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Original article

The association of obesity with disease activity, functional ability and quality of life in early rheumatoid arthritis: data from the Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network UK prospective cohorts

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Abstract

Objectives. To examine associations between BMI and disease activity, functional ability and quality of life in RA.

Methods. Data from two consecutive, similarly designed UK multicentre RA inception cohorts were used: the Early RA Study (ERAS) and the Early RA Network (ERAN). Recruitment figures/median follow-up for the ERAS and ERAN were 1465/10 years (maximum 25 years), and 1236/6 years (maximum 10 years), respectively. Standard demographic and clinical variables were recorded at baseline and annually. Multilevel piecewise longitudinal models with a change point at 2 years were used with the 28-joint DAS (DAS28), ESR, HAQ and 36-item Short Form Health Survey (SF-36) physical (PCS) and mental (MCS) components as dependent variables. BMI was examined in separate models as both continuous and categorical variables (based on World Health Organization definitions) and up to 5 years from disease onset.

Results. BMI data from 2386 newly diagnosed RA patients (11 348 measures) showed an increase in BMI of 0.27 U annually (95% CI 0.21, 0.33). Baseline obesity was associated with a significant reduction in the odds of achieving a low year 2 DAS28 [OR 0.52 (95% CI 0.41, 0.650)]. At year 2, HAQ and SF-36 PCS scores were significantly worse but not at year 5 in patients obese at baseline. Obesity at year 2 was associated with higher DAS28 scores at year 2, but not at year 5, and also associated with significantly higher HAQ and SF-36 PCS scores at years 2 and 5.

Conclusion. Obesity prevalence is rising in early RA and associates with worse disease activity, function and health-related quality of life, with a significant negative impact on achieving a low DAS28. The data argue strongly for obesity management to become central to treatment strategies in RA.

Key words: DAS28, disease activity, early rheumatoid arthritis, rheumatoid arthritis

CLINICAL SCIENCE

Rheumatology key messages

- Obesity adversely affects disease activity, functional ability and quality of life in RA patients.
- Obesity management should form a central part of all treatment strategies for patients with RA.

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Introduction

Obesity is increasing in prevalence [1], has been implicated as a risk factor for developing RA [2–5] and is an increasingly prevalent comorbidity seen on first presentation of RA [6]. There is growing recognition that common mechanistic pathways are shared between the inflammatory states mediated by obesity and those by inflammatory rheumatic diseases [7–10]. Indeed, the immunomodulatory properties of adipose tissue are suggestive of obesity being a low-grade, chronic inflammatory condition [11].

A recent meta-analysis indicates that the BMI category of obesity, but not overweight, reduces the chances of achieving minimal disease activity in people with RA compared with those with normal BMI [12]. However, there is contradictory evidence linking higher BMI and other adverse outcomes such as slower radiographic progression [13, 14] but higher rates of total joint replacement [15, 16]. These paradoxical data raise the question whether the negative impact of obesity on composite DAS is driven by inflammation (ESR and swollen joints) or patient-reported factors (tender joints and patient global assessment). Obesity has been associated with decreased health-related quality of life (HRQoL) and depression across various chronic conditions [17–21], but this has been less well studied in RA [15, 22, 23].

Using two RA inception cohorts, this study investigated the association between BMI and disease activity, functional ability and quality of life at diagnosis, in the short term at 2 years and in the medium term at 5 years.

Methods

Study design and patient recruitment

The study used data from the Early RA Study (ERAS, 1986–2001) and Early RA Network (ERAN, 2002–12), two multicentre early RA inception cohorts recruiting, respectively, from 9 centres in England and 23 centres in England, Wales and Ireland. Information on the two cohorts has been previously described in detail [24]. ERAS and ERAN recruited a total of 2701 patients: ERAS, $n = 1465$, maximum follow-up 25 years and ERAN, $n = 1236$, maximum follow-up 11 years. Combined analysis of ERAS and ERAN is possible since they are consecutive inception cohorts with a similar design, including the variables captured, timing of assessments and patient recruitment, with a median time from symptom onset to first rheumatology outpatient visit being 6 months.

All centres managed RA according to local practice, influenced by contemporary UK guidelines for the management of RA [25], with treatment choice and strategy at the discretion of the treating clinician [26]. The median time to first synthetic DMARD was 2 months after presentation in ERAS and 1 month after presentation in ERAN. Recruiting centres generally favoured SSZ as the first DMARD choice in ERAS, with a gradual switch to MTX being observed, such that SSZ and MTX were used in equal proportions at the start of ERAN (2002) and then MTX became the most frequent first-choice DMARD thereafter [26]. In ERAS, all patients were DMARD naïve, and in ERAN a small proportion (13.5%) of patients used synthetic DMARDs prior to baseline assessment.

Ethical approval

The ERAS study received ethical approval from the West Hertfordshire Local Research Ethics Committee and subsequently from the Caldicott Guardian. The ERAN study received ethical approval from the Trent Research Ethics Committee. No additional ethical approval was required for this study.

Clinical, laboratory and radiographic data

Standard demographic and clinical variables were recorded at baseline and repeated once between 3 and 6 months, again at 12 months and then annually until the patient left the study (deceased, moved away, declined) or the recruiting centre closed to follow-up. Variables recorded in both cohorts included patient demographics (age at disease onset, gender), baseline RF and/or anti-CCP, haemoglobin, ESR, smoking status (past, current, never) and the HAQ disability index [27]. Comorbidities were recorded at every visit and coded using the International Classification of Disease, 10th edition system. Height and weight were recorded at each visit in ERAN and converted to BMI. In ERAS, weight was recorded annually, although height was only available at baseline. Based on the World Health Organization definitions, patients were subsequently categorized into underweight (BMI <18.5), normal (BMI 18.5–24.99), overweight (BMI 25–29.99) and obese (BMI $\geqslant 30$). Based on preliminary analyses and supported by a previous meta-analysis [12], the normal and overweight BMI groups were combined and used as the reference group in the analysis since there were no substantive differences in outcomes between these groups.

In ERAS, disease activity was calculated based on the original three-variable DAS [28], excluding patient global assessment and using a 44 joint count. In ERAN a four-variable 28-joint DAS (DAS28) ESR-based score was used [29]. ERAS DASs were converted to the DAS28 metric to allow combined analysis across cohorts [30]. Data on HRQoL were only available in ERAN, measured using the 36-item Short Form Health Survey (SF-36) [31]. The SF-36 consisted of eight domains with responses subsequently grouped into two higher-order constructs: a physical component summary (PCS) and a mental component summary (MCS). The PCS is based on domains assessing physical function, pain, physical role functioning and general health, whereas the MCS is based on domains assessing mental health, vitality, social functioning and social role functioning.

Statistical analyses

The impact of BMI on the DAS28, ESR, HAQ and SF-36 PCS and MCS scores at baseline and over time was assessed. Data for the two cohorts were combined for analysis and patients with a BMI available at baseline and at least one other time point were included. Due to the

differing length of follow-up between cohorts, data analysis was restricted to 5 years to retain sufficient balance between the cohorts contributing data across time points.

Standardized morbidity ratios (SMRs) were calculated, adjusted for age, gender and year of visit with respect to population rates of underweight, overweight or obese and obese using data from the Health Survey for England 1993–2013 [32]. As population data prior to 1993 were unavailable, data relating to visits before that time were excluded from the calculations.

The association between treatment use and change in BMI was examined using a propensity score approach due to the likelihood of confounding by indication between BMI and treatment. Separate models were estimated for steroid use and DMARD on the change in BMI from baseline to 12 months. The analysis used augmented inverse probability of treatment weights, since this doubly robust estimator protects against potential model misspecification. Propensity scores were conditioned on age, gender, comorbidity, DAS28, HAQ, seropositive status, cohort, prior steroid or DMARD use and symptom duration. The covariates where observed to be well balanced between treatment groups after weighting by the propensity score.

The analyses used longitudinal linear mixed effects regression models with a random intercept for each patient to account for repeated assessments. Separate models were estimated for each outcome (DAS28 and its components, HAQ and SF-36 PCS and MCS) to explore changes in BMI over time. ESR was log transformed for the modelling and back-transformed for presentation in the results. Changes in the outcome over time were accounted for by including covariates relating to a linear spline for time since baseline with a change point at 2 years. This allowed for different estimates of the average yearly change in the outcome between baseline and 2 years and between 2 and 5 years, which was necessary given that changes were non-linear over time capturing initial treatment response [33]. A random slope for each time covariate allowed the rate of change in the outcome to vary across patients. Missing outcome data were allowed under the assumption that data were missing at random conditional on the variables included in the model.

BMI category (normal/overweight *vs* underweight and obese) was initially entered as a predictor in the models, reflecting the level at baseline. Interaction terms with the time covariates allowed the impact of BMI at baseline to moderate the rate of change in the outcome and allow for category-level estimates of outcomes at baseline, 2 and 5 years. Subsequently the BMI category at 2 years was entered into the model again, with interaction terms with the time covariates allowing estimates of the impact of BMI category on outcomes at 2 and 5 years. Prevalence rates for discrete DAS28 categories were estimated using the distributional approach [34]. All models controlled for potential confounding due to age at disease onset, gender, recruitment year, RF or anti-CCP positive at baseline, smoking status, haemoglobin, baseline DAS28 and the baseline level of the outcome (i.e. HAQ, SF-36 PCS, SF-36 MCS). Estimates are presented unadjusted and adjusted for putative confounders. The results in the main text are model-expected mean levels at baseline, 2 and 5 years based on complete case analysis for covariates, as sensitivity analysis using multiple imputation revealed minimal differences. The model-estimated yearly rate of change in the outcome by BMI category for the complete case and imputed data (data not shown).

Table 1 Demographic and clinical characteristics for ERAS and ERAN at the baseline visit

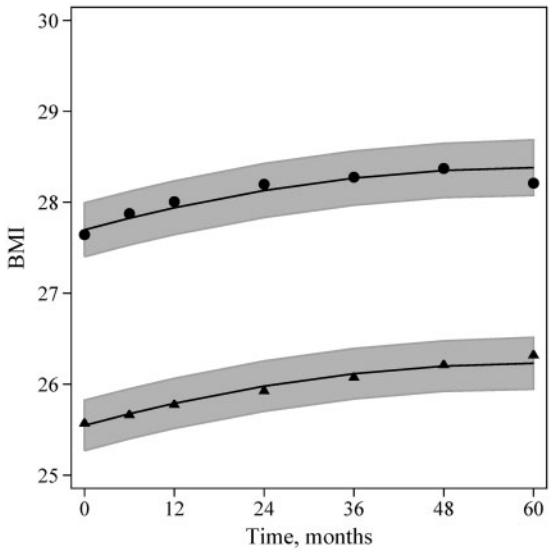
Variable	Cohort		
	ERAS/ ERAN combined (*N* = 2701)	ERAS (1986–2001) (*n* = 1465)	ERAN (2002–12) (*n* = 1236)
Age at disease onset, mean (S.D.), years	56 (14)	55 (15)	57 (14)
Symptom duration, median (IQR), months	6 (8)	6 (7)	6 (9)
Female, *n* (%)	1812 (67)	973 (66)	839 (68)
RF and/or anti-CCP positive, *n* (%)	*N* = 2513 1553 (62)	*N* = 1456 914 (63)	*N* = 1057 639 (60)
BMI, mean (S.D.)	*N* = 2386 26.5 (50)	*N* = 1266 26 (5)	*N* = 1120 27.6 (5.3)
Smoker, *n* (%) Current Ex	*N* = 2124 602 (28) 511 (24)	*N* = 907 199 (22) 175 (19)	*N* = 1217 403 (33) 336 (28)
DAS, mean (S.D.)	*N* = 2642 4.8 (1.4)	*N* = 1452 5.0 (1.2)	*N* = 1190 4.5 (1.6)
MCS, mean (S.D.)		—	*N* = 950 47 (12)
PCS, mean (S.D.)		—	*N* = 950 29 (12)
HAQ, median (IQR)	*N* = 2659 1 (1.1)	*N* = 1460 1 (1.3)	*N* = 1199 1 (1.1)
Haemoglobin, mean (S.D.)	*N* = 2687 13.6 (8.1)	*N* = 1460 12.6 (1.6)	*N* = 1227 14.7 (11.7)
Erosions, *n* (%)	*N* = 2555 698 (27)	*N* = 1433 368 (26)	*N* = 1122 330 (29)
Steroid use pre-recruitment, *n* (%)	—	0 (0)	125 (10)
DMARD use pre-recruitment, *n* (%)	—	0 (0)	168 (14)

Results

Baseline demographics and disease activity

Patient demographics and clinical variables at baseline are shown in Table 1. Age, gender and serological status were similar across both cohorts. In ERAN the baseline mean BMI was higher, more patients were current smokers and the mean DAS was lower. The median HAQ was the same in both cohorts.

Fig. 1 Observed BMI during follow up for ERAS and ERAN



ERAS (triangles) and ERAN (circles) with model-estimated quadratic trends and 95% CIs (lines and shaded areas) shown.

BMI changes over time

In total, 2386 individuals with data on BMI at baseline were included in the analysis (ERAS 1266, ERAN 1120). Over the 5 years of follow-up examined, BMI was recorded on a total of 11 348 occasions (ERAS 6582, ERAN 4766) relating to a mean of 4.8 occasions (range 1–7) per patient. The mean BMI at baseline was 25.5 in ERAS and 27.6 in ERAN. The mean BMI increased from disease onset to 5 years disease duration, with a quadratic trend providing the best fit to the data (Fig. 1). For both cohorts, BMI increased by 0.27 U/year (95% CI 0.21, 0.33), decelerating at a rate of −0.03 U/year (95% CI −0.04, −0.01). For a typical British woman (height 1.62 m) and man (height 1.75 cm) this relates to an average weight gain of 0.71 and 0.83 kg, respectively, in the first year of disease. Using a propensity score approach, steroid use was associated with an increase in BMI of 0.13 U by 12 months ($P = 0.104$; 95% CI −0.03, 0.29). While non-significant, this indicates that approximately half of the change in BMI during the first year may be attributable to steroid use. DMARD use was not associated with a change in BMI (0.01 U difference; $P = 0.879$; 95% CI −0.18, 0.21).

The prevalence of obesity at baseline was 14.3% in ERAS and 25.7% in ERAN, representing an 80% increase in prevalence between the two cohorts [risk ratio 1.79 (95% CI 1.61, 2.02)]. The prevalence of obesity rose at years 2 and 5, respectively, in ERAS to 20.1 and 22.5% and in ERAN to 35.5 and 37.2% (Fig. 2). The prevalence of underweight at baseline was 2.4% in ERAS and 1.0% in ERAN, remaining relatively stable over the follow-up.

SMRs for overweight and obesity indicated that rates across the period of follow-up were in line with the general population for England, adjusting for age, gender and calendar year of visit (SMR range 0.91–1.03; see supplementary Table S1, available at *Rheumatology* online). Underweight prevalence was significantly higher at 2 and 5 years, with adjusted rates increased by 76 and 123%, respectively.

Impact of BMI at baseline on outcomes at baseline, 2 and 5 years

Disease activity

At baseline, DAS28 was significantly higher in patients in the obese BMI category (mean 4.78) compared with those in the normal/overweight category (mean 4.50) in both crude and adjusted analyses ($P < 0.001$) (see Table 2).

At 2 years following DMARD initiation, the mean DAS28 decreased in all baseline BMI categories but remained significantly higher in patients with baseline obesity (mean 3.85) compared with those in the normal/overweight category (mean 3.53, $P = 0.001$). This association was lost at 5 years ($P = 0.727$). In the case of ESR, this was significantly higher at baseline in patients in the obese BMI category (mean 26.9) compared with those in the normal/overweight category (mean 22.4) in adjusted analyses ($P < 0.001$). At 2 years, the mean ESR decreased in all baseline BMI categories but remained significantly higher in patients with baseline obesity (mean 19.5) compared with those in the normal/overweight category (mean 14.3, $P = 0.001$), with this association persisting at 5 years ($P = 0.028$). No significant differences were observed between all other DAS28 components (swollen and tender joint counts and patient global assessment) and BMI categories at any of the time points after adjustment for potential confounders (see supplementary Table S2, available at *Rheumatology* online).

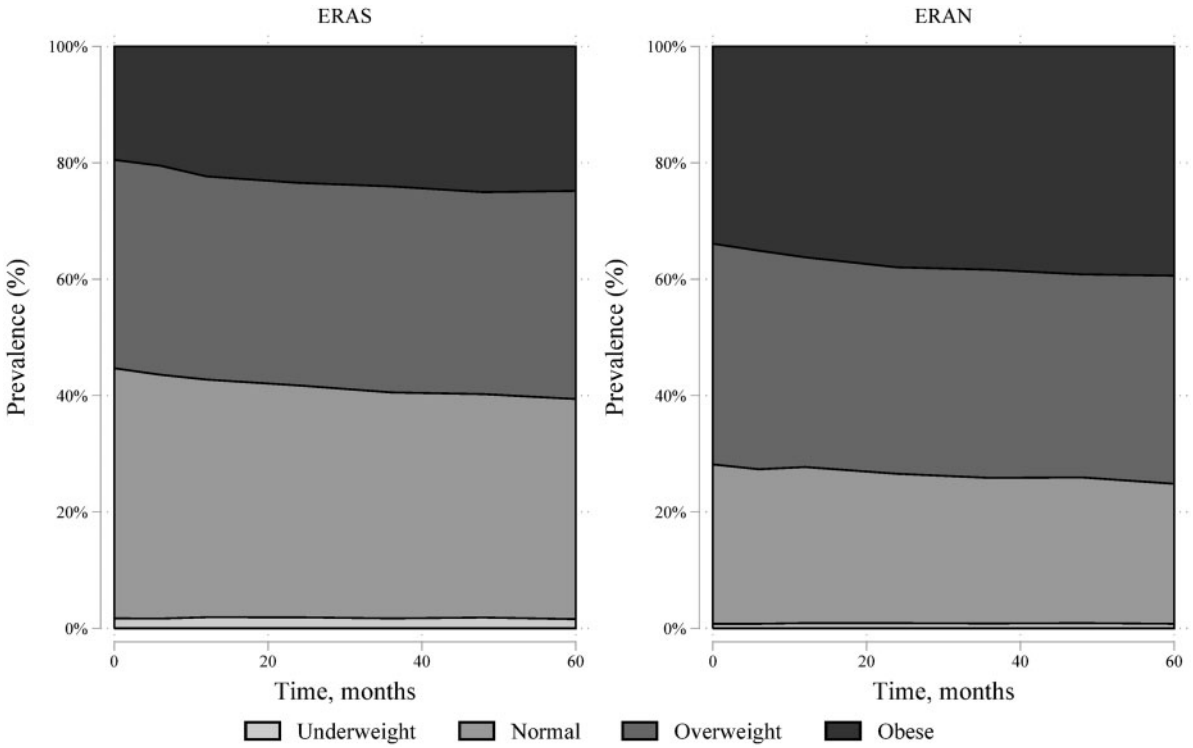
In both ERAS and ERAN, DAS28 reduced from baseline to 2 years, with 624 (49.3%) in ERAS and 596 (53.2%) in ERAN achieving the EULAR DAS28 low disease activity (LDAS) target (DAS28 <3.2) on at least one occasion by 2 years. Fig. 3 illustrates, for ERAS and ERAN combined, the prevalence of discrete DAS28 status at baseline, 2 and 5 years in patients categorized at baseline as obese or normal/overweight. At 2 years, 32.1% of people in the obese category at baseline achieved LDAS compared with 43.2% in the normal/overweight category [risk ratio 0.74 (95% CI 0.67, 0.83)], but this difference was lost at 5 years (Fig. 3).

Logistic regression indicated that being obese at baseline was related to a statistically significant 43% reduction in the odds of achieving LDAS on at least one occasion by year 2 compared with those in the normal/overweight category [OR 0.57 (95% CI 0.61, 0.90)]. After adjusting for potential confounders the effect was more pronounced [OR 0.52 (95% CI 0.41, 0.65)].

Functional ability and HRQoL

HAQ scores at baseline, 2 and 5 years were significantly worse for those who were obese at baseline *vs* normal/overweight in the unadjusted analysis (all $P < 0.001$) (see Table 2). After adjustment, the magnitude of the difference

Fig. 2 Change in the distribution of BMI categories for ERAS and ERAN over the first 5 years



at each time point was attenuated and remained significant at baseline and 2 years ($P < 0.01$). SF-36 PCS scores showed similar trends to HAQ but attenuated to non-significance except at 2 years in the adjusted model. SF-36 MCS scores at 2 and 5 years were significantly worse for those who were obese at baseline *vs* normal/overweight in the unadjusted analysis (all $P < 0.01$). However, after adjusting for potential confounders, the differences were attenuated and non-significant.

Impact of BMI at 2 years on years 2 and 5 outcomes

Obesity at 2 years was associated with a significantly higher DAS28 at 2 years compared with those in the normal/overweight category in both crude and adjusted models, but was attenuated and non-significant at 5 years (Table 3). Using discrete DAS28 categories, 32.6% in the obese category at 2 years had LDAS at 2 years compared with 40.7% in the normal/overweight category [risk ratio 0.80 (95% CI 0.72, 0.89)]. At 5 years, 33.6% in the obese category at 2 years had LDAS compared with 32.6% in the normal/overweight category [risk ratio 1.03 (95% CI 0.93, 1.15)]. Patients in the underweight category at year 2 also had a significantly higher DAS28 at year 2, but not year 5, compared with the normal/overweight category in both crude and adjusted models (Table 3).

For HAQ and the SF-36 PCS, obesity at 2 years was associated with significantly worse scores at both 2 and 5 years in both the crude and adjusted models (all $P < 0.05$). However, while unadjusted differences in SF-36 MCS at 2 and 5 years were significantly worse for those who were obese at 2 years compared with those who were normal/overweight, after adjustment for potential confounders the differences were attenuated and non-significant.

Discussion

We report from two large unique UK inception cohorts of early RA recruited at the time of diagnosis and managed according to contemporary practice and followed for 5 years. Obesity not only was an increasingly prevalent comorbid condition at RA diagnosis from 1986 to 2012, but also weight continued to increase over the first 5 years after recruitment, with the prevalence of obesity growing at each year of follow-up. Thus whereas 14.3% of people at recruitment were obese in ERAS (1986–2002), 37.2% were obese at year 5 after enrolment into ERAN (2007–12).

Across both inception cohorts, obesity had a significant negative impact on baseline and early year 2 composite DAS28 outcomes. This translated into those obese at baseline having a 48% reduction in the odds of achieving LDAS by year 2 compared with the normal/overweight category [OR 0.52 (95% CI 0.41, 0.65)], a difference that was both statistically significant and likely to be clinically important. These findings are generally supportive of those reported from previous cross-sectional analyses

Table 2 Baseline, 2 and 5 year outcomes by BMI category

		Normal/overweight			Obese				Underweight			
Model	Time	Mean	LCL	UCL	Mean	LCL	UCL	*P*-value*	Mean	LCL	UCL	*P*-value*
DAS28 (*N* = 2386)												
Crude	Baseline	4.49	4.43	4.55	4.71	4.60	4.83	0.001	5.10	4.72	5.48	0.002
	2 years	3.47	3.39	3.55	3.83	3.67	3.98	0.000	3.88	3.38	4.37	0.115
	5 years	3.77	3.68	3.85	3.85	3.67	4.03	0.409	3.72	3.16	4.29	0.886
Adjusted	Baseline	4.50	4.44	4.56	4.78	4.66	4.89	0.000	4.67	4.27	5.08	0.414
	2 years	3.53	3.44	3.62	3.85	3.68	4.03	0.001	3.89	3.29	4.50	0.243
	5 years	3.81	3.71	3.90	3.85	3.64	4.05	0.727	3.35	2.68	4.01	0.182
HAQ (*N* = 2386)												
Crude	Baseline	1.01	0.98	1.04	1.20	1.14	1.26	0.000	1.08	0.88	1.28	0.509
	2 years	0.80	0.76	0.84	1.06	0.98	1.14	0.000	0.91	0.65	1.16	0.405
	5 years	1.00	0.96	1.05	1.18	1.09	1.27	0.001	1.03	0.74	1.32	0.842
Adjusted	Baseline	1.02	0.99	1.06	1.15	1.09	1.21	0.000	0.97	0.75	1.18	0.615
	2 years	0.83	0.79	0.87	0.98	0.89	1.07	0.003	0.88	0.57	1.18	0.764
	5 years	0.99	0.94	1.04	1.07	0.97	1.17	0.165	0.84	0.51	1.18	0.405
PCS (*N* = 1030)												
Crude	Baseline	30.20	29.34	31.05	27.64	26.28	28.99	0.002	27.87	21.17	34.57	0.500
	2 years	34.39	33.28	35.50	29.67	27.88	31.45	0.000	34.55	25.85	43.25	0.972
	5 years	33.30	32.02	34.58	30.94	28.83	33.06	0.062	34.50	24.78	44.22	0.811
Adjusted	Baseline	29.94	29.07	30.81	28.81	27.40	30.22	0.182	31.22	23.67	38.77	0.741
	2 years	33.66	32.44	34.88	30.76	28.79	32.73	0.014	32.24	21.33	43.15	0.800
	5 years	33.00	31.61	34.38	31.83	29.51	34.15	0.394	38.17	27.19	49.15	0.360
MCS (*N* = 1030)												
Crude	Baseline	47.84	47.03	48.66	46.67	45.37	47.96	0.132	43.56	37.17	49.96	0.193
	2 years	49.78	48.77	50.80	46.95	45.33	48.58	0.004	44.44	36.50	52.39	0.191
	5 years	50.09	48.99	51.19	47.95	46.13	49.76	0.048	52.29	44.09	60.48	0.602
Adjusted	Baseline	47.88	46.98	48.77	47.16	45.70	48.61	0.411	48.74	40.98	56.50	0.829
	2 years	49.25	48.13	50.37	47.20	45.40	49.01	0.059	41.29	31.24	51.33	0.123
	5 years	50.09	48.85	51.34	48.75	46.67	50.82	0.274	55.16	45.54	64.77	0.306

Crude and adjusted means are presented. **P*-values compared with normal/overweight baseline BMI. UCL: upper control limit; LCL: lower control limit.

and meta-analyses [12, 35, 36]. Our study extends previous findings to demonstrate that baseline obesity is also associated with higher baseline and years 2 and 5 ESR, suggesting that the effect on DAS is at least driven in part by this component.

Obesity might confound assessment of disease activity in RA through soft tissue (adiposity) around joints or effects on pain processing, such as reduced pressure pain thresholds and direct effects on patient global assessment of health [37, 38]. Previous studies have indicated that high BMI is associated with lower rates of radiographic progression after adjusting for DAS28 [14, 39], suggesting that DAS28 might overestimate disease activity in obese participants. This is supported by data showing that RA patients with obesity have lower rates of DAS28 remission but similar rates of low MRI-detected inflammation as patients without obesity, suggesting that obesity can bias composite disease activity measures [39]. We have found that associations of obesity with DAS28 were replicated with laboratory measures of inflammation (ESR), suggesting direct effects on inflammatory mechanisms. However, on exploring other DAS28 components (swollen and tender joint counts and patient global assessment) and their association with obesity, no significant associations were seen, suggesting that central pain sensitization is unlikely to be a main driver for the DAS28 in obese patients. The non-significant association between obesity and swollen joint count also suggests that obesity did not bias the clinical examination and recording of this component. Similarly, no association with obesity and the SF-36 MCS was found in the adjusted analyses. Our results contrast with those of other studies that suggest obesity is associated with increased pain sensitivity and central pain augmentation [37, 38].

Taken together these findings suggest an immediacy of effect on outcomes from obesity. We have found that baseline obesity has a negative effect on DAS28 and functional measures at baseline that persists in the short term to year 2 but is lost by year 5. Similarly in patients who were obese at year 2, worse outcomes were found at that time for DAS28, HAQ and SF-36 PCS and in short-term follow-up at year 5 for function and SF-36 PCS. This would be in keeping with the concept of a real-time effect of obesity, potentially mediated by adipokines, influencing inflammatory mediators, pain and other

Fig. 3 DAS28 categories at baseline, 2 and 5 years by baseline obesity status

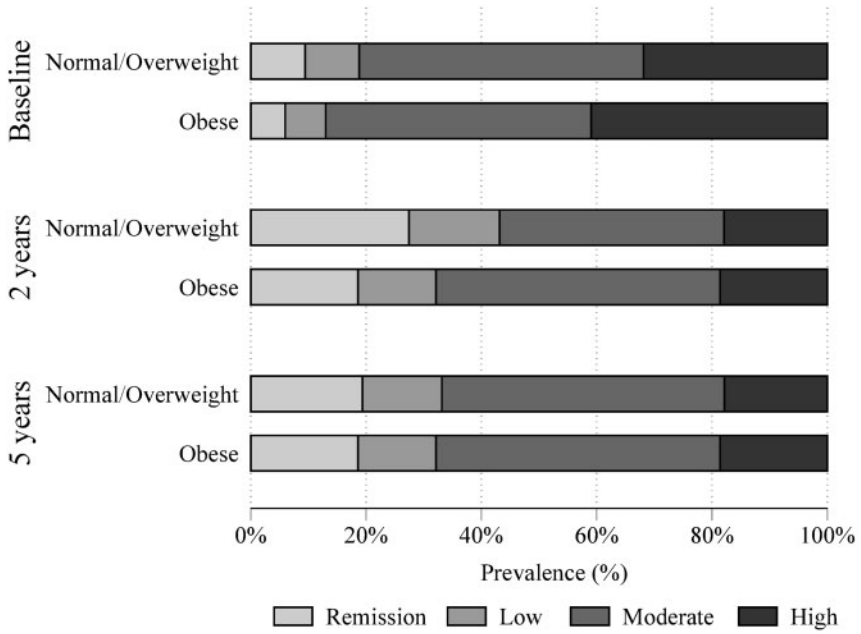


Table 3 Crude and adjusted means by BMI category at 2 years for outcomes at 2 and 5 years follow-up

		Normal/Overweight			Obese				Underweight			
Model	**Time**	**Mean**	**LCL**	**UCL**	**Mean**	**LCL**	**UCL**	***P*-value***	**Mean**	**LCL**	**UCL**	***P*-value***
DAS28 (*N* = 2386)												
Crude	2 years	3.47	3.39	3.55	3.78	3.63	3.93	0.000	4.42	3.95	4.90	0.000
	5 years	3.78	3.69	3.87	3.82	3.65	3.98	0.701	3.91	3.39	4.43	0.615
Adjusted	2 years	3.53	3.44	3.62	3.83	3.66	3.99	0.002	4.17	3.62	4.73	0.024
	5 years	3.83	3.73	3.93	3.79	3.60	3.98	0.759	3.69	3.07	4.31	0.676
HAQ (*N*=2386)												
Crude	2 years	0.91	0.88	0.94	1.15	1.09	1.21	0.000	1.19	1.00	1.39	0.006
	5 years	0.89	0.85	0.93	1.17	0.93	1.42	0.000	1.12	1.05	1.20	0.699
Adjusted	2 years	0.93	0.89	0.96	1.08	1.02	1.14	0.000	1.07	0.85	1.29	0.218
	5 years	0.91	0.87	0.96	1.05	0.96	1.13	0.008	1.04	0.74	1.34	0.982
PCS (*N* = 1030)												
Crude	2 years	32.89	32.05	33.74	28.89	27.64	30.14	0.000	29.23	23.59	34.88	0.209
	5 years	34.61	33.48	35.74	30.82	29.13	32.51	0.000	28.13	20.68	35.58	0.491
Adjusted	2 years	32.59	31.73	33.45	29.50	28.22	30.78	0.000	31.34	24.51	38.17	0.722
	5 years	34.50	33.28	35.72	31.66	29.84	33.47	0.011	29.73	20.31	39.14	0.693
MCS (*N* = 1030)												
Crude	2 years	49.09	48.34	49.83	47.53	46.43	48.63	0.022	45.38	40.43	50.33	0.147
	5 years	50.27	49.32	51.22	48.04	46.62	49.46	0.011	46.48	40.27	52.68	0.630
Adjusted	2 years	48.84	48.03	49.66	48.22	47.01	49.43	0.403	49.71	43.24	56.18	0.794
	5 years	50.07	49.02	51.12	48.86	47.30	50.41	0.206	48.35	40.38	56.31	0.902

*Mean difference compared with normal/overweight. UCL: upper control limit; LCL: lower control limit.

patient-reported outcomes with immediate measurable consequences [36]. It follows that strategies to encourage and support patients to lose weight at any stage of the disease should lead to immediate RA-specific benefits as well as longer-term cardiovascular and general health benefits that might also be expected in people without RA. Indeed, strategies to lose weight either by diet and exercise or bariatric surgery [40] have shown promise in suppressing RA disease activity.

Our study has many strengths, including enrolment of patients with early RA over 3 decades, its longitudinal nature, large patient numbers and long patient follow-

up. However, it also has limitations; importantly, that many patients migrated into the obesity category over time. This may have biased the observations relating to the impact of baseline obesity on 5 year outcomes. To determine whether this was likely, we also examined BMI at 2 years as a predictor of future outcome, noting broadly equivalent results. The HRQoL analysis was also limited by the availability of SF-36 data in ERAN but not ERAS. Finally, our models did not adjust for treatment use (e.g. glucocorticoids or DMARDs) at each time point, but instead controlled for disease activity, which captures the impact of treatment. This was considered the most appropriate approach, as our models assess the impact of BMI on future outcomes in general, which may be partially mediated by treatment since BMI may influence treatment decisions (e.g. steroid use) and BMI may itself be related to past treatment. As a result, it is difficult to draw strong inferences about whether the association between BMI and future outcome is due to BMI and associated factors or to differential treatment selection across the range of BMIs. That is, both explanations are likely but we cannot determine the magnitude of the effect via each pathway.

In conclusion, we have demonstrated in early RA the increasing prevalence of obesity and its negative consequences on DAS28, achieving a treat-to-target LDAS goal, function and HRQoL outcomes in the short term. This effect is synchronous, with current obesity status at baseline and year 2 having an immediate and short-term effect not persisting in the medium-term. These data argue strongly for the screening and management of obesity to become a central part of all treatment strategies for patients with RA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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