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Original article

The association between increased body mass index and response to conventional synthetic disease-modifying anti-rheumatic drug treatment in rheumatoid arthritis: results from the METEOR database

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Abstract

Background. Few data exist on the association between increased BMI and response to conventional synthetic DMARDs (csDMARDs) in RA. We aimed to explore the association between increased (overweight or obese) BMI on csDMARD prescribing, MTX dose and disease activity over 12 months.

Methods. Participants in an international RA database were stratified into early (<1 year post-diagnosis) and established RA. EULAR response, 28-joint DAS (DAS28) remission and treatments were recorded at baseline, 6 months and 12 months. Increased BMI was explored in early and established RA as predictors of good EULAR response, DAS28 remission, number of csDMARDs and MTX dose, using logistic and linear regression.

Results. Data from 1313 patients, 44.3% with early RA, were examined. In early RA, increased BMI was not significantly associated with remission. In established RA, obese patients on monotherapy were significantly less likely to achieve good EULAR response or DAS28 remission at 6 months and more likely to be treated with combination csDMARDs compared with normal BMI. In patients taking MTX, overweight and obese patients with early and established RA were exposed to higher MTX doses (mono- and combination therapy), with a mean dose of 20 mg/week, compared with 15 mg/week in those of normal BMI.

Conclusion. We observed that compared with patients with normal BMI, overweight and obese individuals experienced more intensive csDMARD exposures. Similar response rates were observed in early RA but increased BMI was associated with reduced response in established RA. Optimization of targeted RA treatment remains important, particularly in those with increased BMI where response in established disease may be attenuated.

Key words: rheumatoid arthritis, body mass index, DMARD, treatment, disease activity, response

Rheumatology key messages

- In established RA, increased BMI patients are less likely to achieve remission compared with normal BMI patients.
- In established RA, overweight/obese patients are more likely to be treated with combination therapy than monotherapy.
- Overweight/obese patients are exposed to higher doses of methotrexate compared with normal BMI patients.

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Introduction

Approximately 40% of the world's population are overweight or obese [1]. High body mass index (BMI) is increasingly prevalent, up to 60%, among patients with RA [2–4]. Obesity is a risk factor for developing RA and common on first presentation [5, 6].

Previous studies demonstrate an association between obesity and adverse outcomes in RA, including higher disease activity, elevated inflammatory markers and increased disability [4, 6, 7]. High BMI at diagnosis is

associated with a reduced likelihood of achieving low disease activity or remission compared with those of normal BMI, regardless of DMARD use [7–10]. However, most studies have been conducted in early arthritis, or within the first 3 years of diagnosis. Evidence in patients with established disease is lacking [9].

Despite this, patients with high BMI appear to have slower radiographic progression [11, 12]. The explanation for this apparent paradox between BMI and radiographic progression is unclear, but could reflect increased conventional synthetic DMARD (csDMARD) exposures in obese and overweight patients, particularly if the 28-joint DAS (DAS28) is used as a treatment target ('treat-to-target' approach). Excess adiposity is an inflammatory state and can increase DAS28 scores [4, 13]. This is further compounded by the effect of obesity on global health scores—obesity in RA is strongly associated with decreased health-related quality of life (HRQoL) [8, 10]. A low likelihood of remission may therefore be due to a pro-inflammatory state or patient global assessment.

Despite the difference in remission outcomes between obese and non-obese patients with RA, the same treat-to-target approach is used for all. It is not known whether obese and overweight patients require more intensive csDMARD therapy or an increased dose of csDMARDs, such as methotrexate (MTX), to achieve the same treatment targets as patients with a normal BMI. Such information would enable more informed prescribing practices, along with a holistic approach encompassing diet and lifestyle.

Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) is an international, observational database capturing real-world data of daily clinical practice and management of patients with RA [14, 15]. We aimed to explore associations between overweight or obese (i.e. increased) BMI and response to treatment and DMARD prescribing patterns, stratified by early and established RA, over 12 months. We explored the association between increased BMI and response to csDMARD therapy and remission and identify whether BMI is associated with the use of combination csDMARDs and MTX dose.

Methods

Study design and patient recruitment

This study used real-world data from the METEOR database between 2008 and 2013 (inclusive). Countries were included if data were of sufficient quality and completeness to conduct analyses. Information on the cohort has been described previously elsewhere [15, 16]. Patients with a clinically confirmed diagnosis of RA were recruited at the initial (baseline) visit and were included if they had a confirmed follow-up appointment with a rheumatologist at 6 and 12 months (i.e. data at three time points). Subjects were included if attendance was recorded at baseline, 6 months and 12 months. Patients were stratified by disease duration, with patients $\leq$1 year post-diagnosis of RA having early RA (eRA) and those $>$1 year post-diagnosis having established RA (estRA).

Data were collected during regular healthcare appointments and subsequently anonymized. The METEOR Executive Scientific Committee approved this study and obtained approval to use data from participating centres. As all data were fully anonymized and this study included data collected during regular healthcare (not from intervention studies) reviews, approval of the protocol by local ethics committees was not deemed necessary. All study procedures were in accordance with the Declaration of Helsinki.

Data collection and analysis

Variables recorded include patient demographics (gender, age at onset and baseline visit, height, weight), duration of disease, RF, anti-CCP and smoking status. Clinical and laboratory data comprised ESR, CRP, tender joint count (TJC) and swollen joint count (SJC) (as per the DAS28 score [17]), patient global and pain assessment scores and HAQ recorded at the baseline visit and 6 and 12 months. DAS28 was calculated at each visit and remission (DAS28 $\leq$2.6) and EULAR response criteria (good EULAR response defined as DAS28 $\leq$3.2 and a decrease in DAS28 $>$1.2 compared with baseline) [18]. EULAR response and DAS28 at subsequent visits (6 and 12 months) were compared with the baseline visit.

DAS28 was calculated differently depending on the completeness of the submitted data from different participating centres. This included DAS28-ESR, DAS28-CRP and DAS28 based on three variables. Of note, there were varying levels of missing data, especially for patient global assessment scores and HAQ. Due to the manner in which data are entered into the METEOR database (i.e. anonymized), it was not possible to retrospectively investigate reasons for incomplete data.

Doses of csDMARD medication were variable in completeness. Analyses on dosing variability between patients of varying BMIs were therefore only conducted for MTX, as the most frequently prescribed csDMARD and the drug for which the most complete dosing information was available.

Exposure

BMI was calculated at baseline using the recorded height and weight, as per the World Health Organization (WHO) definitions: normal weight (18.5–$<$25 kg/m^2), overweight (25–$<$30 kg/m^2) and obesity ($\geq$30 kg/m^2) [1]. Underweight individuals (BMI $<$18.5 kg/m^2) were excluded from analyses due to the low prevalence of cases and unclear impact on response to treatment [19]. Exposure variables were overweight or obese BMI at baseline as compared with patients in the WHO-defined normal BMI category.

Outcome

Increased BMI at baseline (overweight or obese, as per the above definitions) was explored as a predictor of

DAS28 remission and good EULAR response (and their components) compared with individuals of normal BMI. Analyses were performed separately in patients with eRA and estRA and also at 6 and 12 months. Increased BMI was explored as a predictor of the number of DMARDs prescribed and MTX dose [20].

Covariates

Covariates were age, gender, smoking and baseline outcome variables (where applicable). When assessing outcomes of EULAR response and DAS28 remission, baseline DAS28 was considered a covariate. When assessing for individual components of either remission outcome, the respective baseline component of DAS28 or EULAR response was included as a covariate.

Statistical analysis

Analyses were conducted using logistic and linear regression models, controlling for the above covariates. Sensitivity analyses were subsequently performed for corticosteroid use (dose and duration of corticosteroids were unavailable).

Linear regression models assessing the dose of MTX prescribed at 6 and 12 months were controlled for baseline MTX dose. Repeated measures multivariate analysis of variance (MANOVA) was undertaken to assess for within-person correlation.

Sensitivity analyses were performed for symptom duration and to explore how representative the study sample was to all METEOR participants from included countries.

Results

Baseline demographics and disease activity

From the complete database we identified the patients with sufficient quantity and quality of data to be included in this study. Complete exposure and outcome data were available for 1313 patients from 11 countries at baseline and follow-up visits and these were included in the analyses. Overall, 1056 of the 1313 patients were female (80.4%), with a mean age of 53.5 years (S.D. 13.3). With regards to disease stage, 582 patients were classed as eRA and 731 with estRA. Table 1 shows demographic and clinical variables in patients with eRA and Table 2 describes variables in patients with estRA, stratified by BMI. In both eRA and estRA there was a relatively similar distribution of patients of normal BMI and overweight, with slightly fewer classed as obese,

Table 1 Baseline demographic and clinical variables for patients with eRA stratified by BMI category (as per the WHO definition, described in 'Methods')

Variables	Normal BMI [*n* = 196 (33.7%)]	Overweight [*n* = 200 (34.4%)]	Obese [*n* = 157 (27.0%)]	Underweight [*n* = 29 (5.0%)]	Overall (*N* = 582)
Female, *n* (%)	159 (81.1)	142 (71.0)	128 (81.5)	27 (93.1)	456 (78.4)
Age at diagnosis, years, mean (S.D.)	48.0 (15.7)	51.1 (12.4)	52.0 (11.6)	41.6 (11.8)	49.8 (13.6)
Age at baseline visit, years, mean (S.D.)	48.0 (15.8)	51.1 (12.4)	52.1 (11.6)	41.6 (11.8)	49.8 (13.6)
Time since diagnosis, years, mean (S.D.)	0.0284 (0.396)	0.0209 (0.330)	0.0893 (0.208)	0.0227 (0.0776)	0.0420 (0.320)
RF, *n* (%)					
Negative	55 (28.1)	57 (28.5)	54 (34.4)	2 (6.9)	168 (28.9)
Positive	136 (69.4)	140 (70.0)	99 (63.1)	27 (93.1)	402 (69.1)
Unknown	5 (2.6)	3 (1.5)	4 (2.5)	0 (0)	12 (2.1)
aCCP, *n* (%)					
Negative	38 (19.4)	40 (20.0)	46 (29.3)	1 (3.4)	125 (21.5)
Positive	73 (37.2)	71 (35.5)	58 (36.9)	10 (34.5)	212 (36.4)
Unknown	85 (43.4)	89 (44.5)	53 (33.8)	18 (62.1)	245 (42.1)
Baseline smoking status, *n* (%)					
Never	142 (72.4)	156 (78.0)	120 (76.4)	24 (82.8)	442 (75.9)
Current	33 (16.8)	19 (9.5)	20 (12.7)	3 (10.3)	75 (12.9)
Previous	21 (10.7)	25 (12.5)	17 (10.8)	2 (6.9)	65 (11.2)
Baseline DAS28, mean (S.D.)	5.41 (1.64)	5.23 (1.66)	5.26 (1.56)	6.37 (1.07)	5.36 (1.62)
Baseline ESR, mm/h, mean (S.D.)	53.7 (37.7)	48.4 (33.9)	48.5 (32.3)	76.3 (29.5)	51.6 (35.1)
Baseline TJC, mean (S.D.)	11.5 (9.05)	11.1 (9.30)	10.9 (9.47)	15.1 (8.47)	11.4 (9.25)
Baseline SJC, mean (S.D.)	6.52 (5.62)	5.89 (5.83)	6.30 (5.27)	7.59 (5.38)	6.30 (5.59)
Baseline patient global score					
Mean (S.D.)	48.5 (24.2)	50.7 (22.3)	52.9 (23.6)	58.4 (19.3)	51.0 (23.2)
Missing, *n* (%)	57 (29.1)	37 (18.5)	25 (15.9)	7 (24.1)	126 (21.6)
Baseline HAQ					
Mean (S.D.)	1.06 (0.626)	1.09 (0.751)	1.15 (0.766)	1.50 (0.661)	1.11 (0.719)
Missing, *n* (%)	144 (73.5)	139 (69.5)	94 (59.9)	25 (86.2)	402 (69.1)

TABLE 2 Baseline demographic and clinical variables for patients with estRA stratified by BMI category (as per the WHO definition described in 'Methods')

Variables	Normal BMI [*n* = 270 (36.9%)]	Overweight [*n* = 264 (36.1%)]	Obese [*n* = 189 (25.9%)]	Underweight [*n* = 8 (1.1%)]	Overall (*N* = 731)
Female, *n* (%)	228 (84.4)	206 (78.0)	159 (84.1)	7 (87.5)	600 (82.1)
Age at diagnosis, years, mean (S.D.)	44.1 (14.1)	47.8 (13.2)	48.5 (12.3)	45.1 (13.5)	46.6 (13.4)
Age at baseline visit, years, mean (S.D.)	54.2 (13.3)	57.6 (12.2)	57.7 (10.6)	59.6 (18.0)	56.4 (12.4)
Time since diagnosis, years, mean (S.D.)	10.0 (7.75)	9.73 (7.71)	9.20 (7.48)	14.5 (7.56)	9.76 (7.67)
RF, *n* (%)					
Negative	67 (24.8)	62 (23.5)	45 (23.8)	1 (12.5)	175 (23.9)
Positive	186 (68.9)	184 (69.7)	131 (69.3)	6 (75.0)	507 (69.4)
Unknown	17 (6.3)	18 (6.8)	13 (6.9)	1 (12.5)	49 (6.7)
aCCP, *n* (%)					
Negative	53 (19.6)	60 (22.7)	43 (22.8)	1 (12.5)	157 (21.5)
Positive	128 (47.4)	119 (45.1)	90 (47.6)	7 (87.5)	344 (47.1)
Unknown	89 (33.0)	85 (32.2)	56 (29.6)	0 (0)	230 (31.5)
Baseline smoking status, *n* (%)					
Never	164 (60.7)	192 (72.7)	134 (70.9)	5 (62.5)	495 (67.7)
Current	56 (20.7)	30 (11.4)	18 (9.5)	2 (25.0)	106 (14.5)
Previous	50 (18.5)	42 (15.9)	37 (19.6)	1 (12.5)	130 (17.8)
Baseline DAS28, mean (S.D.)	4.05 (1.62)	4.05 (1.65)	4.11 (1.56)	3.36 (2.16)	4.06 (1.62)
Baseline ESR (mm/h)					
Mean (S.D.)	27.4 (23.2)	27.7 (23.4)	29.8 (22.6)	30.6 (42.2)	28.2 (23.3)
Missing, *n* (%)	2 (0.7)	0 (0)	0 (0)	0 (0)	2 (0.3)
Baseline TJC					
Mean (S.D.)	6.00 (7.29)	6.62 (7.50)	6.37 (7.13)	4.00 (4.31)	6.30 (7.30)
Missing, *n* (%)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.1)
Baseline SJC					
Mean (S.D.)	4.68 (5.15)	4.11 (5.13)	3.49 (4.50)	3.25 (4.40)	4.15 (4.98)
Missing, *n* (%)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.1)
Baseline patient global score					
Mean (S.D.)	42.8 (28.0)	45.1 (25.8)	45.5 (25.8)	51.9 (23.3)	44.4 (26.6)
Missing, *n* (%)	18 (6.7)	22 (8.3)	16 (8.5)	0 (0)	56 (7.7)
Baseline HAQ					
Mean (S.D.)	1.12 (0.733)	1.21 (0.760)	1.33 (0.741)	1.42 (0.361)	1.21 (0.747)
Missing, *n* (%)	73 (27.0)	63 (23.9)	58 (30.7)	5 (62.5)	199 (27.2)

and a small proportion who were underweight (excluded from analyses).

A sensitivity analysis was performed to compare participants with complete data at the three study visits with all of the METEOR participants with baseline data from the 11 included countries ($n = 8262$). No significant differences were observed for gender, age, BMI category, smoking status or CCP status (Supplementary Table 1, available at *Rheumatology* online).

Summary of medication use

Table 3 summarizes csDMARD use at baseline and 6 and 12 months, stratified by baseline BMI. A small number of patients stopped taking the drug after the second visit, although the reason was not recorded.

Results in early RA

With regards to patients with eRA, 582 patients were included, with a mean age of 49.8 years (S.D. 13.6). The mean symptom duration was 3.91 years (S.D. 6.13) with a mean time since diagnosis of 0.042 years (S.D. 0.320). A total of 196 patients had a normal BMI at baseline, 200 were overweight, 157 were obese and 29 were underweight. Patients who were underweight were excluded from the analyses, meaning 553 were ultimately included. At baseline, 112 patients were taking at least one csDMARD, increasing to 507 at 6 months and 505 at 12 months. With regards to co-prescription of biologic DMARDs (bDMARD), two patients were taking a bDMARD at the baseline visit, 18 at 6 months and 32 at 12 months. Of the included patients, 115 were in DAS28 remission at 6 months and 132 at 12 months.

With regard to patients newly starting a csDMARD, 398 patients with eRA commenced a csDMARD at the baseline visit and 384 of these patients remained on this csDMARD at the second visit. The reasons for stopping medications were not recorded. Overall, in eRA, no associations were observed between increased BMI and the likelihood of achieving DAS28 remission or good EULAR response at either 6 or 12 months, both in patients newly starting monotherapy or combination csDMARDs (Supplementary Table 2, available at *Rheumatology* online). There was also no significant

TABLE 3 Summary of csDMARD use by all patients at baseline visit and 6 and 12 months, stratified by BMI category

Drug used	Normal BMI ($n = 466$)	Overweight ($n = 464$)	Obese ($n = 346$)	Underweight ($n = 37$)	Overall ($n = 1313$)
csDMARD, *n* (%)					
Baseline	259 (55.6)	246 (53.0)	210 (60.7)	9 (24.3)	724 (55.1)
6 months	400 (85.8)	394 (84.9)	314 (90.8)	33 (89.2)	1141 (86.9)
12 months	392 (84.1)	380 (81.9)	306 (88.4)	33 (89.2)	1111 (84.6)
MTX, *n* (%)					
Baseline	224 (48.1)	214 (46.1)	180 (52.0)	6 (16.2)	624 (47.5)
6 months	355 (76.2)	341 (73.5)	267 (77.2)	27 (73.0)	990 (75.4)
12 months	345 (74.0)	327 (70.5)	256 (74.0)	27 (73.0)	955 (72.7)
Leflunomide, *n* (%)					
Baseline	18 (3.9)	10 (2.2)	12 (3.5)	0 (0)	40 (3.0)
6 months	23 (4.9)	23 (5.0)	20 (5.8)	1 (2.7)	67 (5.1)
12 months	20 (4.3)	17 (3.7)	20 (5.8)	1 (2.7)	58 (4.4)
Sulfasalazine, *n* (%)					
Baseline	47 (10.1)	57 (12.3)	40 (11.6)	3 (8.1)	147 (11.2)
6 months	66 (14.2)	76 (16.4)	59 (17.1)	10 (27.0)	211 (16.1)
12 months	58 (12.4)	65 (14.0)	52 (15.0)	10 (27.0)	185 (14.1)
Azathioprine, *n* (%)					
Baseline	2 (0.4)	2 (0.4)	2 (0.6)	0 (0)	6 (0.5)
6 months	1 (0.2)	2 (0.4)	1 (0.3)	0 (0)	4 (0.3)
12 months	1 (0.2)	1 (0.2)	1 (0.3)	0 (0)	3 (0.2)
Ciclosporin, *n* (%)					
Baseline	2 (0.4)	2 (0.4)	2 (0.6)	0 (0)	6 (0.5)
6 months	1 (0.2)	1 (0.2)	2 (0.6)	0 (0)	4 (0.3)
12 months	0 (0)	1 (0.2)	2 (0.6)	0 (0)	3 (0.2)
Hydroxychloroquine, *n* (%)					
Baseline	58 (12.4)	55 (11.9)	53 (15.3)	3 (8.1)	169 (12.9)
6 months	91 (19.5)	93 (20.0)	82 (23.7)	11 (29.7)	277 (21.1)
12 months	74 (15.9)	72 (15.5)	69 (19.9)	10 (27.0)	225 (17.1)

association between BMI and the likelihood of taking combination csDMARD therapy in patients with eRA (Table 4).

Results in estRA

With regards to patients with estRA, 731 were included, with a mean age of 56.4 years (S.D. 12.4). The mean symptom duration was 12 years (S.D. 8.98) with a mean time since diagnosis of 9.76 years (S.D. 7.67). Of the 731 patients, 270 had a normal BMI, 264 were overweight, 189 were obese and 8 were underweight. Since underweight patients were excluded from analyses, 763 patients with estRA were ultimately included. A total of 612 patients were taking at least one csDMARD at the baseline visit, increasing to 634 at both 6 and 12 months. With regards to co-prescription of a bDMARD, 182 patients were taking a bDMARD at the baseline visit, increasing to 417 at 6 months and 423 at 12 months. At 6 months, 249 patients were in DAS28 remission, with 248 in remission at 12 months.

The number of patients with estRA newly starting a csDMARD at the baseline visit was too low to conduct meaningful analyses ($n = 35$). Therefore all analyses were conducted in patients already taking a csDMARD. In estRA, obese patients were significantly less likely to achieve DAS28 remission at 6 and 12 months and good EULAR response at 6 months compared with those of normal BMI (Fig. 1). No significant association between BMI and remission outcomes was demonstrated in overweight patients with estRA.

Obese patients with estRA taking csDMARD monotherapy were significantly less likely to achieve DAS28 remission [odds ratio (OR) 0.47 (95% CI 0.24, 0.88)] or good EULAR response [OR 0.4 (95% CI 0.23, 0.7)] at 6 months compared with those of normal BMI (Supplementary Table 3, available at *Rheumatology* online). A similar point estimate was observed at 12 months. Analysing specific components of remission, only TJC was increased in overweight individuals with estRA taking monotherapy at 6 months follow-up [$\beta = 1.05$ (95% CI 0.05, 2.06)]. Sensitivity analyses for corticosteroid use did not significantly change outcomes.

Obese estRA patients were more likely to be taking combination csDMARD therapy than monotherapy compared with those of normal BMI, significant at 6 months [OR 1.59 (95% CI 1.03, 2.45)] (Table 4).

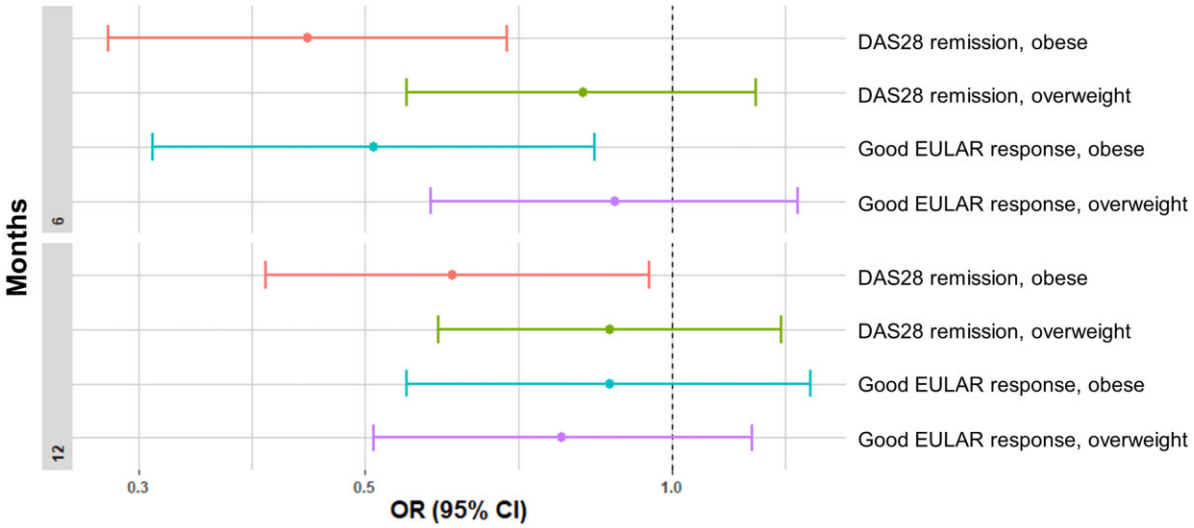
Association between BMI and MTX dose in all patients

The MTX dose was available for 613 patients at sequential visits. Within this subgroup, overweight and obese patients with eRA and estRA were exposed to higher

TABLE 4 Association between BMI and likelihood of taking combination csDMARD therapy (as opposed to monotherapy), stratified by eRA and estRA, compared with patients with normal BMI

Disease stage	BMI category	Baseline		6 months		12 months	
		OR	95% CI	OR	95% CI	OR	95% CI
eRA	Overweight	0.74	0.28, 1.92	0.80	0.53, 1.20	0.80	0.53, 1.21
	Obese	0.63	0.24, 1.62	0.69	0.44, 1.07	1.02	0.67, 1.56
estRA	Overweight	1.31	0.88, 1.94	1.37	0.91, 2.07	1.15	0.75, 1.75
	Obese	1.33	0.89, 2.02	1.59	1.03, 2.45	1.36	0.88, 2.12

FIG. 1 Association between overweight or obese BMI and DAS28 remission and good EULAR response at 6 months and 12 months in patients with estRA



[**Upper panel** (6 month outcomes)] Obese patients with estRA were significantly less likely to achieve DAS28 remission [OR 0.44 (95% CI 0.28, 0.69)] and good EULAR response [OR 0.51 (95% CI 0.31, 0.84)] at 6 months compared with patients of normal BMI. [**Lower panel** (12 month outcomes)] Obese patients with estRA were significantly less likely to achieve DAS28 remission [OR 0.61 (95% CI 0.40, 0.95)] at 12 months compared with those of normal BMI.

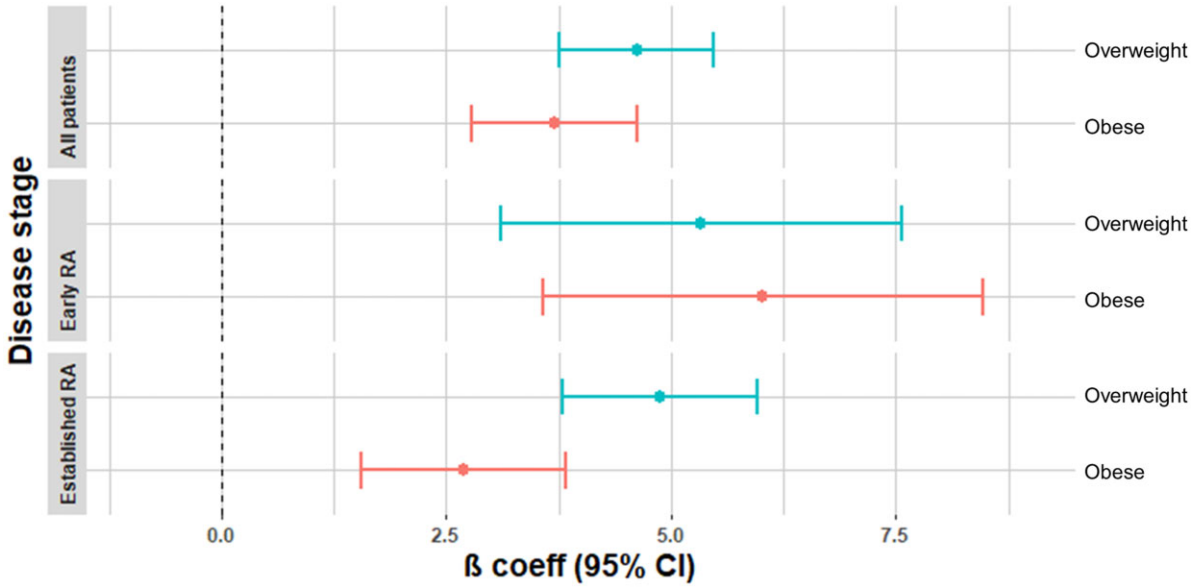
doses of MTX at the 6 and 12 month follow-up compared with those of normal BMI (Fig. 2). At follow-up in overweight patients with eRA, linear regression analysis of BMI and MTX dose demonstrated $\beta = 5.33$ (95% CI 3.10, 7.56) and in obese patients with eRA $\beta = 6.01$ (95% CI 3.57, 8.46). In overweight patients with estRA, similar linear regression models demonstrated $\beta = 4.87$ (95% CI 3.79, 5.95), while in obese patients with estRA $\beta = 2.69$ (95% CI 1.56, 3.83). This included patients taking MTX as part of combination therapy. Looking at MTX dosing at the baseline visit alone, a mean weekly dose of 20 mg (S.D. 6.91) was prescribed in patients with overweight and obese BMI at baseline compared with 15 mg (S.D. 5.70) in those with normal BMI.

In all models, sensitivity analyses for symptom duration and geographical location did not change the significance of results. In order to investigate the influence of geographical location, all models were conducted by region. This did not statistically significantly change the point estimate. It is not known, however, if the variation in geographical location leads to a change in clinical significance.

Discussion

Here we report results from an observational study in an international 'real-world' database of RA patients with associations between BMI and response to csDMARD therapy that are relevant to the management of patients with RA. Previous studies have demonstrated an association between increased BMI and a reduced response to csDMARDs in RA [8, 21, 22]. Our study adds to this in several ways. We observed that the stage of disease is important when assessing response to csDMARDs in RA patients with increased BMI. In our cohort of patients with estRA, results are consistent with previous data demonstrating a decreased likelihood of achieving

Fig. 2 Association between overweight or obese BMI and MTX dosing at all disease stages



Overweight and obese BMI in both eRA and estRA was associated with taking increased doses of MTX compared with patients of normal BMI.

remission in obese patients despite similar therapy with csDMARDs as those with normal BMI [7]. This has previously been shown in clinical trials and a large meta-analysis of 5131 patients with RA [7, 8, 23]. However, we did not demonstrate a similar association in patients with early RA.

Obese patients with estRA taking monotherapy were less likely to attain DAS28 remission or good EULAR response in our cohort compared with non-obese patients on monotherapy. Overweight and obese patients with estRA were more likely to be on combination csDMARD therapy compared with patients of normal BMI (Table 4). Despite this, having estRA and increased BMI was associated with a decreased likelihood of achieving remission.

Increased BMI was not associated with reduced remission in RA patients treated in the first 2–3 years of symptom duration. This may reflect the treat-to-target approach in eRA, partly supported by our observation that both eRA and estRA patients took higher doses of MTX in our cohort than similar patients of normal BMI. The lack of association between increased BMI in eRA patients and remission may also reflect the limitations of real-world data, e.g. inconsistencies in recording time since diagnosis, components of DAS28 and height and weight at baseline (see 'Strengths and limitations').

While the association between BMI and response to treatment in RA is well-described [6, 8, 9], our study also demonstrates altered prescribing patterns in overweight and obese individuals, including an increased number of csDMARDS in estRA and increased MTX dose in both eRA and estRA. It is possible that these more intensive treatment regimens are required to attain remission or good EULAR response, although we were unable to demonstrate in our study whether patients prescribed higher MTX doses would have had similar outcomes had they been prescribed doses similar to those of patients of lower BMI. However, given that obese patients with both eRA and estRA were exposed to higher doses of MTX compared with patients of normal BMI, this may account for the similar responses seen in patients of all BMI categories with eRA.

Previous studies show that regardless of BMI, patients with estRA have less frequent remissions compared with eRA [24]. A recent meta-analysis reported the frequency of remission in estRA as 19%, compared with 49% in eRA [25]. In patients with estRA and very high BMI, disease activity and physical dysfunction are significantly increased [19]. In this study we observed similar outcomes for patients with established RA and increased BMI despite increased csDMARD exposure in these individuals.

Obesity is a risk factor for developing RA and is highly prevalent at first presentation [4, 5]. One reason suggested for this is adipokines, secreted from adipose tissue, which serve multiple regulatory functions including energy intake and inflammation [4, 7]. Increased adiposity leads to increased adipokines. Obesity may therefore be considered a pro-inflammatory state. Several adipokines may underpin the pathogenesis and disease evolvement of RA [7, 13, 26, 27], e.g. leptin and adiponectin. Leptin, a satiety factor secreted by adipose tissue, is directly correlated with adipose mass. Increased leptin in RA contributes to joint damage [28] and disease activity [29]. A recent study demonstrated low leptin levels and low disease activity in patients with eRA treated

with 3 months of MTX [30]. Adiponectin decreases with increasing body mass and has both anti- and pro-inflammatory properties [13, 26]. The high adiponectin levels in patients with RA may increase inflammation via mediation of factors such as IL-6 and leads to radiographic progression, irrespective of BMI [31–33].

While increased adiposity is a plausible suggestion for poorer clinical outcomes in overweight or obese RA patients, it does not tell the full story. BMI is not a true indicator of percentage body fat mass, and patients with RA and cachexia may in fact have increased fat mass, potentially increasing activation of adipokines and subsequent poor clinical outcomes [19, 34]. Furthermore, our results demonstrate an association between obesity and a decreased likelihood of DAS28 remission, suggesting other mechanisms than simply increased inflammation leading to poorer clinical outcomes. DASs may remain higher in overweight or obese patients *vs* patients of normal BMI for multiple reasons, including those not associated with RA, such as increased pro-inflammatory cytokines. This can lead to increases in inflammatory markers such as ESR and CRP, contributing to increased DAS28 [6, 35].

It is possible that the association between increased BMI and decreased likelihood of remission is due to limitations in DAS28 measurement rather than underlying inflammation, although in reality it is likely to be a combination of the two. Obesity has the potential to influence disease outcomes through multiple mechanisms in addition to immunological changes. Decreased pain thresholds in patients with increased BMI may contribute to higher patient global assessment scores [36], while increased mental health comorbidities such as depression, anxiety and fatigue, associated with obesity, impact quality of life [37–39]. Furthermore, given the lack of association between BMI and radiographic disease progression, DAS28 may falsely overestimate disease activity in patients with increased BMI, partly due to joint assessment being more difficult in obese patients [12, 23].

While obesity is clearly associated with RA at disease onset, it carries prognostic implications throughout the disease trajectory. Factors including corticosteroids and inactivity due to disease burden can further contribute to increased BMI and cardio-metabolic comorbidities [3], highlighting the need to address BMI as part of RA management. More work is therefore required in this field, particularly with a view to using BMI to guide management.

Strengths and limitations

Our study is strengthened by the use of 'real-life' data from multiple countries, representative of a broad patient demographic and management practices. The database comprises longitudinal follow-up, enabling patient characteristics, DAS28 and components and medication use to be monitored and analysed over time. We were able to determine DAS28 and EULAR response outcomes for patients taking a broad range of RA drugs and stratify analyses by eRA and estRA.

Our study had several limitations. First, this is a retrospective observational cohort study and therefore associations between BMI and response to csDMARD therapy are not necessarily causal in nature, i.e. increased BMI does not necessarily lead directly to a given response to therapy. Furthermore, real-life data come with limitations, in this case, a high incidence of missing data that greatly reduced sample size. Subjects were only included if they had data recorded at each of the three time points (baseline visit, 6 months and 12 months). Due to inconsistencies in the recording of data and the extent of missing variables, it was deemed inappropriate to use imputation to account for the missing data in excluded individuals. Possible inaccuracies in data recording are difficult to correct due to the multinational nature of the dataset. However, comparison of the study sample with all country-specific METEOR registrants at this time did not reveal differences in age and gender in the registrant group and no significant differences between the prevalence of BMI categories. Symptom duration for patients with eRA was a mean of 3.91 years, longer than would be expected for patients with early disease. This could be due to numerous factors, including inaccurate data recording, but also regional variations in eRA diagnostic and management pathways. DAS28 was calculated differently based on the available data. It was not possible because of anonymization to obtain complete DAS28 component scores for all included participants. This may lead to bias, but since it was not unidirectional, it is unlikely to influence the results significantly.

Missing data included dosing and duration data for most drugs, including corticosteroids, meaning we were unable to account for these. However, we attempted to overcome these limitations by including only those countries with complete baseline and follow-up data at 6 and 12 months and performing sensitivity analyses for corticosteroid use, despite a lack of dosing data. We were also unable to account for sequential DMARD use, due to having only 12 months of data. In a study of extended duration, this is something we would wish to explore.

Many patients with estRA were co-prescribed a bDMARD with a csDMARD. Due to the small numbers of patients with estRA on just csDMARD therapy, it would not have been possible to exclude patients with bDMARDs. Results on the associations between bDMARD therapy and remission outcomes in patients with estRA are reported elsewhere [40] and form part of ongoing work. Initial results demonstrate obesity to be associated with delayed response to mAb TNF inhibitors, with no change in response to etanercept with varying BMI.

While we demonstrate multiple associations with the potential to improve clinical practice, the small final cohort size means results may not be fully applicable at the population level. There is therefore a need to repeat

this study in a larger international cohort. Finally, our analyses include data only until 2014; however, our findings remain relevant due to the continued large-scale use of traditional csDMARDs and the persisting prevalence of increased BMI in this population.

Conclusion

In conclusion, our data confirm the decreased likelihood of clinical remission in obese patients with RA, but add to the field in multiple ways. Patients with eRA and increased BMI have similar rates of remission as those with normal BMI, but have increased csDMARD exposure. In estRA, increased BMI is associated with increased csDMARD exposure, but the likelihood of DAS28 remission remains low. Based on these data, patients with both eRA and estRA, who are overweight or obese, may require increased doses of MTX to achieve remission compared with those of normal BMI.

Optimization of early treatment of RA remains important, particularly in those with increased BMI, where response in established disease may be attenuated. Consideration of treatment regimens should be tailored to the individual patient, being mindful that higher doses or combination csDMARD treatment may be required in RA patients with increased BMI.

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Data availability statement

Data are available from the authors upon request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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