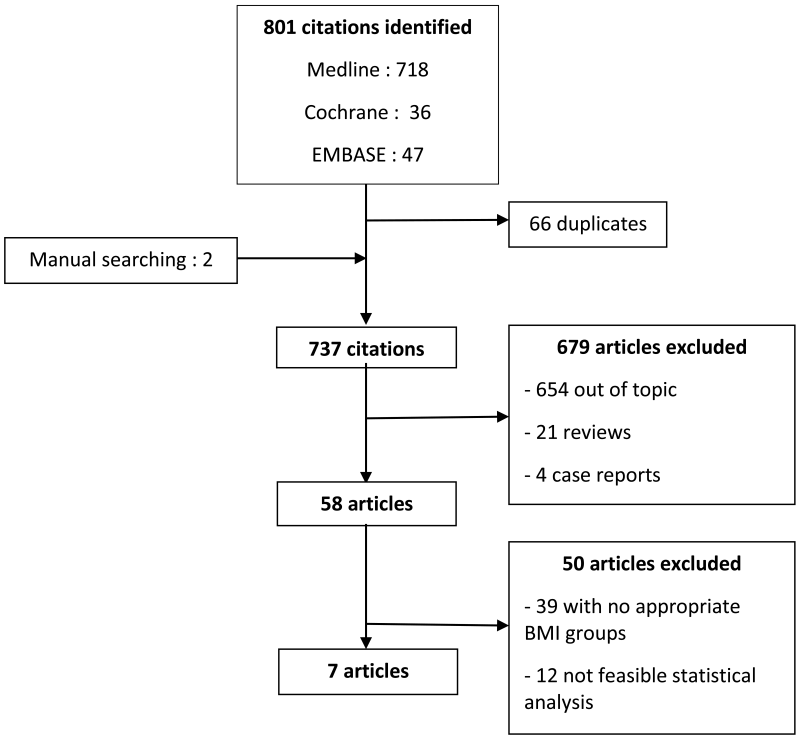

Figure 1. Flowchart of articles selected for the metaanalysis. BMI: body mass index.

Table 1. Characteristics of studies included in the metaanalysis. Values are % unless otherwise specified.

Articles	BMI, kg/m²	n (%)	Age, Yrs, Mean ± SD	Women	RA Duration, Mean ± SD or Median (IQR)	Smoking Ever	RF Positivity	Anti-CCP Positivity	Treatment Use GC	Treatment Use DMARD
Ajeganova, *et al*[33]	20–24.99	775 (48.5)	53.9 ± 15.4	71.4	≤ 1 yrs	55.8	62.2	NA	36.7	77.9
	≥ 30	206 (12.9)	57.9 ± 12.2	68.4	≤ 1 yrs	59	61.9	NA	30.9	84.9
Baker, *et al*[31]	20–24.9	156 (31.2)	47.6 ± 13.6	85.9	1.15 (0.6–4.4) yrs	28.9	78.1	78.1	54.5	NA
	≥ 30	127 (25.5)	50.8 ± 11.7	82.7	1.3 (0.5–3.3) yrs	39.8	63.8	62.5	54.7	NA
Brown, *et al*[34]	18.5–24.99	65 (38.7)	63.5 ± 12.3	75.4	17.35 ± 10.1 mos	NA	NA	NA	26.7	75.4
	> 30	44 (26.2)	63.2 ± 9.1	72.7	15.8 ± 8.1 mos	NA	NA	NA	29.5	68.2
Straburzyńska-Lupa, *et al*[32]	18.5–24.9	19 (37.3)	55.6 ± 4.5	100	11.9 ± 6.6 yrs	NA	72.7	NA	77.3	95.5
	> 30	22 (32.2)	57.5 ± 4.29	100	11.3 ± 7.1 yrs	NA	84.2	NA	57.9	94.7
Tekaya, *et al*[25]	< 25	43 (36.1)	51.0 ± 12.6	77	15.5 ± 12.3 yrs	NA	68.9	56.3	NA	NA
	≥ 30	36 (30.3)								
Van der Helm-van Mil, *et al*, EAC[29]	< 25	156 (47)	54.5 ± 17.1	74	8 yrs	42	NA	51	NA	NA
	≥ 30	30 (9)	55.4 ± 13.5	67		30		50		
BeST[29]	< 25	110 (44.5)	53.1 ± 14.7	76	25 (15–45) weeks	41	NA	66	NA	NA
	≥ 30	36 (14.6)	54.2 ± 10.4	86		31		59		
Westhoff, *et al*[30]	< 25	303 (39.5)	54.9 ± 13	71.9	12.3 ± 7 mos	NA	64.4	NA	NA	93.6
	≥ 30	149 (19.4)	58.7 ± 12	82.6	11.0 ± 7 mos	NA	55.7	NA	NA	95.4

BMI: body mass index; RA: rheumatoid arthritis; IQR: interquartile range; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; GC: glucocorticoids; DMARD: disease-modifying antirheumatic drugs; EAC: Early Arthritis Clinic; BeST: Behandel Strategieën, i.e., Treatment Strategies Study; NA: not applicable.

rheumatic drug (DMARD) and corticosteroid use. Patients were classified in different groups by BMI: low BMI (< 18.5 or < 20 kg/m^2), normal BMI (18.5–25 or 20–25 kg/m^2), overweight (25–30 kg/m^2), and obese (> 30 kg/m^2).

DAS28. DAS28 according to BMI was reported in 15 studies; 4 studies involving 1402 patients were included in the metaanalysis because they showed similar BMI groups and comparable expression of DAS28 (means and not medians)[31,32,33,34]. DAS28 was higher for obese than non-obese patients (mean difference 0.14, 95% CI 0.01–0.27, p = 0.04; Figure 2), with no heterogeneity among studies (I^2 = 0%). Among the 11 remaining studies, 9 supported this result for a trend of higher DAS28 in obese patients than those with normal BMI[15,17,18,20,22,23,28,30,35] (Table 2)[15,16,17,18,20,22,23,27,28,29,30,31,32,33,35,36]. Two studies showed conflicting results, but in 1 study, obese and overweight patients were in the same BMI group (> 25 kg/m^2), and the second study was a retrospective study[16,36].

TJC and SJC. Metaanalysis was not feasible for the analysis of TJC or SJC because of different BMI groups and different measurement tools (means or medians). TJC was assessed in 6 studies, which showed a trend of higher TJC for obese patients than those with normal BMI (Table 2)[17,20,27,28,29,31]. SJC was assessed in 5 studies showing conflicting results (Table 2)[17,20,27,28,31].

GPA and GHA. Metaanalysis was not feasible for GPA or GHA because of different BMI groups and different measurement tools (means or medians). Six and 3 studies reported GPA and GHA, respectively, by BMI groups, revealing a trend of increased GPA and GHA for obese patients over those with normal BMI (Table 2)[16,20,28,29,30,31,33].

ESR and CRP level. Metaanalysis was not feasible for ESR or CRP because of lack of comparable BMI groups and different measurement tools (means or medians). The association of ESR and BMI was assessed in 12 studies showing conflicting results (Table 2)[15,16,17,20,22,23,27,28,31,32,33,36]. The association of CRP level and BMI was assessed in 12 studies showing conflicting results, but a trend of lower CRP in obese patients than those with normal BMI (Table 2)[15,16,17,20,22,23,29,30,31,33,35,36].

Functional disability: HAQ score. HAQ score was assessed by BMI in 5 studies, 2 involving 1264 patients who were included in the metaanalysis because the studies involved similar BMI groups and comparable expression of HAQ (means and not medians)[31,33]. HAQ score was higher for obese than non-obese patients (mean difference 0.10, 95% CI 0.01–0.19, p = 0.03; Figure 3), with no heterogeneity among studies (I^2 = 0%). Among the remaining 3 studies, 1 found a median HAQ score of 0.75 [interquartile range (IQR) 0.250–1.375], 0.875 (0.312–1.562), and 1.375 (0.625–1.870) for patients with BMI < 25 kg/m^2, 30–35 kg/m^2, and > 35 kg/m^2, respectively[18]. Another study found a median HAQ score of 1.46 (IQR 0.39–2) and 2.25 (1.71–2.86) for patients with BMI 19.5–22.9 kg/m^2 (considered normal BMI for patients with RA in this study) and > 28 kg/m^2 (considered obese), respectively[23]. The last study reported a median HAQ score of 1.5 (1.4), 1.5 (1.5), and 1.75 (1.5) for patients with BMI < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2, respectively[15]. These findings suggested higher HAQ score for obese patients than for those with normal BMI.

Radiographic joint damage. Radiographic joint damage at baseline was assessed by BMI in 8 studies, 3 involving 1465 patients were included in the metaanalysis because the studies involved similar BMI groups and comparable expression of radiographic joint damage (means and not medians)[25,29,30]. Radiographic joint damage was lower among obese than non-obese patients (standardized mean difference –0.15, 95% CI –0.29 to –0.02, p = 0.03; Figure 4). Heterogeneity was acceptable with I^2 = 38%. Among the remaining 5 studies, 1 found a median modified SvdH score of 4.5 (IQR 1.5–11), 5.5 (2.5–20), and 7 (2–27.5) for BMI ≥ 30 kg/m^2 (obesity), 25–29.9 kg/m^2 (overweight), and 20–24.9 kg/m^2, respectively[31]. Another study reported a median modified SvdH score of 5.5 (1.5–18), 7 (2.5–25), and 12 (2.5–46.5) for patients with BMI ≥ 30 kg/m^2, 25–30 kg/m^2, and < 25 kg/m^2, respectively[26]. The third study showed less erosive RA among obese patients than patients with BMI 20–30 kg/m^2 (53% vs 85%)[22]. The fourth study, supporting the finding of lower radiographic joint damage in obese patients than non-obese patients, found a mean SENS of 11.27 ± 7.40 and 16.05 ± 8.34 for patients with BMI > 25 kg/m^2 and 18.5–24.9 kg/m^2, respectively[37]. The last study had conflicting results[33].

Analysis with the overweight group. Analyses were made comparing the normal BMI group with the overweight and the obese groups (BMI > 25 kg/m^2), but no significant results were found, although they showed a trend toward higher DAS28 and HAQ and lower radiographic joint damage among the overweight and obese groups. The forest plots are in the Supplementary Data (available online at jrheum.org).

Publication bias. Publication bias was not assessed for HAQ

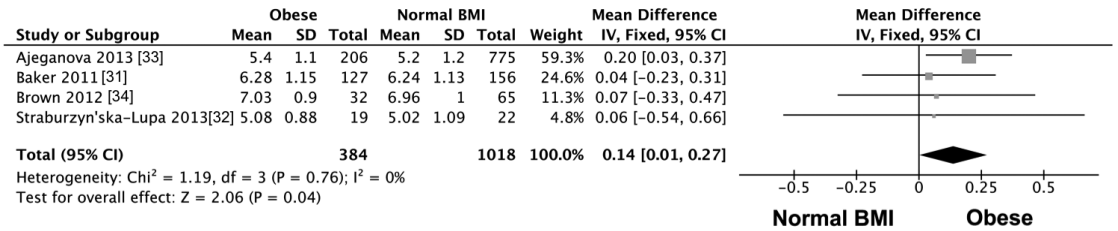

Figure 2. Forest plot of the effect of BMI (obesity ≥ 30 kg/m^2 vs normal weight 18.5–25 or 20–25 kg/m^2) on DAS28. BMI: body mass index; DAS28: Disease Activity Score in 28 joints; IV: independent variable.

Table 2. Systematic review of the literature for DAS28, ESR, CRP, TJC, SJC, and GPA, and GHA. GPA was evaluated by VAS from 0 (no pain) to 100 (worst imaginable pain). GHA was evaluated by VAS from 0 (best imaginable health state) to 100 (worst imaginable health state). Values are mean (SD) or median (IQR).

Articles	n	BMI Group, kg/m²	DAS28	ESR, mm/h	CRP, mg/l	TJC	SJC	GPA	GHA
Ajeganova, *et al*[33]	89	< 20		35.5 (25)	26 (9–56)			42.2 (23.59)	45.2 (24.2)
	775	20–24.99		35 (25.9)	17 (9–42)			45.7 (23.6)	45.7 (25.2)
	526	25–29.99		34.7 (22.9)	20 (9–44)			46.1 (23.9)	43.7 (25.9)
	206	≥ 30		37.1 (24.6)	17 (9–40)			50.4 (24.6)	49.3 (24.7)
Baker, *et al*[31]	41	< 20		63.5 (40–80)	24 (10–48)	20 (13–38)	13 (6–25)	64 (51–76)	
	156	20–24.9		40 (25–60)	14 (4–41)	24.5 (13–37)	12 (8–19)	62.5 (45.5–77)	
	175	25–29.9		38 (20–60)	13 (5–28)	24 (15–38)	13 (8–22)	71 (52–82)	
	127	≥ 30		35 (24–51)	9 (5–27)	8 (16–38)	13 (8–19)	67 (54–80)	
Choe, *et al*[20]	50	< 18.5	3.5 (1.3)	36.6 (32.4)	11 (1.9)	2.6 (3.2)	1.3 (2.5)	38 (22)	
	294	18.5–23	3.3 (1.1)	32.5 (23.1)	6 (1.3)	2.2 (3.8)	0.6 (1.3)	37 (27)	
	116	23–25	3.3 (1.1)	27.7 (18.8)	9 (2.4)	2.6 (4.3)	0.7 (1.5)	40 (28)	
	108	≥ 25	3.4 (1.2)	29.1 (20.1)	6 (0.9)	3 (4.2)	0.7 (1.2)	43 (28)	
Escalante, *et al*[27]	38	< 20		47 (29)		13 (10)	5 (6)		
	195	20–25		38 (28)		14 (13)	6 (6)		
	264	25–30		43 (27)		15 (13)	8 (7)		
	282	≥ 30		42 (25)		16 (12)	8 (7)		
Fukuda, *et al*[35]	131	< 20	3.66 (1.16)		8.8 (1.22)				
	191	20–25	3.42 (1.23)		11.4 (2.01)				
	63	≥ 25	3.61 (1.13)		9.8 (1.15)				
Humphreys, *et al*[18]	459	< 25	3.5 (2.6–4.5)						
	456	25–30	3.4 (2.4–4.4)						
	217	30–35	3.8 (2.9–4.9)						
	87	≥ 35	4.2 (3.3–5.2)						
Iannone, *et al*[15]	117	< 25	5.4 (0.9)	38 (16)	24 (25)				
	109	25–30	5.6 (0.9)	36 (11)	20 (14)				
	66	> 30	5.6 (1.3)	38.5 (3.4)	22 (13)				
Jawaheer, *et al*[28]	Total of 5161	< 18.5	4.3 (0.24)						
		18.5–24.9	4.1 (0.07)						
		25–29.9	4.3 (0.06)						
		≥ 30	4.4 (0.09)						
	1079 Men	< 18.5		30.2 (12.15)		5.5 (2.94)	5.5 (2.52)	46 (8.8)	
		18.5–24.9		26.4 (2.83)		5.6 (0.64)	3.8 (0.48)	37 (2.5)	
		25–29.9		26.5 (2.8)		5.3 (0.66)	3.8 (0.59)	36 (2.2)	
		≥ 30		22.3 (3.64)		5.3 (1.28)	2.9 (0.72)	36 (4.7)	
	4082 Women	< 18.5		30.2 (4.05)		6.7 (1.33)	4.8 (0.78)	42 (4.4)	
		18.5–24.9		27.3 (0.8)		6.4 (0.28)	4.4 (0.25)	40 (1.4)	
		25–29.9		30.6 (1.21)		7.6 (0.4)	4.8 (0.3)	43 (1.5)	
		≥ 30		32.5 (1.62)		7.1 (0.52)	4.5 (0.36)	44 (1.7)	
Klaasen, *et al*[22]	8	< 20	5.6 (1.2)	31 (21)	23 (27)				
	66	20–30	5.9 (1)	36 (27)	24 (33)				
	15	> 30	6.5 (1)	31 (24)	17 (15)				
Oranskiy, *et al*[36]	18	< 18.5	7.4 (6.2–8.1)	29.0 (15.0–38.0)	22.0 (13.0–29.0)				
	39	18.5–24.9	7.3 (6.3–7.8)	33.5 (26.0–37.5)	20.5 (14.9–20.2)				
	26	≥ 25	7.2 (6.9–7.7)	20.0 (14.0–28.0)	20.0 (14.0–28.0)				
Ottaviani, *et al*[16]	25	< 25	5.3 (1.6)	22 (9–44)	12 (5–30)			57.5 (27.9)	
	29	25–30	5.5 (1.4)	30 (16–44)	19 (8–24)			58.5 (25)	
	22	> 30	5.3 (1.1)	27 (17–36)	14 (5–30)			67.7 (18.9)	
Pers, *et al*[17]	121	< 25	5.04 (1.34)	24 (10–39)	6.3 (2.6–24.8)	7 (4–13)	4 (1–7)		
	54	25–30	5.14 (1.36)	28 (11–44)	8.0 (2.5–22.1)	10 (5–16)	4 (2–7)		
	32	> 30	5.22 (1.11)	32 (21–57)	11.2 (7.4–24.1)	8 (5.5–13)	3 (1–5)		
Stavropoulos-Kalinoglou,*et al*[23]	Total of 294	< 18.5	4 (3.5–5.58)	20 (6.25–27.5)	16.6 (5.8–17.5)				
		18.5–22.9	2.83 (2.33–4.08)	13.75 (2.5–20)	5 (1.6–10)				
		23–28	4.03 (3.33–5.33)	17.5 (7.5–22.5)	9.1 (3.3–12.5)				
		> 28	4.33 (3.17–5)	21.25 (8.75–30)	10 (3.3–17.5)				
Straburzyńska-Lupa, *et al*[32]	22	18.5–24.9		33.73 (22.78)					
	18	25–29.9		32.22 (15.97)					
	19	≥ 30		27.74 (18.45)					

Table 2. Continued.

Articles	n	BMI Group, kg/m²	DAS28	ESR, mm/h	CRP, mg/l	TJC	SJC	GPA	GHA
van der Helm-van Mil, *et al*, EAC[29]	156	< 25			38.4 (44.3)	7.4 (5.1)			53.2 (23.8)
	146	25–30			35 (36.9)	7.7 (5.6)			45.5 (23.2)
	30	≥ 30			32.4 (33.1)	6.3 (5.6)			51.8 (22.9)
BeST[29]	110	< 25			43.7 (54.7)	14.7 (6.4)			51.9 (19.7)
	101	25–30			39.2 (40)	16 (7)			52 (20.5)
	36	≥ 30			27 (27.1)	13.2 (6.5)			51.7 (17.1)
Westhoff, *et al*[30]	303	< 25	4.6 (1.6)		20.5 (25)			3.9 (2.5)	3 (2)
	315	25–29.9	4.9 (1.4)		22 (25)			4.5 (2.6)	3.3 (1.9)
	149	≥ 30	4.9 (1.5)		22.4 (24)			4.6 (2.8)	3.7 (1.9)

DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; GPA: patient's global pain assessment; GHA: global health assessment; VAS: visual analog scale; BMI: body mass index; EAC: Early Arthritis Clinic.

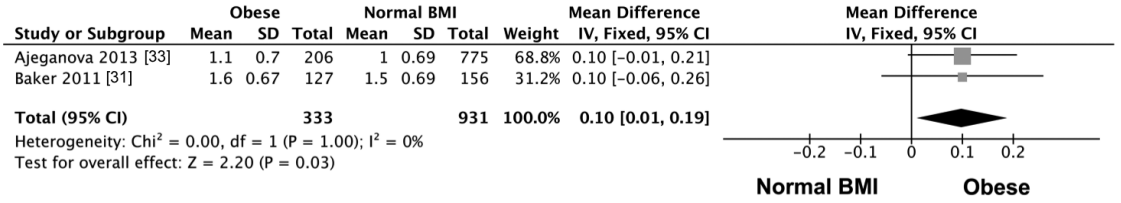

Figure 3. Forest plot of the effect of BMI (obesity ≥ 30 kg/m² vs normal weight 18.5–25 or 20–25 kg/m²) on HAQ score. BMI: body mass index; HAQ: Health Assessment Questionnaire; IV: independent variable.

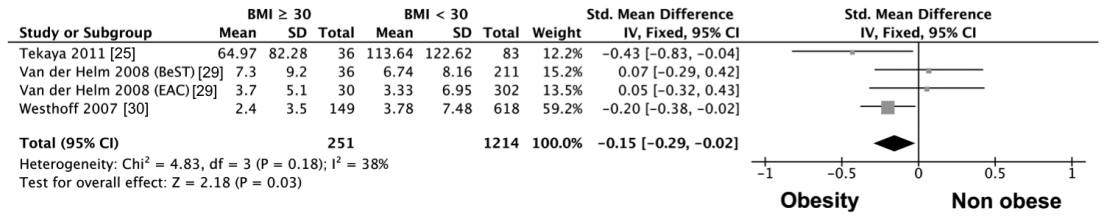

Figure 4. Forest plot of the effect of BMI (obesity ≥ 30 kg/m² vs non-obese < 30 kg/m²) on radiographic joint damage (standardized means). BMI: body mass index; IV: independent variable.

because only 2 studies were included. We found no publication bias for DAS28 (Egger test p = 0.294) or radiographic joint damage (Egger test p = 0.716). The funnel plots are in the Supplementary Data (available online at jrheum.org).

DISCUSSION

Our systematic review with metaanalysis found significantly higher RA disease activity in obese than non-obese patients. As well, obesity in RA was associated with increased HAQ score. Conversely, radiographic joint damage was lower for obese than non-obese patients.

This increase of 0.14 in DAS28 for obese patients with RA may seem low and with a small clinical relevance, but this result was statistically significant with no heterogeneity among selected studies. If all articles could have been included in the metaanalysis, we probably would have found a higher difference and a stronger association. Indeed, studies included in our systematic review showed increased DAS28 among obese patients, between 0.1 and 1.6.

To better understand why DAS28 was increased in obese patients with RA, we evaluated each of its components. Increased DAS28 could result from an overestimation of SJC among obese patients because of evaluation difficulties. However, our systematic review did not reveal an association of SJC and obesity. Moreover, a study found that SJC predicted RA disease activity and severity in obese subjects at least as well as in subjects with lower BMI[38]. Another cause for the increased DAS28 could be the increased levels

of inflammation markers among obese patients independent of RA because of the production of IL-6 by adipose tissue, which stimulates hepatic secretion of CRP[39]. However, our systematic review revealed lower CRP levels in obese patients than others. The increased DAS28 may mainly result from increased scores for subjective measures such as TJC, GPA, and GHA. Indeed, our systematic review revealed higher TJC, GPA, and GHA in obese than non-obese patients. Moreover, obesity is known to be associated with pain and reduced quality of life[40]. Therefore, the increase in subjective measure scores may be explained by comorbidities of obese patients, independent of RA features. Mechanisms of this association remain to be explored in prospective studies to evaluate the respective roles of subjective measures and adipokines in increased DAS28.

The association of obesity and increased HAQ score in RA revealed by our metaanalysis may seem irrelevant because the difference was 0.1 and only 2 studies were included. However, we may have found a stronger association if all articles had been included in the metaanalysis. Indeed, the other 3 studies in the systematic review found an increased HAQ score of 0.25 to 0.79 among obese patients. This association could reveal greater severity of RA in obese than non-obese patients, but as demonstrated before, those patients had higher subjective measure scores. Therefore, this association may result from increased joint pain and comorbidities in obese patients. Indeed, several studies revealed an association of increased BMI and impaired health-related quality of life[41]. The association of HAQ score and obesity among patients with RA may be associated with obesity, independent of RA course. Obese patients also seem to be less responsive to treatment. Indeed, 1 study showed lower response to DMARD among obese than non-obese patients[42]. Others found lower remission rate with anti-TNF-α therapy, particularly infliximab (IFX)[16,22,43]. However, 1 recent retrospective study reported conflicting results with tocilizumab (TCZ)[17]. This finding could also be explained by increased DAS28, independent of RA course. Therefore, DAS28 may not be the best way to evaluate therapeutic response in obese patients, and objective measures such as ultrasonography could be considered in some cases.

The lower radiographic joint damage among obese compared with non-obese patients with RA could be considered as a paradoxical effect in considering the results for DAS28 and HAQ score. As seen before, the association of obesity with increased DAS28 and impaired HAQ score results from subjective measures and may not reflect the exact disease severity. Obese patients may have lower radiographic joint damage and a slower radiographic joint damage progression as reported in 1 study, for early RA after 3 years of followup, but other longitudinal studies assessing radiographic progression among the obese are needed[30]. This favorable effect on radiographic joint damage may have different explanations. First of all, obese patients are more likely to develop seronegative RA, which is known to be associated with a better structural prognosis. However, in 3 studies, radiographic damage and progression remained significantly lower in obese patients after adjustment for anticitrullinated protein antibodies (ACPA) status and for ACPA and RF status[25,30,31]. Then, adiponectin is decreased in obese patients and is associated with radiographic damage[44,45]. This may be explained by a proinflammatory effect of adiponectin on fibroblast-like synoviocytes with an increase of vascular endothelial growth factor, matrix metalloproteinase (MMP) 1, and MMP-13 production[46]. Thus, obese patients with RA may have a lower level of circulating adiponectin that may protect against radiographic joint damage. Indeed, several studies found an association of radiographic disease progression and increased adiponectin level[7,47]. Another explanation could be a more intensive therapy because of high DAS28 levels and/or high plasmatic drug concentrations for treatment with dosage adapted to the weight, such as IFX, abatacept, and TCZ. Finally, it could also result from an inverse correlation between BMI and osteoporosis because patients with osteoporosis present with more radiographic joint damage attributable to common pathophysiological mechanisms[48,49]. This might explain in part the increased risk of seronegative RA, the lower radiographic joint damage, and the poorer therapeutic response[9,16,22,31,43,50].

The main limitation of our metaanalysis is the lack of comparable studies, which led to the inclusion of only 7 articles, whereas more studies were available in the literature. Indeed, data for BMI groups and measurements (means or medians) were often different. Another limitation is the difference of obesity and overweight BMI intervals between studies included in our metaanalysis. However, almost all studies included in our systematic review found the same trends.

Obesity is associated with increased disease activity and HAQ score, but reduced radiographic joint damage in RA. Further studies are needed to reveal the involved mechanisms and to evaluate the effect of obesity on RA course.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

REFERENCES

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-55.
2. Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, et al; QUEST-RA Group. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.
3. Pereira RM, de Carvalho JF, Bonfá E. Metabolic syndrome in

rheumatological diseases. Autoimmun Rev 2009;8:415-9.
4. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab 2000;85:3338-42.
5. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006; 6:772-83.
6. Ebina K, Fukuhara A, Ando W, Hirao M, Koga T, Oshima K, et al. Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. Clin Rheumatol 2009;28:445-51.
7. Giles JT, van der Heijde DM, Bathon JM. Association of circulating adiponectin levels with progression of radiographic joint destruction in rheumatoid arthritis. Ann Rheum Dis 2011;70:1562-8.
8. García-Poma A, Segami MI, Mora CS, Ugarte MF, Terrazas HN, Rhor EA, et al. Obesity is independently associated with impaired quality of life in patients with rheumatoid arthritis. Clin Rheumatol 2007;26:1831-5.
9. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Mod Rheumatol 2009;19:273-82.
10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62:2569-81.
12. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37.
13. Rau R, Wassenberg S, Herborn G, Stucki G, Gebler A. A new method of scoring radiographic change in rheumatoid arthritis. J Rheumatol 1998;25:2094-107.
14. Dias EM, Lukas C, Landewé R, Fatenejad S, van der Heijde D. Reliability and sensitivity to change of the Simple Erosion Narrowing Score compared with the Sharp-van der Heijde method for scoring radiographs in rheumatoid arthritis. Ann Rheum Dis 2008;67:375-9.
15. Iannone F, Fanizzi R, Notarnicola A, Scioscia C, Anelli MG, Lapadula G. Obesity reduces the drug survival of second line biological drugs following a first TNF-α inhibitor in rheumatoid arthritis patients. Joint Bone Spine 2015;82:187-91.
16. Ottaviani S, Gardette A, Tubach F, Roy C, Palazzo E, Gill G, et al. Body mass index and response to infliximab in rheumatoid arthritis. Clin Exp Rheumatol 2015;33:478-83.
17. Pers YM, Godfrin-Valnet M, Lambert J, Fortunet C, Constant E, Mura T, et al. Response to tocilizumab in rheumatoid arthritis is not influenced by the body mass index of the patient. J Rheumatol 2015;42:580-4.
18. Humphreys JH, Verstappen SM, Mirjafari H, Bunn D, Lunt M, Bruce IN, et al. Association of morbid obesity with disability in early inflammatory polyarthritis: Results from the Norfolk Arthritis Register. Arthritis Care Res 2013;65:122-6.
19. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). [Internet. Accessed September 22, 2015.] Available from: www.who.int/nutrition/publications/obesity/WHO_TRS_894/en
20. Choe JY, Bae J, Lee H, Park SH, Kim SK. Lack association of body mass index with disease activity composites of rheumatoid arthritis in Korean population: cross-sectional observation. Clin Rheumatol 2014;33:485-92.
21. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
22. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum 2011;63:359-64.
23. Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF, Nevill AM, Jamurtas AZ, Koutedakis Y, et al. Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis. Clin Rheumatol 2009;28:439-44.
24. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis 2007;66:1316-21.
25. Tekaya R, Sahli H, Zribi S, Mahmoud I, Ben Hadj Yahia C, Abdelmoula L, et al. [Obesity has a protective effect on radiographic joint damage in rheumatoid arthritis]. [Article in French] Tunis Med 2011;89:462-5.
26. Baker JF, Ostergaard M, George M, Shults J, Emery P, Baker DG, et al. Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years. Ann Rheum Dis 2014;73:1923-8.
27. Escalante A, Haas RW, del Rincón I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Arch Intern Med 2005;165:1624-9.
28. Jawaheer D, Olsen J, Lahiff M, Forsberg S, Lähteenmäki J, da Silveira IG, et al; QUEST-RA. Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA Study. Clin Exp Rheumatol 2010;28:454-61.
29. van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;67:769-74.
30. Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007;56:3575-82.
31. Baker JF, George M, Baker DG, Toedter G, Von Feldt JM, Leonard MB. Associations between body mass, radiographic joint damage, adipokines and risk factors for bone loss in rheumatoid arthritis. Rheumatology 2011;50:2100-7.
32. Straburzyńska-Lupa A, Nowak A, Romanowski W, Korman P, Pilaczyńska-Szcześniak Ł. A study of the link between bone turnover markers and bone mineral density with inflammation and body mass in postmenopausal women with active rheumatoid arthritis. J Bone Miner Metab 2013;31:169-76.
33. Ajeganova S, Andersson ML, Hafström I; BARFOT Study Group. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: A long-term followup from disease onset. Arthritis Care Res 2013;65:78-87.
34. Brown RA, Spina D, Butt S, Summers GD. Long-term effects of anti-tumour necrosis factor therapy on weight in patients with rheumatoid arthritis. Clin Rheumatol 2012;31:455-61.
35. Fukuda W, Omoto A, Ohta T, Majima S, Kimura T, Tanaka T, et al. Low body mass index is associated with impaired quality of life in patients with rheumatoid arthritis. Int J Rheum Dis 2013; 16:297-302.
36. Oranskiy SP, Yeliseyeva LN, Tsanaeva AV, Zaytseva NV. Body composition and serum levels of adiponectin, vascular endothelial growth factor, and interleukin-6 in patients with rheumatoid arthritis. Croat Med J 2012;53:350-6.
37. Velpula UD, Agrawal S, Thomas J, Prabu VN, Rajasekhar L,

Narsimulu G. Low body mass index is adversely associated with radiographic joint damage in Indian patients with early rheumatoid arthritis. J Rheumatol 2011;38:434-8.
38. Caplan L, Davis LA, Bright CM, Kerr GS, Lazaro DM, Khan NA, et al. Body mass index and the rheumatoid arthritis swollen joint count: an observational study. Arthritis Care Res 2013;65:101-6.
39. Gentile M, Panico S, Rubba F, Mattiello A, Chiodini P, Jossa F, et al. Obesity, overweight, and weight gain over adult life are main determinants of elevated hs-CRP in a cohort of Mediterranean women. Eur J Clin Nutr 2010;64:873-8.
40. Taylor R Jr, Pergolizzi JV, Raffa RB, Nalamachu S, Balestrieri PJ. Pain and obesity in the older adult. Curr Pharm Des 2014; 20:6037-41.
41. Heo M, Allison DB, Faith MS, Zhu S, Fontaine KR. Obesity and quality of life: mediating effects of pain and comorbidities. Obes Res 2003;11:209-16.
42. Sandberg ME, Bengtsson C, Källberg H, Wesley A, Klareskog L, Alfredsson L, et al. Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. Ann Rheum Dis 2014;73:2029-33.
43. Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al; Gruppo Italiano di Studio sulle Early Arthritis (GISEA). Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. Arthritis Care Res 2013;65:94-100.
44. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? J Mol Med 2002; 80:696-702.
45. Frommer KW, Schäffler A, Büchler C, Steinmeyer J, Rickert M, Rehart S, et al. Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis? Ann Rheum Dis 2012;71:1724-32.
46. Choi HM, Lee YA, Lee SH, Hong SJ, Hahm DH, Choi SY, et al. Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediators. Arthritis Res Ther 2009;11:R161.
47. Meyer M, Sellam J, Fellahi S, Kotti S, Bastard JP, Meyer O, et al. Serum level of adiponectin is a surrogate independent biomarker of radiographic disease progression in early rheumatoid arthritis: results from the ESPOIR cohort. Arthritis Res Ther 2013;15:R210.
48. Barrera G, Bunout D, Gattás V, de la Maza MP, Leiva L, Hirsch S. A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. Nutrition 2004;20:769-71.
49. Zhang J, Redden DT, McGwin G Jr, Callahan LF, Smith EA, Alarcón GS, et al; Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis Investigators. Generalized bone loss as a predictor of three-year radiographic damage in African American patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2010;62:2219-26.
50. Wesley A, Bengtsson C, Elkan AC, Klareskog L, Alfredsson L, Wedrén S; Epidemiological Investigation of Rheumatoid Arthritis Study Group. Association between body mass index and anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis: results from a population-based case-control study. Arthritis Care Res 2013;65:107-12.