

# Paradoxical Effect of Body Mass Index on Survival in Rheumatoid Arthritis

## Role of Comorbidity and Systemic Inflammation

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**Background:** Despite high cardiovascular mortality in rheumatoid arthritis (RA), few studies of body mass index (BMI) and obesity as risk factors for death in RA have been published.

**Methods:** We estimated the effect of BMI on survival in a cohort of 779 patients with RA adjusting for comorbidity, RA disease severity, erythrocyte sedimentation rate (ESR), and other potential confounders.

**Results:** The cohort accrued 123 deaths in 3460 person-years (3.6 deaths per 100 person-years; 95% confidence interval [CI], 3.0-4.2). The BMI was inversely associated with mortality. Patients with BMIs of 30 or higher had the lowest mortality, 1.7 deaths per 100 person-years (95% CI, 1.1-2.5). Mortality was higher in each lower BMI category, reaching its highest rate among patients with BMIs lower than 20 with 15.0 deaths per 100 person-

years (95% CI, 9.9-23.0). The survival advantage of high BMI was independent of RA onset age, RA duration, sex, ethnic group, socioeconomic status, smoking status, and use of methotrexate but was lost on adjusting for comorbidity and RA severity. We observed an interaction between BMI and ESR, where the BMI protective influence occurred only if the ESR was low. The BMI  $\times$  ESR interaction was independent of all covariates, including comorbidity and RA severity.

**Conclusions:** Body mass has a paradoxical effect on mortality in RA. Patients with high BMI have lower mortality than thinner patients. This effect is mediated in part by comorbidity. The effect of body mass on survival seems to be modified by the level of systemic inflammation.

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**O**BESITY AND LOW BODY weight have a negative influence on survival in normal populations.<sup>1,2</sup> Body mass and mortality display a J- or U-shaped relationship. Above or below an “optimal” body mass, a person’s lifespan decreases.<sup>1</sup>

Survival is also diminished in rheumatoid arthritis (RA),<sup>3-10</sup> most likely because of an excess of cardiovascular (CV) disease.<sup>5,11-17</sup> The role of CV risk factors in RA’s increased mortality is under intense investigation.<sup>18,19</sup> In addition, chronic systemic inflammation and its treatment are suspect.

Body mass has not been studied sufficiently as a CV risk factor in RA. Obesity may increase a person’s susceptibility to RA.<sup>20,21</sup> However, not all published studies agree on this finding.<sup>22,23</sup> Body weight may also influence the clinical picture of RA. Obese patients with RA experience less joint damage than do lean ones.<sup>24</sup> Patients with excessively low body weight,

so-called rheumatoid cachexia,<sup>25</sup> display elevated levels of inflammatory markers in the blood.<sup>26</sup> A recent study found an increased risk of death from CV causes among patients with RA and a low body mass index (BMI), calculated as the weight in kilograms divided by the height in meters squared.<sup>27</sup>

Herein, our objective is to examine an RA cohort’s mortality in relation to BMI and systemic inflammation. We hypothesized a negative influence of BMI on survival, modified by inflammation markers. We accounted for potential confounders, including age at RA onset, disease duration, sex, ethnic group, socioeconomic status (SES), RA severity, cigarette smoking, methotrexate use, and comorbidity.

## METHODS

### PATIENTS

From 1996 to 2000, we enrolled consecutive patients who met classification criteria for RA<sup>28</sup>

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and were aged 18 years or older from 6 outpatient rheumatology clinics in San Antonio, Tex: (1) an Army and (2) Air Force Medical Center, (3) a private, university-based clinic, (4) a community-based private rheumatology practice, (5) a county-funded clinic, and (6) a Veterans Affairs clinic. All baseline evaluations were done on location. Follow-up evaluations were performed at the Bartter General Clinical Research Center, San Antonio, Tex, the recruitment clinical facility, or the patient's residence. Our study was approved by the institutional review board. After obtaining written, informed consent, a trained physician or research nurse conducted a comprehensive clinical evaluation and medical record review.

Starting in 1997, patients were contacted annually for follow-up. The censoring date for the present analysis was May 31, 2004. We learned of deaths through family members, friends, neighbors, other physicians, and public death databases. We obtained a state-issued certificate for all deaths.

## DATA ELEMENTS

We ascertained the date of birth and sex by self-report, as described elsewhere.<sup>29</sup> For race/ethnicity, we asked "In which of the following race or ethnic groups do you feel you belong?" Patients could choose among white, black, Asian, Hispanic, and other.

We classified SES according to Nam and Powers,<sup>30</sup> using years of education, inflation-adjusted monthly household income, and current or past occupation to calculate an SES score on an ascending 0 to 100 scale.<sup>30</sup>

At each visit, we calculated each patient's BMI and categorized them as underweight (BMI  $\leq 20$ ), normal weight (BMI 20 to  $< 25$ ), overweight (BMI 25 to  $< 30$ ), or obese (BMI  $\geq 30$ ). These are consistent with current definitions for overweight and obesity.<sup>31</sup> In a sensitivity analysis, we defined an additional group with BMI of 35 or higher.

A physician examined 48 joints for tenderness or pain on motion, swelling, or deformity.<sup>32</sup> The Spearman-Brown reliability coefficient was 0.90 or higher for counts of each of these.

We used the Duke Severity of Illness Checklist (DUSOI),<sup>33</sup> as described previously.<sup>34</sup> Briefly, a physician rated each of the patient's health problems on 4 dimensions: symptoms, complications, prognosis, and treatability. Each dimension was graded on a 0 to 4 scale using predefined criteria.<sup>33</sup> Ratings were then summed, divided by 16, and multiplied by 100. This resulted in a 0 to 100 ascending severity score for each health problem. These were then severity ranked and entered into a formula that assigns full weight to the highest-ranking problem and progressively diminishing weight to lower-ranking health problems.<sup>33,34</sup> Physicians who scored the DUSOI were trained using a standardized protocol. Patient's health problems and scores were reviewed by 1 or more physicians. Disagreements were discussed before assigning a final value. In the ORALE (Outcome of Rheumatoid Arthritis Longitudinal Evaluation) cohort, the DUSOI proved reliable and predictive of mortality over a 6-year period.<sup>34</sup>

To separate the contribution of comorbidity to mortality from that of RA severity, we excluded the latter from the overall score. We refer to this RA-free scale as the comorbidity DUSOI or COMDUSOI. We used a similar approach to measure RA severity. We rated each patient's RA symptoms, complications, prognosis, and treatability to obtain the RADUSOI. As a measure of RA severity, the RADUSOI correlates with joint damage, disability and extra-articular manifestations and predicts mortality independent of comorbidity.<sup>34</sup>

We defined disease duration from the self-reported time of RA diagnosis. We asked whether the patients had ever smoked cigarettes. At every visit, we recorded whether patients were using methotrexate for the treatment of RA. We searched for subcutaneous nodules on physical examination.

We measured the erythrocyte sedimentation rate (ESR) using a manual Westergren technique or an automated analyzer (Diesse Diagnostic Senese, Milan, Italy). Values obtained with either system correlate highly ( $r=0.97$ ).<sup>35</sup> Serum rheumatoid factor titer was measured using the latex agglutination technique.

## STATISTICAL ANALYSIS

We calculated the mortality rate using a person-years approach with Cox 95% confidence intervals (CIs).<sup>36</sup> We obtained age- and sex-adjusted estimates of the mortality rate using Poisson regression. We used the Kaplan-Meier method to estimate survival differences between the BMI categories.<sup>37</sup> We tested differences using the log-rank method. We used multivariable Cox proportional hazards models to estimate the effect of BMI and ESR on survival adjusting for potential confounders.<sup>38</sup> In these models, BMI, ESR, COMDUSOI, RADUSOI, methotrexate use, and RA duration were included as time-varying covariates, with age at RA onset, sex, racial/ethnic group, SES score, and cigarette smoking status as unvarying covariates.<sup>38</sup>

We tested models with and without the COMDUSOI and RADUSOI and with and without a BMI  $\times$  ESR product term. To obtain hazard ratios for BMI at different levels of ESR, we stratified the ESR into quintiles and used linear combinations to calculate stratum-specific hazard ratios. We tested the proportional hazard assumption using Schoenfeld residuals after all Cox proportional hazards models.<sup>39</sup> All analyses were conducted using a desktop personal computer and the Stata statistical software package, version 8.0 (College Station, Tex).

## RESULTS

We performed a baseline evaluation on 779 patients. Their characteristics according to BMI at baseline are shown in **Table 1**. Compared with the patients with a normal BMI (20 to  $< 25$ ), obese patients (BMI  $\geq 30$ ) were younger, less likely to be white, more likely to be Hispanic, and had lower SES scores. Their RA was diagnosed more recently, and they had accrued less joint damage. Patients with BMIs lower than 20 were older and had more deformed joints and more comorbidity than heavier patients (Table 1).

The 779 patients accrued 3460 person-years of observation. During this time, 123 patients died, for a mortality rate of 3.6 per 100 person-years (95% CI, 3.0-4.2). Mortality decreased in each successively higher BMI category (**Table 2** and **Figure 1**). Because of the age differences between BMI categories, we estimated age-adjusted mortality rates to determine if the BMI effect was confounded by age. As shown by the data listed in Table 2, age adjustment did not remove the protective influence of the higher BMI.

It should be noted that in contrast to findings in the general population where a J- or U-shaped association between BMI and mortality is seen, the present cohort displayed a near-linear decrease in mortality from the lowest to the highest BMI category. This was the case in both the gross and age-adjusted mortality rates.

The beneficial effect on mortality of a BMI of 30 or higher in this cohort is paradoxical. To further test this effect, we created an additional category for patients with BMIs of 35 or higher to see if the protective influence was lost above this level. In unadjusted comparisons of the mortality risk

**Table 1. Baseline Characteristics and BMI of 779 Patients With Rheumatoid Arthritis\***

Baseline Characteristic	BMI			
	<20 (n = 38)	20 to <25† (n = 195)	25 to <30 (n = 264)	≥30 (n = 282)
Age, y	63 (16)‡	56 (14)	58 (12)	52 (13)‡
Men	11 (29)	58 (30)	99 (38)	60 (21)§
White	22 (58)	86 (44)	96 (36)	68 (24)
Black	1 (3)	14 (7)	22 (8)	16 (6)
Hispanic	15 (39)	83 (43)	141 (53)§	195 (69)
Disease duration, y	15 (13)	12 (11)	12 (11)	9 (10)
SES score	44 (28)	42 (24)	41 (26)	35 (24)
Ever smoked cigarettes	22 (58)	116 (59)	109 (59)	176 (62)
Tender joint count	13 (10)	14 (13)	15 (13)	16 (12)
Swollen joint count	5 (6)	6 (6)	8 (7)§	8 (7)
Deformed joint count	18 (13)	12 (12)	11 (11)	7 (9)
Subcutaneous nodules	11 (30)	46 (24)	94 (36)‡	83 (29)
Positive rheumatoid factor	26 (81)	148 (78)	208 (82)	234 (85)
Current methotrexate use	13 (34)§	110 (56)	153 (58)	179 (64)
ESR, mm/h	47 (29)	38 (28)	43 (27)	42 (25)
Rheumatoid arthritis DUSOI score	53 (17)	49 (14)	49 (13)	49 (13)
Comorbidity DUSOI score	58 (24)§	50 (23)	51 (20)	51 (22)

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by the height in meters squared); DUSOI, Duke Severity of Illness Checklist<sup>33</sup>; ESR, erythrocyte sedimentation rate; SES, socioeconomic status.

\*Data are reported as either number (percentage) or mean (SD), as appropriate.

†Referent category.

‡ $P \leq .01$ .

§ $P \leq .05$ .

|| $P \leq .001$ .

**Table 2. Numbers and Mortality Rates\* in 779 Patients With Rheumatoid Arthritis by BMI**

BMI	Number				Mortality Rate (95% CI)	
	Patients at First Visit	Patients Ever in Category	Person-Years	Deaths	Unadjusted	Age- and Sex-Adjusted
<20	38	69	156	24	15.0 (9.9-23.0)	6.8 (4.2-11.1)
20 to <25	195	272	676	37	5.4 (4.0-7.5)	3.3 (2.3-4.9)
25 to <30	264	414	1145	38	3.3 (2.4-4.5)	2.1 (1.4-3.0)
≥30	282	378	1434	24	1.7 (1.1-2.5)	1.4 (0.1-2.2)
<b>Overall</b>	<b>779</b>	<b>NA</b>	<b>3412</b>	<b>123</b>	<b>3.6 (3.0-4.2)</b>	<b>NA</b>

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by the weight in meters squared); CI, confidence interval; NA, not applicable.

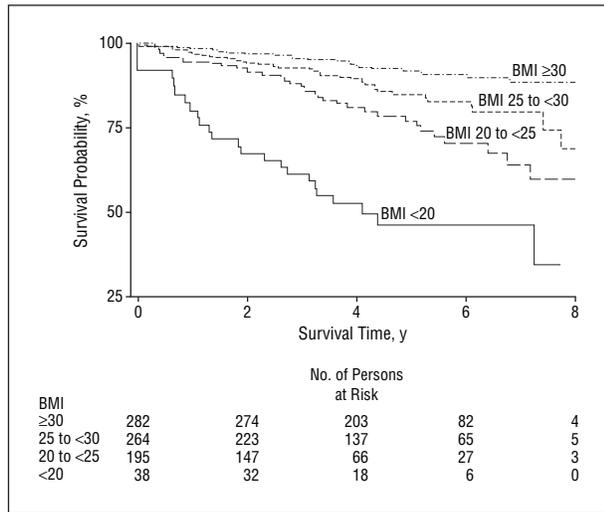
\*Rates are per 100 person-years.

associated with a BMI of 30 or higher, but lower than 35, compared with the normal BMI of 20 to lower than 25, the death hazard ratio was 0.33 (95% CI, 0.18-0.60). The mortality hazard ratio for a BMI of 35 or higher compared with the 20 to less than 25 BMI category was even lower, 0.26 (95% CI, 0.13-0.64). The difference between the 2 hazard ratios was not statistically significant. Adjustment for covariates did not modify this effect. This suggests that the protective effect of a high body mass in RA is not lost at extremely high BMI levels.

Because these analyses suggested a noncurve proportional decrease in mortality from the lowest to the highest BMI without a J or U curve, we used the uncategorized BMI in the Cox proportional models. In these models, the mortality hazard ratio associated with the BMI was 0.91 (95% CI, 0.88-0.95) (Table 3). This represents a 9% reduction in the death risk for each unit in-

crease in BMI. This effect on BMI was independent of age at RA onset, disease duration, sex, ethnic group, SES, methotrexate use, and cigarette smoking status. In the same model, ESR also had an effect on survival. The hazard ratio associated with a 10-mm/h difference in ESR was 1.14 (95% CI, 1.07-1.22), or a 15% increase in mortality for each 10-unit increase in ESR. This effect was also independent of the covariates listed above.

Because of the strong negative effect of comorbidity and RA severity on survival evidenced in this cohort in an earlier analysis,<sup>34</sup> it was important to adjust our estimates for these 2 variables. When we added them to the model, the effect of BMI was diminished, and that of the ESR was effaced altogether (Table 3). This suggests that the protective effect of the BMI against mortality was mediated in part by comorbidity: leaner patients had a higher death risk in part because they had more comorbidity.



**Figure 1.** Kaplan-Meier graph of the survival function in 779 patients with rheumatoid arthritis categorized according to their body mass index (BMI), which is calculated as the weight in kilograms divided by the height in meters squared. Numbers of persons at risk are detailed in the chart below the graph. Survival probabilities differed significantly among the 4 groups (log-rank  $\chi^2=83.3$ ;  $P\leq .001$ ).

The significant effects of both the ESR and BMI in the initial model prompted us to test how these variables might modify each other's effect. Effect modification is also known as statistical interaction. To determine whether this was occurring, we added a BMI  $\times$  ESR product term to our Cox regression models. In these models, the product term was significant ( $P\leq .001$ ), providing evidence that the 2 variables modify each other's effect. Of note, the product term was significant in models that did not include the comorbidity and RA severity as well as in models that did include these variables.

To explore the nature of the BMI  $\times$  ESR interaction, we separated the patients into groups defined by ESR quintiles. We then tested the relationship between the BMI and mortality within each of the ESR groups. The results of this analysis are shown in **Figure 2**, which graphs the hazard ratio of death associated with the BMI at each ESR category. The BMI's strongest protective effect was observed among patients in the lowest ESR stratum. The survival advantage conferred by a higher BMI weakened but remained significant in the second and third quintiles but was lost in the top 2 fifths of the ESR distribution. It is noteworthy that the protective effect of the BMI at low ESR levels persisted even in the models that adjusted for comorbidity (Figure 2).

To exclude the possibility that the protective effect of a high body mass was mediated solely by an excess death risk in patients with BMIs lower than 20, we performed additional sensitivity analyses excluding these lean patients. The unadjusted hazard ratio for death associated with the uncategorized BMI among patients with BMI of 20 or higher was 0.91 (95% CI, 0.88-0.95). After adjusting for age at RA onset, RA duration, sex, ethnic group, SES, smoking status, and methotrexate use, the hazard ratio for death associated with BMI in patients with BMIs of 20 or higher was 0.93 (95% CI, 0.89-0.98). Adding comorbidity and RA severity to the adjustment model raised the hazard ratio to 0.97 (95%

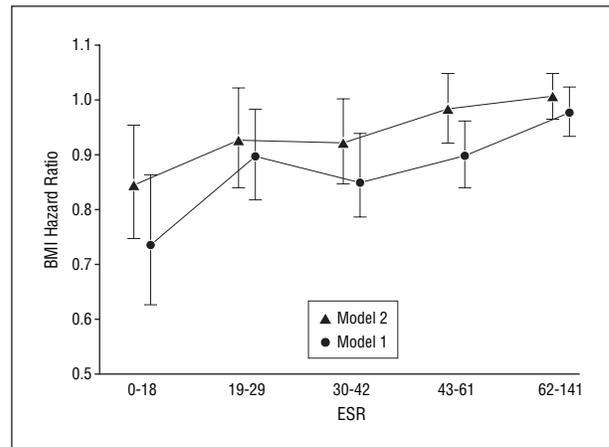
**Table 3. Adjusted Death Risk Associated With BMI and ESR in 779 Patients With Rheumatoid Arthritis**

Variable	Hazard Ratio (95% CI)	P Value	Model $\chi^2$ (df)
<b>Without Controlling for Comorbidity and RA severity*</b>			
BMI	0.91 (0.88-0.95)	$\leq .001$	177.9 (10)
ESR, per 10 mm/h	1.14 (1.07-1.22)	$\leq .001$	
<b>Controlling for Comorbidity and RA Severity†</b>			
BMI	0.97 (0.94-1.00)	.08	452.4 (12)
ESR, per 10 mm/h	0.99 (0.93-1.07)	.90	

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by the height in meters squared); CI, confidence interval; ESR, erythrocyte sedimentation rate; HR, hazard ratio; RA, rheumatoid arthritis.

\*Adjustment covariates are age at RA onset, RA disease duration, sex, ethnic group, socioeconomic status score, having ever smoked cigarettes, and use of methotrexate at each visit.

†Adjustment covariates are age at RA onset, RA disease duration, sex, ethnic status score, socioeconomic status score, having ever smoked cigarettes, and use of methotrexate at each visit, comorbidity DUSOI score (Duke Severity of Illness Checklist), and RA severity DUSOI score.



**Figure 2.** Adjusted mortality hazard ratio associated with the body mass index (BMI), calculated as the weight in kilograms divided by the height in meters squared, at different levels of erythrocyte sedimentation rate (ESR) in 779 patients with rheumatoid arthritis (RA). Circles represent hazard ratios for death associated with BMI. They were estimated from a Cox proportional hazards model that included age at RA onset, sex, ethnic group, socioeconomic status, and smoking status as fixed covariates and disease duration and use of methotrexate as time-varying covariates (model 1). Triangles represent hazard ratios after adding comorbidity and RA severity as time-varying covariates (model 2). The graph shows that the risk of death associated with BMI varies according to ESR. In model 1, increasing BMI was associated with a reduced mortality risk in all but the highest fifths of the ESR distribution. In model 2, comorbidity and RA severity effaced this effect partially, but a significant protective effect of BMI persisted among patients with ESRs of 18 or lower. Error bars indicate 95% confidence intervals.

CI, 0.94-1.00). A significant BMI  $\times$  ESR interaction was present in all models that left out patients with BMIs lower than 20, even with adjustment for comorbidity. These data suggest that the protective effect of the BMI is not explained solely by a high mortality among lean patients. Tests of the proportional hazards assumption after each Cox model did not reveal significant deviations.<sup>39</sup>

We observed an inverse association between body mass and mortality in this RA cohort without a J- or U-shaped relationship. This represents a paradoxical effect of BMI on mortality, being counter to what occurs in apparently healthy individuals.<sup>1,2</sup> In the general population, mortality reaches its highest rate among people in the top BMI categories.<sup>1</sup> Obesity is a risk factor for CV disease and may raise the risk of death from other causes.<sup>40</sup> The lower mortality we observed among the heaviest patients in this RA cohort is thus unexpected.

The mechanism that protects patients with RA and a high BMI from death is not proven by this study. Loss of the protective effect of the BMI on adjustment for comorbidity and RA severity suggests that these 2 variables mediate the BMI effect. This is consistent with the higher comorbidity observed in patients in the lowest BMI category. However, systemic inflammation seems to play a modifying role. In the lower ESR strata, the BMI protective effect remained even after fully adjusting for RA severity and comorbidity. This interaction between body mass and systemic inflammation is novel and represents an extension of prior work in this field.

A “reverse epidemiology” of obesity and other cardiovascular risk factors has been noted in other contexts, notably with congestive heart failure,<sup>41,42</sup> recovery from heart surgery,<sup>43</sup> and also among the aged.<sup>44</sup> A high BMI in these chronic disease groups displays a beneficial effect similar to that noted in our RA cohort. Persistence of the BMI effect after adjustment for comorbidity and RA severity suggests that the role of adiposity in RA may be more important than previously thought.

Emerging information suggests a relation between systemic inflammation and obesity.<sup>45</sup> Obese and overweight adults have increased concentrations of inflammatory markers in the blood.<sup>46</sup> Macrophages infiltrate adipose tissue in obese people and secrete inflammatory cytokines. Adipocytes themselves can secrete tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 6. In the setting of the metabolic syndrome (characterized by obesity, insulin resistance, and atherosclerosis), both adipocytes and macrophages are capable of lipid storage and cytokine secretion.<sup>45</sup> Despite these findings of adipose tissue as a potential inflammatory organ, however, it should be noted that a protective effect of adiposity remains paradoxical. Available evidence suggests that adipose tissue should augment mortality, not diminish it. These facts underscore the need for further research in this area.

Increased mortality in underweight patients with RA may also be an example of underadjustment for “reverse causation.”<sup>47</sup> In the reverse causation model, severe RA would be the primary cause of both low body weight and increased mortality. We and others have shown that patients with the most severe RA are likely to die the earliest.<sup>3,34,48</sup> Certain patients with RA experience a substantial loss of body weight as a manifestation of their disease.<sup>25,26</sup> Patients with this rheumatoid cachexia display high circulating levels of TNF- $\alpha$  and other systemic inflammation markers.<sup>25,26</sup> These mediators may

induce a catabolic state that leads to severe weight loss. An additional potential factor linking severe RA to weight loss is the improvement in signs and symptoms that follows fasting.<sup>49</sup> Some patients with severe disease may learn to self-limit caloric intake as a way of controlling their RA symptoms.

In a recent analysis from the Rochester Epidemiology Project, a BMI below 20 was predictive of CV-related death in patients with RA.<sup>27</sup> Although we focused on all-cause mortality, the higher risk of death among lean patients in the  $\text{ORALE}$  cohort is consistent with the Rochester study’s findings and supports hypotheses of a detrimental effect of low body mass in RA.<sup>27</sup> Our results extend prior work by underscoring the roles of comorbidity and systemic inflammation.

Some cautions in interpretation are warranted. This RA cohort was recruited consecutively from rheumatology clinics, not from a random population sample. Estimates derived from the  $\text{ORALE}$  cohort may be more representative of patients under the care of rheumatologists rather than of patients cared for by generalists or receiving no care at all. One of our study’s merits is the broad range of clinical, demographic, and socioeconomic features present in the cohort, which facilitates testing hypotheses about the influence of these variables on mortality. Nevertheless, readers should keep in mind the possibility that the changes we attribute to BMI could be due to an unmeasured confounder. We have aimed to minimize this possibility by means of multivariate Cox regression models, adjusting for a variety of factors that could influence mortality in RA.

Should clinicians encourage their patients with RA to lose or gain weight? Our results do not support either recommendation. We did not attempt to influence patients’ weights in this study. The BMI is subject to multiple potential influences, and we could adjust for only a limited number of these. Any recommendation for weight modification should be based on evidence from controlled trials. There is currently limited information suggesting that a weight loss program might improve physical fitness in obese patients with RA.<sup>50</sup>

In conclusion, underweight patients with RA are at increased risk of dying. A higher BMI seems to diminish the death risk. Its effect might be mediated in part by comorbidity and RA severity. Systemic inflammation modifies the effect of body mass on mortality in RA, at the higher levels completely effacing adiposity’s protective influence. These findings illustrate the complex behavior of traditional mortality risk factors in RA.

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