

Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA study

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Abstract Objective

To investigate whether body mass index (BMI), as a proxy for body fat, influences rheumatoid arthritis (RA) disease activity in a gender-specific manner.

Methods

Consecutive patients with RA were enrolled from 25 countries into the QUEST-RA program between 2005 and 2008. Clinical and demographic data were collected by treating rheumatologists and by patient self-report. Distributions of Disease Activity Scores (DAS28), BMI, age, and disease duration were assessed for each country and for the entire dataset; mean values between genders were compared using Student's t-tests. An association between BMI and DAS28 was investigated using linear regression, adjusting for age, disease duration and country.

Results

A total of 5,161 RA patients (4,082 women and 1,079 men) were included in the analyses. Overall, women were younger, had longer disease duration, and higher DAS28 scores than men, but BMI was similar between genders. The mean DAS28 scores increased with increasing BMI from normal to overweight and obese, among women, whereas the opposite trend was observed among men. Regression results showed BMI (continuous or categorical) to be associated with DAS28. Compared to the normal BMI range, being obese was associated with a larger difference in mean DAS28 (0.23, 95% CI: 0.11, 0.34) than being overweight (0.12, 95% CI: 0.03, 0.21); being underweight was not associated with disease activity. These associations were more pronounced among women, and were not explained by any single component of the DAS28.

Conclusion

BMI appears to be associated with RA disease activity in women, but not in men.

Key words

Rheumatoid arthritis, gender, BMI, disease activity

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Grant support from: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Career Development Award (K01AR053496) and Abbott Pharmaceuticals.

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Received on November 4, 2009; accepted in revised form on January 19, 2010.

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Introduction

The influence of body mass index (BMI) and/or body fat on rheumatoid arthritis (RA) disease activity is unclear. Some studies have shown high BMI to be associated with RA (1) and poor disease outcome (2), whereas others have found low BMI to be associated with increased erosion in small joints and decreased survival, with high BMI being protective (3, 4). Previous investigations of an association between serum leptin and disease activity in RA have yielded contradictory findings (5-8). Recently, an association between body fat and levels of C-reactive protein (CRP) in RA patients has been demonstrated (9), although this did not extend to RA disease activity.

White adipose tissue (WAT) plays an active role in regulating physiologic and pathologic processes, including immunity and inflammation (10). The adipocytes in WAT secrete a variety of pro-inflammatory adipokines such as leptin and resistin, as well as inflammatory cytokines tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL6) (11). CRP, another marker of inflammation, is also increased in obesity (12). It has been hypothesised that adipokines, cytokines and other factors released by WAT lead to the pro-inflammatory state observed in obesity although the mechanism by which this happens is not known (10).

Given the inflammatory nature of RA, in the present study, we have investigated whether BMI, as a proxy for body fat, is associated with the composite index of disease activity score based on a 28-joint count (DAS28), in the context of the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) study (13). We further examined whether such an association, if present, is modified by gender since women tend to have higher DAS28 scores than men.

Patients and methods

Patients

Consecutive incident or prevalent RA patients receiving usual care, were recruited from 70 sites in 25 different countries, namely Argentina, Brazil, Canada, Denmark, Estonia, Finland,

France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, the Netherlands, Poland, Russia, Serbia, Spain, Sweden, Turkey, United Arab Emirates, United Kingdom, and the United States to the QUEST-RA program from January 2005 to April 2008, as described elsewhere (13). All patients satisfied the 1987 American College of Rheumatology (ACR) criteria for RA. Approval for the study was obtained from all relevant ethics committees and all participating patients were enrolled by informed consent.

Data collection

Patients were examined by their treating rheumatologists according to a standard protocol to evaluate RA (14), which included a review of the classification criteria for RA, as well as an assessment of the number of tender and swollen joints. The rheumatologists also collected clinical and demographic data for the study. The patients completed an expanded self-report health questionnaire that had been translated into each language, and which included a global health visual analogue scale and questions regarding their height and weight.

Statistical analyses

BMI was calculated as a continuous variable, from the self-reported heights and weights, as weight in kilograms divided by the square of height in meters. BMI values were also categorised into the widely used underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²) and obese (\geq 30 kg/m²) categories, based on the 1998 clinical guidelines (15). The composite DAS28 score was computed as DAS28 = [0.56*sqrt (number of tender joints) + 0.28*sqrt (number of swollen joints) + 0.70*ln (erythrocyte sedimentation rate) + 0.014* (patient global score)].

Summary statistics

Distributions of DAS28 scores, BMI, age, disease duration were assessed using scatter plots and box plots. The overall mean values between genders were compared using Student's *t*-tests. Mean DAS28 scores were plotted against BMI categories, for each coun-

Competing interests: none declared.

Table I. shows the mean values and 95% confidence intervals for DAS28, BMI, age and disease duration, including the minimum and maximum values for the combined dataset, as well as those among male and female patients separately. The *p*-values from the *t*-tests to assess the difference in mean values between genders are also shown.

Characteristic	Range across countries (n=5161) (mean \pm S.D.)		Combined data (n=5161) (mean \pm S.D.)	Males (n=1079) (mean \pm S.D.)	Females (n=4082) (mean \pm S.D.)	<i>p</i> -value
	Min	Max				
DAS28 scores	3.0 \pm 1.2	5.9 \pm 1.3	4.2 \pm 1.7	3.8 \pm 1.8	4.3 \pm 1.6	<0.00001
BMI (kg/m ²)	24.7 \pm 4.7	27.9 \pm 5.9	25.9 \pm 4.8	26.0 \pm 3.8	25.8 \pm 5.0	0.8
Age (years)	51.6 \pm 13.6	61.5 \pm 14.0	56.2 \pm 13.7	58.7 \pm 12.8	56.1 \pm 14.1	<0.00001
Disease duration (years)	9.2 \pm 7.8	15.4 \pm 11.3	11.4 \pm 9.7	10.3 \pm 9.5	11.9 \pm 9.9	<0.00001

try, as well as by gender in the combined dataset. Mean values of the individual components of the DAS28, *i.e.* erythrocyte sedimentation rate (ESR), patient global score, swollen and tender joint counts were also plotted by BMI categories and gender.

Comparisons of mean DAS28 scores between BMI categories

The analysis of variance (ANOVA) method was used to determine whether the mean and variance of the DAS28 differed between BMI categories in the combined dataset. A pair-wise comparison of the mean values of DAS28, using the Tukey adjustment for multiple testing, as well as an unadjusted regression of DAS28 on BMI categories, were performed to assess the difference in mean DAS28 scores between BMI categories.

Multivariate linear regression of DAS28 on BMI

A possible association between BMI and DAS28 scores was investigated using an additive linear regression model, (a) without adjusting for any covariates, and (b) adjusting for age, gender, disease duration, as well as for each country participating in the QUEST-RA study. Since DAS28 scores were normally distributed in this dataset, they were not log-transformed for the regression analyses. The influence of BMI was examined first as a continuous variable. This model assumed that the DAS28 changes linearly with BMI. Underweight patients were excluded from the analyses where BMI was included as a continuous variable since it is possible that being underweight could lead to other conditions that could

influence the association between BMI and DAS28.

To allow for more flexibility in the model, we then used BMI as a categorical variable, so as not to assume that the DAS28 would change linearly with BMI for all values of BMI; the “normal BMI” range was used as the reference. To determine whether gender was an effect modifier, we tested for interaction between BMI and gender, including an interaction term in the model. We also repeated the regression analyses separately for men and women. For each of the models used, assumptions for linear regression were satisfied. To assess whether any specific component of the DAS28 was associated with BMI, we repeated the analyses using each component in turn as the outcome (ESR, patient global score, swollen and tender joint counts), with BMI categories as the main predictor, adjusting for age, gender, disease duration and country, as well as for each of the other DAS28 components.

Test for “reverse causation”

We assessed the influence of disease duration on BMI (as a continuous outcome) in a linear regression model, adjusting for age, gender and country, in order to examine for potential “reverse causation”. If increased disease activity led to physical inactivity and hence to an increase in BMI, we would expect increasing disease duration to correlate with higher BMI, at least for those with a high DAS28 score.

Results

Of the 6004 RA patients in the QUEST-RA study, complete data on BMI, DAS28, gender and age variables were available on a total of 5,161 patients,

consisting of 4,082 women and 1,079 men, with a corresponding 3.8:1 female to male ratio. The range of values of DAS28, BMI, age, and disease duration varied between countries (Table I). Overall, the patients had moderately active disease (mean DAS28=4.2 \pm 1.7); there was no difference in mean BMI between genders; however, women had significantly higher mean DAS28, longer disease duration and younger age than men (Table I).

Distributions of mean DAS28 scores by BMI category

The mean DAS28 scores among patients in different BMI categories increased with increasing BMI in most countries (Fig. 1a), as well as in the combined dataset (Fig. 1b). However, patients in the underweight category appeared to have higher mean DAS28 scores compared to those with normal or overweight BMIs.

Comparisons of mean DAS28 scores between BMI categories

At least one of the BMI categories had a mean DAS28 that was statistically different from the other categories (ANOVA: *p*<0.0002). A pair-wise comparison using the Tukey adjustment showed that the mean DAS28 values of the overweight and obese patients were 0.18 higher (95% CI: 0.04, 0.32), and 0.26 higher (95% CI: 0.09, 0.43), respectively, compared to the normal BMI category. Among the underweight patients, the mean DAS28 was also higher than among the normal group by 0.19 (95% CI: -0.53, 0.15). An unadjusted regression of DAS28 on BMI categories produced the same differences in mean DAS28.

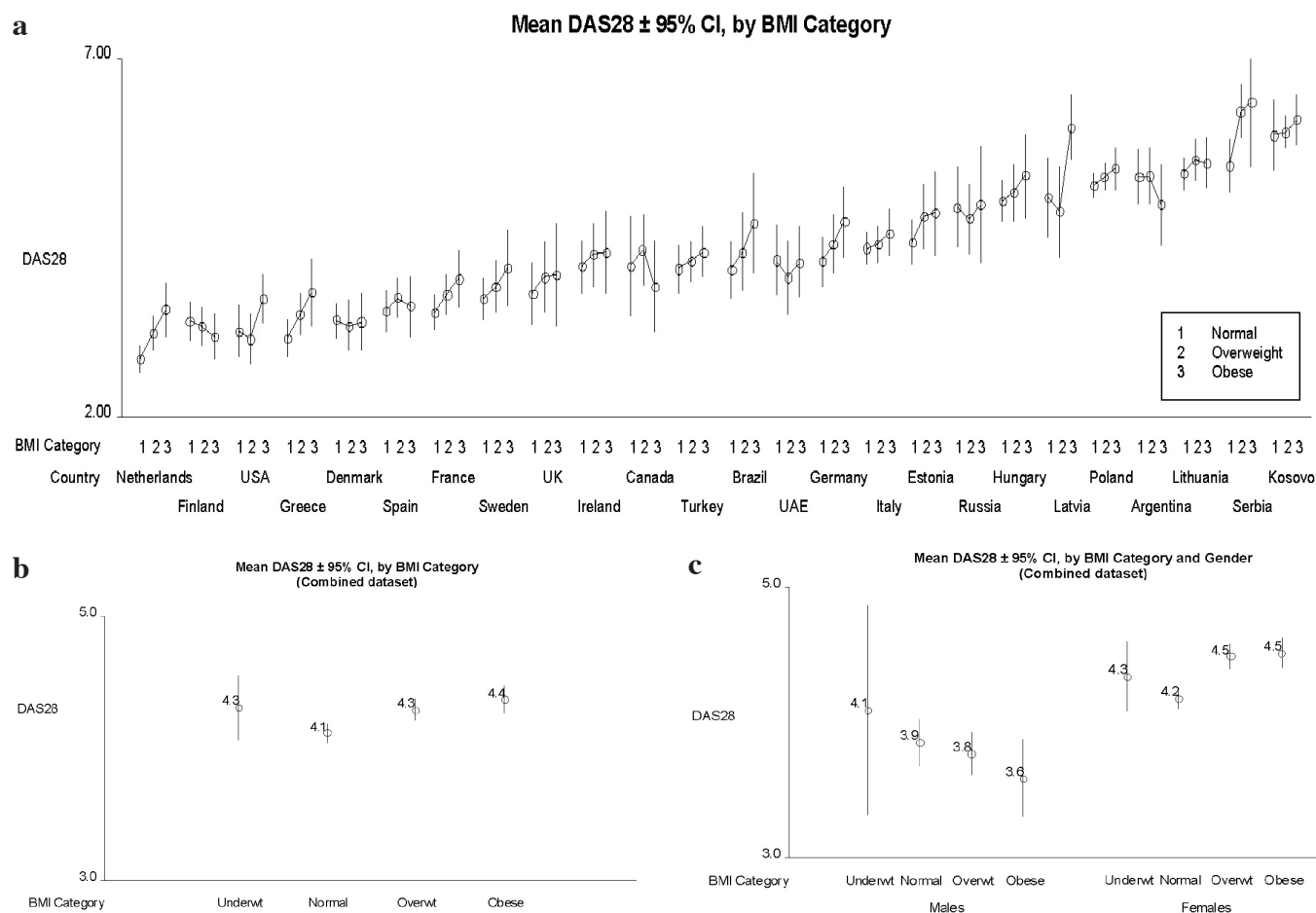


Fig. 1. Plots showing the mean DAS28 scores and the 95% confidence intervals (y-axis) by BMI category (x-axis), i.e. normal, overweight and obese, (a) for each country participating in the QUEST-RA study, (b) for the combined dataset and (c) for female and male patients separately

Stratification by gender

When the data were stratified by gender, the mean DAS28 scores increased with BMI only among women (Fig. 1c), although the underweight category had higher scores than the normal category. In contrast, among men, the mean DAS28 scores decreased with increasing BMI.

Individual components of the DAS28

The distribution of the mean values for ESR, patient global scores, tender and swollen joint counts by BMI category for men and women are shown in Fig. 2a-d. The regression results showed that, compared to women with normal BMI, only obese women had a significantly higher mean ESR (difference=3.03, 95% CI: 1.20, 4.86) and patient global scores (difference=0.29; 95% CI: 0.09, 0.49). On the other hand, only obese men had significantly different mean tender joint count (differ-

ence=1.05; 95% CI: 0.09, 2.02) and swollen joint count (difference= -1.03; 95% CI: -1.78, -0.29), compared to men with normal BMI.

Multivariate linear regression of DAS28 on BMI

BMI as a continuous variable: There was a significant but weak association between BMI (continuous), and DAS28 adjusting for other variables. This corresponded to a mean increase of 0.02 in the DAS28 for a unit increase in BMI in the overall group of patients (regression coefficient (β)=0.02, 95%CI=0.006, 0.023) and among the women (β =0.02, 95%CI=0.01, 0.03), whereas among men, there was a non-significant trend in the opposite direction (β =-0.02, 95% CI= -0.04, 0.007).

BMI as a categorical variable: Using normal BMI as the reference category, the regression model revealed that the overweight and obese categories were

weakly, but significantly associated with DAS28, compared to the normal BMI range, after adjusting for age, sex, disease duration and each country. Moreover, being obese was associated with a higher mean DAS28 compared to those with normal BMI (difference=0.23, 95% CI: 0.11, 0.34) than being overweight (difference=0.12, 95% CI: 0.03, 0.21). Being underweight was not significantly associated with disease activity.

Influence of gender on the association between BMI and DAS28

There was significant evidence for an interaction between BMI categories and gender (p =0.001) in the adjusted model above. Repeating the analyses separately by gender showed that the associations were only seen among women. The obese category was more strongly and more significantly associated with DAS28 than the over-

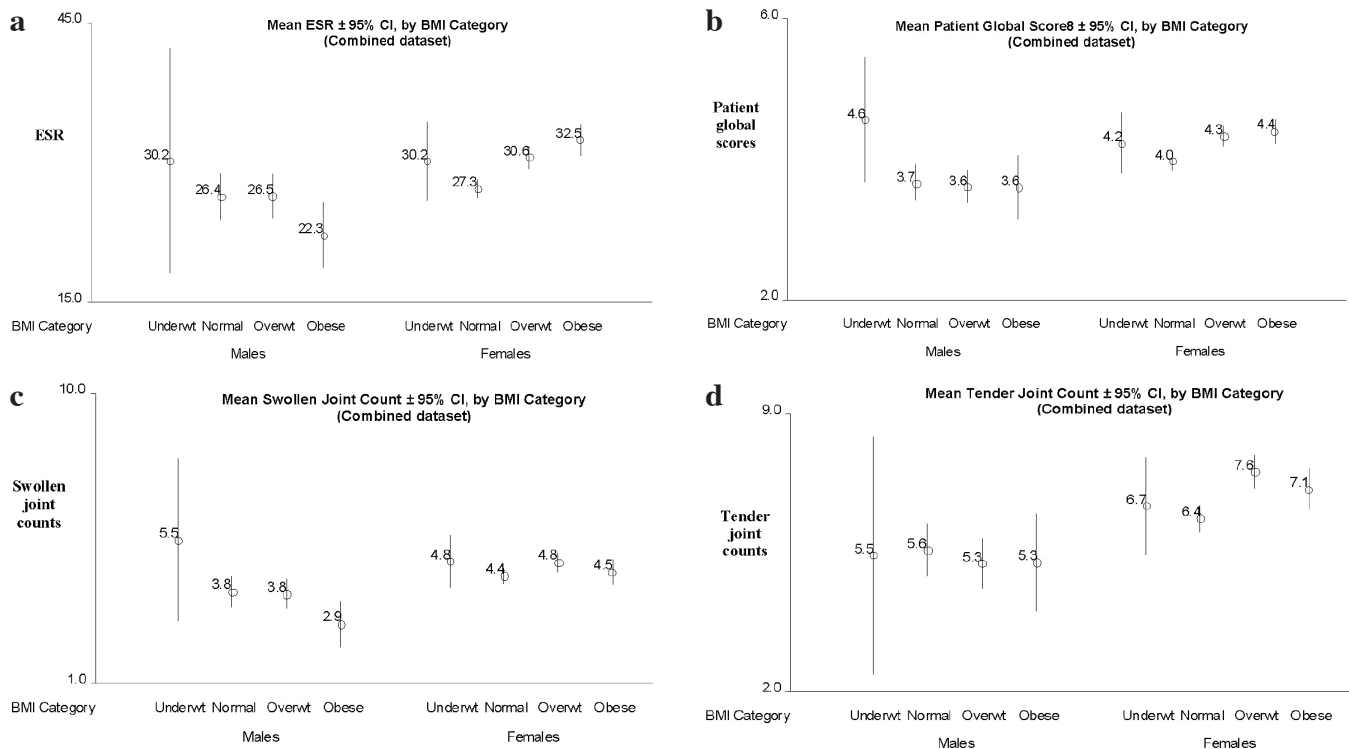


Fig. 2. Plots showing the mean (a) Erythrocyte Sedimentation Rate (ESR), (b) Patient Global Scores, (c) Swollen Joint Counts, and (d) Tender Joint Counts, with 95% confidence intervals (y-axis) by BMI category (x-axis) in the combined dataset, for female and male patients separately.

weight category (difference in mean DAS28=0.29, 95% CI: 0.17, 0.41 and 0.18, 95% CI: 0.08, 0.28, respectively), compared to the reference group with normal BMI. In contrast, among men, an opposite effect was observed, with higher BMI categories relating to decreasing DAS28 (difference in mean DAS28= -0.05, 95% CI: -0.35, 0.25 and 0.04, 95% CI: -0.24, 0.17, for the obese and overweight groups respectively); this association did not reach statistical significance in the model adjusted for other covariates. The underweight category was again not associated with disease activity.

Testing for “reverse causation”

BMI was negatively associated with disease duration in the combined dataset ($\beta=-0.05$, 95% CI: -0.06, -0.04), as well as among women ($\beta=-0.054$, 95% CI: -0.070, -0.038) and men ($\beta=-0.03$, 95% CI: -0.06, -0.006) separately, after adjusting for age and each country.

Discussion

Our results show that high BMI was associated with increased disease activity in RA among women. Moreover,

being obese was associated with a higher mean DAS28 than being overweight, compared to patients in the normal BMI range. Given the international scale of this study, it is of interest that the association between BMI and DAS28 scores in the combined dataset, suggested by the regression analyses, was also supported by the distribution of mean values of DAS28 between BMI categories observed within each country, and is not just a statistical artifact of the large overall sample size. Despite recent findings of higher DAS28 among women being due to measures of disease activity (16), the association between BMI and DAS28 among women in the QUEST-RA dataset could not be explained by any single component of the DAS28. Associations between waist circumference and CRP (17), and more recently, between adiposity and CRP or IL6 (9) have been reported; nevertheless, these associations did not extend to RA disease activity. Interestingly, the association between adiposity and CRP reported by Giles *et al.* (9) in a total of 118 women and 78 men with RA, was also observed only among women, with men showing

an opposite, but non-significant, trend. The novel finding from our study is that BMI, as a proxy for body fat, also influences RA disease activity in a gender-specific manner. Although this association is small and clinically may not appear to be significant, it could be one of many factors contributing to disease activity in RA and should not be ignored. Given that the male sample size in our study was almost 4-fold less than the female sample size, we are not making any inferences regarding an association among the male patients until these findings can be replicated in independent datasets. Among underweight patients, disease activity appeared to increase with decreasing BMI; however, it is possible that this observed association is confounded by co-morbidities that are associated with being underweight.

Since most patients in the QUEST-RA dataset are physically inactive (18), we cannot exclude the possibility of reverse causation. The association of BMI with disease activity could be due to physical inactivity as a result of active RA, leading to an increase in BMI. However, if increased disease activity

led to physical inactivity, we would expect disease duration to correlate with increasing BMI, at least for those with a high DAS28 score, in men and women, which was not the case. Further, a regression of BMI (as the outcome) on disease duration, adjusting for age, gender and each country, revealed a decrease in BMI with increasing disease duration in the combined dataset, as well as among women and men separately. It is likely therefore that BMI, as a marker of body fat, is a predictor of disease activity, and not a mere consequence of reverse causation. The decrease in BMI with increasing RA duration could be the result of progressive weight loss from having severe RA and/or loss of muscle mass due to inactivity, also because of severe RA.

The exact mechanism by which body fat may influence disease activity is not known, and is beyond the scope of this paper, but is possibly related to levels of pro-inflammatory cytokines and adipokines being produced by WAT, contributing to an increased DAS28 score. It is also unclear why high BMI, above the normal range, should have contrasting associations with disease activity among men and women. Bias in patient selection or treatment cannot be ruled out. We also do not expect BMI to correlate with body fat equally in the two sexes. Men tend to have more muscle mass contributing to BMI than women, and the higher fat content among women could explain an increased pro-inflammatory state responsible for their higher disease activity. The site of fat accumulation may also play an important role; for example, insulin resistance has been associated with visceral fat, but not sub-cutaneous fat which may be beneficial (19). Interestingly, the association between body fat and CRP among RA patients, more specifically in women (9), provides further evidence for increased body fat being associated with a pro-inflammatory state in a gender-specific manner. Thus, there could be some as yet unknown epigenetic mechanism in operation, which may be highly influenced by gender-specific factors, predisposing men and women to respond differently to increasing body fat. Further research

relating to possible mechanisms linking body fat to disease activity in RA, as well as possible gender specific mechanisms, is therefore warranted.

The study has a number of limitations that need to be addressed. First, since there is no gold standard measure of disease activity in RA, we used the DAS28 as a surrogate although it is not a perfect measure of RA disease activity. Second, since measurement of body fat requires tools that are not readily available in standard clinical practice, and BMI has been shown to correlate with body fat in RA (9), we have used BMI as a proxy for body fat. However, we do not know how well BMI correlates with body fat within our dataset or between the sexes. Third, we do not know how accurate the self-reported height and weight data are. It has been shown that, although men and women tend to over-report height and under-report weight (20, 21), there is a high correlation between self-reported and measured height and weight (21). Given the consistent trends in mean DAS28 by BMI category across countries observed in our dataset among men and women, irrespective of differences in culture, diet, ethnicity or geographical location, it seems unlikely that these trends would be due to any biases in self-reported height and weight. Fourth, the data were obtained from 70 recruitment sites in 25 different countries. Although the patients were examined according to a standard protocol, the tender and swollen joint counts used in computing the DAS28, can vary by rheumatologist. Differences observed between countries in terms of disease activity, duration, BMI and age of the patients were assumed to be related to differences in routine clinical care, standard treatment practices or other factors such as diet or environmental risk factors, which might be specific to certain countries. In addition, despite the striking consistency in the relationship between BMI and DAS28 across countries, there were a few countries in which this trend was not observed, and it is not clear why that was the case. Fifth, selection bias may have been introduced by specific patients declining to participate in the

study, or by a bias in prevalent versus incident cases in any of the recruitment sites. However, data regarding selection bias was not available. Sixth, although treatment is likely to be a confounder in the association between BMI and disease activity, the treatment history of the patients was not adjusted for in the results presented. Last, the cross-sectional design of the QUEST-RA study is not optimal to investigate associations between BMI or body fat and RA disease activity; the preferred approach would be to follow up an incidence cohort over time to examine how changes in body fat correlate with DAS28 scores, which would be time-consuming and costly. Nonetheless, despite the limitations, the data available from QUEST-RA does have its strengths in that it has a large sample size, and provides good clinical data on RA on an international level, but the results should be interpreted with caution. Overall, although the exact clinical implications of the association between BMI and RA disease activity are not clear, it may be beneficial to encourage women with RA who are overweight or obese to lose weight, not just from a cardiovascular risk perspective, but also because it may help in terms of disease activity and pro-inflammatory state.

Appendix

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