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Body Mass Index, Weight Loss, and Cause-Specific Mortality in Rheumatoid Arthritis

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Abstract

Objectives—To examine associations of body mass index (BMI) and weight loss with cause-specific mortality in rheumatoid arthritis (RA).

Methods—A cohort of U.S. Veterans with RA were followed until death or through 2013. BMI was categorized as underweight, normal, overweight, and obese. Weight loss was calculated as the: 1) annualized rate of change over the preceding 13 months and 2) cumulative percent. Vital status and cause of death were obtained from the National Death Index. Multivariable competing-risks regression models were utilized to assess the time-varying associations of BMI and weight loss with cause-specific mortality.

Results—Among 1,600 participants and 5,789 patient-years of follow-up, 303 deaths occurred (95 cardiovascular, 74 cancer, 46 respiratory). The highest weight loss rate and weight loss percentage were associated with a higher risk of cardiovascular (rate: sHR 2.27 [95% CI 1.61–3.19]; percent: sHR 2.31[1.06–5.01]) and cancer mortality (rate: sHR 2.36 [1.11–5.01]; percent: sHR 1.90 [1.00–3.62]). Overweight BMI was protective of cardiovascular mortality (sHR 0.59 [0.38–0.91]), while underweight BMI was associated with a near 3-fold increased risk of respiratory mortality (sHR 2.93 [1.28–6.67]). Incorporation of time-varying BMI and weight loss

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in the same models did not substantially alter individual associations for cardiovascular and cancer mortality, but an association between weight loss percent and respiratory mortality was attenuated after BMI adjustment.

Conclusion—Both BMI and weight loss are predictors of cause-specific mortality in RA. Weight loss is a strong predictor of cardiovascular and cancer mortality, while underweight BMI is a stronger predictor of respiratory mortality.

Keywords

Body mass index; weight loss; mortality; rheumatoid arthritis

Introduction

Cardiovascular disease is the leading cause of death in rheumatoid arthritis (RA) and a number of studies have now been conducted to identify risk factors for incident cardiovascular disease and cardiovascular outcomes in this patient group [1, 2]. In the general population, being overweight or obese is well known to be associated with cardiovascular disease directly and through pro-atherogenic risk factors [3, 4]. Studies in RA patients, however, have paradoxically demonstrated that being overweight or obese is actually protective against cardiovascular outcomes and mortality, with underweight individuals having the highest relative mortality risk [5–8]. This observation, present in a number of chronic illnesses, has often been termed the “obesity paradox.”

In addition to the findings in RA described above, other examples of this paradox exist in the general population. Accumulating evidence, for example, implicates obesity as an independent risk factor for malignancy [9], yet a similar paradoxical survival benefit has been observed among overweight and obese individuals with active cancer [10]. Although obesity has not been linked to the development of chronic obstructive pulmonary disease (COPD), a meta-analysis of 22 studies that included over 21,000 patients with COPD similarly found overweight and obese patients experienced lower disease mortality while being underweight was associated with accelerated mortality [11].

One hypothesis to explain these findings is that an underweight BMI simply reflects the consequence of weight loss due to the severity of the underlying illness. In other words, an overweight or obese BMI reflects the absence of significant previous weight loss. This is rarely accounted for in epidemiologic studies, which often only have cross sectional rather than longitudinal weight histories. We have previously shown that rapid weight loss, rather than absolute weight, is strongly associated with all-cause mortality in RA, and may serve to explain the obesity paradox reported in other studies [12]. While prior studies have assessed BMI and its associations with cause-specific mortality in RA, none have assessed the impact of weight loss across multiple causes of death. Thus, there exists a knowledge gap regarding the prognostic implications of absolute weight versus weight loss on specific causes of death in RA. The purpose of this study was to investigate the associations of both BMI and weight loss with cardiovascular, cancer, and respiratory mortality in a cohort of U.S. Veterans with RA. We hypothesized that compared to absolute BMI, weight loss, both recent and cumulative, would be more strongly associated with all three major causes of death in RA.

Methods

Study design and participants

Participants were enrollees in the Veterans Affairs RA (VARA) registry [13], which is a multicenter, longitudinal observational study of U.S. Veterans age >18 years fulfilling the 1987 American College of Rheumatology (ACR) classification for RA [14]. Demographic and clinical data, including ACR core measures and medications, are collected at enrollment and follow-up visits as part of usual care [13]. The VARA registry has received institutional review board approval at each site, and all participants provide written informed consent at enrollment. The VARA Scientific Ethics Advisory Committee approved this study.

Variables

From the electronic medical record, we extracted weight measurements within 14 days of each study visit. Height was fixed at the modal value to limit BMI misclassification due to height measurement error. Because of the limited sample size for subjects in the underweight category using 18.5 kg/m^2 (1% subjects; World Health Organization classifications [15]), we categorized time-varying BMI values as: underweight (<20 kg/m^2), normal (20–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2). We calculated the rate of weight loss at each visit as the annualized rate of BMI change over the preceding 13 months and categorized this as: none (or weight gain), <2 kg/m^2/year, 2–3 kg/m^2/year, and >3 kg/m^2/year as previously described [12]. In addition to the assessment of weight loss over the preceding year, we also examined whether more gradual weight change might also contribute to mortality risk. In order to do this, we calculated the cumulative percent of weight loss at each visit (baseline BMI minus the current BMI divided by the baseline BMI × 100) then categorized this value at each visit into none (or weight gain), <5%, 5–10%, and >10%.

Covariates included age, sex, race, smoking status (current, former, never), comorbidity, multidimensional health assessment questionnaire (MD-HAQ), and 28-disease activity score (DAS28), which were identified in exploratory analyses and prior studies [7]. Prevalent cardiovascular, cancer, and lung disease comorbidity was obtained using linkages with national VA administrative records over the 12 months prior to enrollment and Healthcare Cost and Utilization Project Clinical Classification Software. All other baseline covariates were collected through the VARA registry. A second-generation anti-cyclic citrullinated peptide (anti-CCP) measured with a commercial ELISA (Diastat, Axis-Shield), rheumatoid factor measured by nephelometry, medications (disease-modifying antirheumatic drugs, prednisone, nonsteroidal anti-inflammatory drugs), education level (years), and disease duration were also collected from the VARA registry, but did not meaningfully impact the multivariable models and thus were not included as covariates.

Outcome

Patients were followed from enrollment until death or censoring at December 31, 2013. Vital status and cause of death were obtained through the National Death Index. Cause of death was classified as cardiovascular (International Classification of Diseases 10^{th} edition

[ICD-10] Chapter IX, codes I00-I99), cancer (ICD-10 Chapter II, codes C00-D48), respiratory (ICD-10 Chapter X, codes J00-J99), or other.

Statistical analysis

To account for the obscuration of the event of interest by other causes of death (competing risks), we calculated subdistribution hazard ratios (sHR) and 95% confidence intervals (CI) from multivariable competing-risks regression models based on the methods of Fine and Gray (Stata command, stcrreg) [16]. Three multivariable models were constructed: 1) a "base" model including age and sex; 2) an "intermediate" model additionally including race, smoking status, and comorbidity; and 3) a "full" model additionally including time-varying MD-HAQ and DAS28. The associations of time-varying BMI, weight loss rate categories, and cumulative weight loss categories with cause-specific mortality were assessed separately in each of the three models. In multivariable models, MD-HAQ and DAS28 were allowed to vary over time while sex, race, smoking status, and comorbidity were fixed at enrollment. Missing MD-HAQ and DAS28 values were imputed using the last value carried forward. For homogeneity across models, subjects with entirely missing covariates from the full multivariable model were excluded from all analyses (n=51; smoking status n=2, sex n=4, MD-HAQ n=36, DAS28 n=9).

To assess if associations of BMI and weight loss were independent, BMI and weight loss rate were included within the same model, and then BMI and cumulative weight loss were included in the same model, both using the aforementioned covariates from the full model. Normal BMI (20–25 kg/m^2) and the weight loss category of "none" served as the reference categories. We tested interactions between weight loss, BMI, and other model components (DAS28, smoking status, medications) which were not significant and thus not further reported. Standard errors were adjusted for clustering by site (n=12) and a two-tailed P value < 0.05 was considered statistically significant. All analyses were completed using Stata v14 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics and weight loss

Of the 1,819 VARA participants during the study period, 1,651 had serial BMI measurements, and 1,600 had complete covariates and were included in the analysis. Participants were predominantly male (91.2%), had a mean age of 63.4 years (standard deviation [SD] 11.0 years), a median RA disease duration of 8.2 years (interquartile range [IQR] 2.5–11.6 years), and a frequent smoking history (26.4% current and 52.8% former) (Table 1). The majority of participants were either overweight (37.8%) or obese (34.6%) at the time of enrollment, with only 3.3% classified as underweight. Median duration of follow-up was 3.2 years (IQR 1.4–5.5 years). The highest percent of weight loss that occurred during follow-up was 0–5% of body mass in 30.9%, 5–10% in 18.4%, and >10% in 20.2% of patients, and the highest weight loss rate that occurred during follow-up was 0–2 kg/m^2/year in 34.8%, 2–3 in 15.1%, and >3 in 36.6% of patients. Over 5,789 patient-years of follow-up, 303 deaths occurred with cardiovascular being the most frequent cause of death (n=95), followed by cancer (n=74) and respiratory (n=46) causes. Specific causes of

death were consistent with previously published findings in this cohort [7] and causes of death by enrollment BMI categories are included in Supplemental Table 1.

Cardiovascular mortality

Before accounting for weight loss, time-varying overweight BMI (25–30 kg/m^2) was associated with a 41% lower risk of cardiovascular mortality (Table 2; full model: sHR 0.59, 95% CI 0.38–0.91, P=0.02). Other BMI categories were not associated with cardiovascular mortality. Prior to considering current weight, weight loss >3 kg/m^2/year was associated with more than a 2-fold higher risk of cardiovascular mortality in each of the three models (full model: sHR 2.27, 95% CI 1.61–3.19, P<0.001), but lower rates of weight loss were not significantly associated with cardiovascular mortality. A trend test across weight loss rate categories was highly significant (P<0.001). Cumulative weight loss was also associated with increased cardiovascular mortality in all models in a dose-dependent manner with >10% loss being associated with over a 2-fold increased risk (full model: sHR 2.31, 95% CI 1.06–5.01, P=0.03). A trend test across categories of cumulative weight loss was significant (P=0.02). We performed sensitivity analyses to examine if associations between weight loss and cardiovascular mortality were limited to those with comorbid CVD. In stratified analyses, associations between weight loss and cardiovascular mortality were not significantly different among those with the aforementioned comorbidity at baseline (all P for interactions >0.05, data not shown).

Cancer mortality

Time-varying BMI was not associated with cancer mortality. Underweight BMI appeared to confer a higher risk of cancer mortality, but the estimate was imprecise and not statistically significant (Table 3; full model: sHR 1.43, 95% CI 0.65–3.13, P=0.38). Weight loss >3 kg/m^2/year was again associated with over a 2-fold increased risk of cancer mortality in all models (full model: sHR 2.36, 95% CI 1.11–5.01, P=0.03) with less rapid weight loss not significantly associated with cancer mortality. A trend test across weight loss rate categories was marginally significant (P=0.05 to 0.08 across models). Cumulative weight loss >10% was associated with cancer mortality, though in the full model this did not reach statistical significance (full model: sHR 1.90, 95% CI 1.00–3.62, P=0.05), while less substantial weight loss was not associated with cancer mortality. Trend tests across percent weight loss categories were marginally significant (P=0.03 to 0.07 across models).

Respiratory mortality

A time-varying BMI corresponding to being underweight was associated with a near 3-fold increased risk of respiratory mortality in each model (Table 4; full model: sHR 2.93, 95% CI 1.28–6.67, P=0.01). Annualized weight loss of more than 3 kg/m^2/year was marginally associated with respiratory mortality after adjusting for age and sex (sHR 2.01, 95% CI 1.00 to 4.03, P=0.05). However, the association was attenuated following additional adjustments (Table 4). Trend tests across annualized weight loss rate categories were not significant in any models. Percent of weight lost was associated with respiratory mortality in a dose-dependent manner in each model with both 5–10% loss and >10% loss being significantly associated (full model: 5–10% sHR 1.86, 95% CI 1.07–3.25, P=0.03; >10% sHR 2.19, 95%

CI 1.30–3.70, P=0.003). Tests of trend across cumulative weight loss categories were highly significant in all models (P≤0.001).

BMI and weight loss examined in combination

We then examined the independent associations of time-varying BMI and weight loss in fully-adjusted multivariable models (Table 5; models including all covariates are provided in Supplemental Tables 2 and 3). The 40% decreased risk of cardiovascular mortality for overweight individuals persisted after adjusting for weight loss rate (P=0.009) and percent of weight loss (P=0.01) (Table 5). A rate of weight loss exceeding 3 kg/m^2/year was associated with a 2.15-fold increased risk of cardiovascular mortality, independent of time-varying BMI category. Cumulative weight loss percent was also associated with cardiovascular mortality, independent of time-varying BMI, though only <5% loss reached statistical significance (Table 5). In a sensitivity analysis, we modeled interaction terms between BMI categories (underweight, normal, and overweight/obese) and weight loss (dichotomized as loss or no loss) which were not statistically significant (P≥0.19, data not shown)

As analyzed independently, no time-varying BMI categories were associated with cancer mortality after adjusting for weight loss rate or percent weight loss (Table 5). Adjusting for time-varying BMI, weight loss >3 kg/m^2/year was associated with a 2.20-fold increased risk of cancer mortality (P=0.04). The association of >10% weight loss with cancer mortality was no longer significant after adjusting for time-varying BMI (sHR 1.71, 95% CI 0.88–3.32, P=0.11).

Time-varying underweight BMI was associated with a near 3-fold increased risk of respiratory mortality after adjustment for weight loss rate (Table 5, P=0.01). This association was minimally attenuated with adjustment for percent weight loss (sHR 2.69, 95% CI 1.09–6.60, P=0.03). After accounting for absolute BMI, weight loss rate was not associated with respiratory mortality (Table 5). Associations of percent weight loss (5–10% and >10%) with respiratory mortality were no longer significant after adjusting for time-varying BMI (Table 5).

Discussion

To our knowledge, this is the first study to simultaneously investigate the associations of both BMI and weight loss with cause-specific mortality in RA. We found both the highest rates and percent of weight loss to be predictive of cardiovascular mortality in a dose-dependent manner, independent of absolute BMI. Similarly, higher rates of weight loss were strong predictors of cancer mortality. For respiratory death, however, time-varying underweight BMI appeared to be most predictive. These results therefore demonstrate a differential prediction of mortality risk for BMI, rapid weight loss, and percent weight loss based on the cause of death. Overall, these data illustrate the importance of considering the dynamic nature of body composition when assessing mortality risk in RA.

In this study, overweight BMI was protective of cardiovascular mortality. Neither adjustment for rapid, nor cumulative, weight loss mitigated the apparent protective effect of an overweight BMI on cardiovascular mortality. One potential explanation is that we did not

capture the entirety of weight loss; participants may have already lost a substantial or rapid amount of weight prior to enrollment as a result of left censoring. Confounding by smoking has been proposed as an explanation for this paradox in the general population [17], but we did not find smoking status to be a strong confounder in multivariable models. Another proposed explanation for the obesity paradox is through a type of selection bias termed collider-stratification (or index-event) bias [18]. Finally, this observed paradox may be impacted by the simplicity of BMI as a measure of body composition since BMI alone does not differentiate fat and fat-free mass [20]. Whether more specific measures of body composition might help explain this paradox requires additional study.

Underweight BMI has previously been associated with increased all-cause and cardiovascular mortality in RA patients, but these studies did not account for preceding weight loss [5, 6, 8]. Our previous study in this cohort was the first to simultaneously examine BMI and weight loss, finding that both were associated with all-cause mortality [12]. In this study of cause-specific mortality, we again demonstrate that underweight BMI and weight loss both drive mortality risk, but importantly this risk may differ across causes. In cardiovascular and cancer mortality, we identified rapid and cumulative weight loss as the weight parameters most predictive of death, while in respiratory mortality underweight BMI was the weight parameter most predictive. These observations may reflect the different weight loss trajectories across different causes of death. In a cohort of older males without RA (demographics similar to our study), the trajectory of weight loss was shown to differ by cause of death. Weight loss prior to death was confined to 3 years before cancer death, 5 years before cardiovascular death, and 5–20 years before other deaths [21].

While previous studies have not directly investigated weight loss for different causes of death in RA, Kremers et al reported that RA patients who were not initially underweight, but became underweight during follow-up had a 2-fold higher risk of cardiovascular mortality [6]. Our findings are in agreement with this study. In contrast to prior reports [5, 6], we did not find underweight BMI to be associated with higher risk of cardiovascular mortality. This discrepancy may be due to differences in underweight BMI cut-offs (18.5 kg/m^2 vs 20 kg/m^2) or the study designs (inception vs open cohort).

Our study does not identify a causal link between weight loss and cardiovascular disease in RA, nor do we propose that weight loss is the cause of cardiovascular death. More likely, weight loss reflects a systemic process, such as systemic inflammation, that is pathogenic in cardiovascular mortality. Systemic inflammation has been well elucidated as an important risk factor for cardiovascular disease/mortality in RA patients and similarly has been shown to play an important role in the pathogenesis of cachexia [22]. Cytokines (particularly Interleukin-1 and 6, tumor necrosis factor-α, interferon-γ) activate transcription factor NF-κB, which decreases muscle protein synthesis and similarly activates the ubiquitin-mediated proteolytic system resulting in hypercatabolism [23]. In addition to systemic inflammation, it is likely that chronic illness, disease phenotype, comorbid illness, aging, smoking, and other factors also contribute to changes in weight over time [24].

Only one study has examined BMI and cancer mortality in RA, finding an underweight BMI to be associated with a 60% increased cancer mortality risk [5]. While no studies have

specifically examined BMI and respiratory mortality, this previous study found that an underweight BMI carried more than 2-fold increased risk of non-cardiovascular / non-cancer death [5]. We similarly found in that underweight BMI was most predictive of respiratory death when including both body weight and weight loss in the same models. To date, there has not been study of weight loss and cancer- or respiratory-related mortality in RA. We found weight loss rate, independent of BMI, was strongly associated with cancer but not respiratory mortality. Weight loss percent, however, was associated with both cancer and respiratory mortality, but attenuated such that the association was no longer significant after accounting for BMI. These findings may again reflect the difference in trajectory of weight loss preceding different causes of death with a more rapid loss occurring prior to cancer death and a more prolonged loss before respiratory death.

There are limitations to this study. We were unable to determine if the weight loss that occurred was intentional or unintentional. However, prior studies support a cardioprotective benefit from intentional weight loss [25] and several previous studies have demonstrated that more than 60% of weight loss in this age group is unintentional [26, 27]. Therefore, we can infer the relevant weight loss in our study was likely unintentional, and our results in no way suggest that RA patients refrain from healthy weight loss. Our study population was predominantly older males with established RA, so the generalizability of our findings may be limited. The association between BMI and mortality has been shown to differ by age [28] and sex [29] in the general population. Our findings are largely in agreement with prior reports that included a higher proportion of women, suggesting generalizability of our results to the demographic most commonly impacted by RA. Last, our duration of follow-up limits the conclusions that can be drawn regarding the prognostic importance of long-term body mass and weight loss changes. As weight loss may have occurred earlier in the RA disease course or prior to diagnosis, causal associations between obesity and mortality may have been underestimated.

The many strengths to this study include the availability of longitudinal weight measures, simultaneous examinations of BMI and weight loss, linkage with a national death registry, a robust comorbidity assessment, confirmed diagnosis of RA by a rheumatologist, and the availability of longitudinal disease activity and functional status measures. Longitudinal disease activity measures and functional status measures are a critical strength because these act as confounders by being associated with both weight loss/cachexia and mortality [1, 30–32].

In summary, we demonstrate the importance of considering more than the absolute BMI when assessing mortality risk in RA. Weight loss is strongly associated with cardiovascular and cancer mortality independent of current BMI, while the risk of weight loss for respiratory mortality appears to vary by the magnitude and rate of loss and adjustment for BMI, possibly due to more protracted weight loss over time. Clinicians should consider the weight trajectory and degree of loss, in addition to the BMI, when monitoring RA patients. Investigators should continue efforts to explain the obesity paradox and might begin by measuring and including long-term weight assessments as covariates, particularly in studies of cardiovascular and cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACR	American College of Rheumatology
BMI	Body mass index
CCP	Cyclic-citrullinated peptide
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAS28	28-joint disease activity score
ICD	International Classification of Disease
IQR	Interquartile range
MD-HAQ	Multidimensional health assessment questionnaire
RA	Rheumatoid arthritis
sHR	Sub-hazard ratio
VARA	Veterans Affairs Rheumatoid Arthritis

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Significance and Innovation

- Recent weight loss is a poor prognostic marker for cardiovascular and cancer mortality, while an underweight BMI is poor prognostic marker for respiratory death in rheumatoid arthritis (RA).
- Adjustment for recent weight loss does not fully explain either the protective association of overweight BMI on cardiovascular mortality or the heightened risk of underweight BMI on respiratory mortality in RA patients.
- The relationships between weight loss, current BMI, and mortality may vary by individual causes of death and may reflect different weight loss trajectories prior to death.

Table1

Baseline characteristics of study population *

Variable	Value*
Age at enrollment, years	63.4 (11.0)
Male, %	91.2
Caucasian, %	76.7
High-school education, %	85.5
Smoking status, %	
Current	26.4
Former	52.8
Never	20.9
Disease duration, years	8.2 (2.5–11.6)
Rheumatoid factor positive, %	79.8
Anti-CCP positive, %	78.2
28-joint Disease activity score	3.92 (1.58)
Multidimensional HAQ	0.92 (0.60)
Myocardial infarction, %	20.3
Other cardiovascular disease, %	20.0
Cancer, %	14.2
Lung disease, %	34.6
Body mass index, %	
≤20 kg/m^2	3.3
20–25 kg/m^2	24.3
25–30 kg/m^2	37.8
>30 kg/m^2	34.6
Leflunomide, %	11.8
Methotrexate, %	55.1
Biologic, %	29.6
Prednisone, %	42.3

* Abbreviations: CCP = cyclic-citrullinated peptide, HAQ = health assessment questionnaire; Values = mean (standard deviation) or median (interquartile range) unless otherwise note

Table 2

Associations of BMI and weight loss with cardiovascular mortality*

	Base Model		Intermediate Model		Full Model	
	sHR (95% CI)	**P**	**sHR (95% CI)**	**P**	**sHR (95% CI)**	**P**
Model 1. Time-varying BMI (kg/m^2)						
<20	1.52 (0.41, 5.67)	0.53	1.50 (0.47, 4.79)	0.50	1.30 (0.34, 5.00)	0.71
20–25	*Referent*	-	*Referent*	-	*Referent*	-
25–30	0.64 (0.38, 1.07)	0.09	0.60 (0.37, 0.98)	0.04	0.59 (0.38, 0.91)	0.02
>30	0.88 (0.37, 2.14)	0.79	0.79 (0.33, 1.89)	0.59	0.73 (0.31, 1.73)	0.47
Model 2. Time-varying weight loss rate (kg/m^2/year)						
None	*Referent*	-	*Referent*	-	*Referent*	-
0–2	0.92 (0.65, 1.30)	0.63	0.98 (0.74, 1.31)	0.90	1.01 (0.77, 1.33)	0.94
2–3	1.29 (0.74, 2.26)	0.37	1.33 (0.72, 2.46)	0.36	1.29 (0.68, 2.45)	0.43
>3	2.46 (1.77, 3.42)	<0.001	2.49 (1.72, 3.59)	<0.001	2.27 (1.61, 3.19)	<0.001
P trend		<0.001		<0.001		<0.001
Model 3. Time-varying percent weight loss						
None	*Referent*	-	*Referent*	-	*Referent*	-
<5%	1.27 (0.94, 1.72)	0.12	1.34 (1.02, 1.78)	0.04	1.37 (1.04, 1.81)	0.03
5–10%	1.33 (0.91, 1.94)	0.14	1.43 (0.97, 2.10)	0.07	1.39 (1.00, 1.94)	0.05
>10%	2.74 (1.26, 5.98)	0.01	2.58 (1.16, 5.73)	0.02	2.31 (1.06, 5.01)	0.03
P trend		0.008		0.009		0.02

*Bare model covariates: age and sex; Intermediate model: bare model + race, smoking status, cardiovascular disease; Full model: intermediate model + MDHAQ, DAS28

Abbreviations: BMI = body mass index; sHR = sub-hazard ratio; CI = confidence interval

Table 3

Associations of BMI and weight loss with cancer mortality *

	Base Model		Intermediate Model		Full Model	
	sHR (95% CI)	**P**	**sHR (95% CI)**	**P**	**sHR (95% CI)**	**P**
Model 1. Time-varying BMI (kg/m^2)						
<20	1.58 (0.67, 3.71)	0.29	1.49 (0.68, 3.26)	0.32	1.43 (0.65, 3.13)	0.38
20–25	*Referent*	-	*Referent*	-	*Referent*	-
25–30	0.82 (0.38, 1.77)	0.61	0.85 (0.39, 1.84)	0.68	0.87 (0.40, 1.86)	0.72
>30	0.63 (0.38, 1.07)	0.09	0.72 (0.38, 1.34)	0.29	0.71 (0.38, 1.33)	0.29
Model 2. Time-varying weight loss rate (kg/m^2/year)						
None	*Referent*	-	*Referent*	-	*Referent*	-
0–2	0.82 (0.54, 1.24)	0.35	0.81 (0.53, 1.25)	0.34	0.82 (0.54, 1.25)	0.36
2–3	1.41 (0.84, 2.38)	0.20	1.29 (0.75, 2.21)	0.35	1.25 (0.72, 2.17)	0.43
>3	2.36 (1.12, 4.96)	0.02	2.43 (1.18, 5.02)	0.02	2.36 (1.11, 5.01)	0.03
P trend		0.05		0.05		0.08
Model 3. Time-varying percent weight loss						
None	*Referent*	-	*Referent*	-	*Referent*	-
<5%	0.92 (0.48, 1.78)	0.81	0.90 (0.45, 1.80)	0.77	0.92 (0.47, 1.83)	0.82
5–10%	1.43 (0.82, 2.48)	0.21	1.31 (0.75, 2.30)	0.34	1.30 (0.76, 2.23)	0.34
>10%	2.07 (1.11, 3.88)	0.02	1.99 (1.07, 3.72)	0.03	1.90 (1.00, 3.62)	0.05
P trend	0.03	0.05	0.07			

* Bare model covariates: age and sex; Intermediate model: bare model + race, smoking status, cancer; Full model: intermediate model + MDHAQ, DAS28

Abbreviations: BMI = body mass index; sHR = sub-hazard ratio; CI = confidence interval

Table 4

Associations of BMI and weight loss with respiratory mortality *

	Base Model		Intermediate Model		Full Model	
	sHR (95% CI)	**P**	**sHR (95% CI)**	**P**	**sHR (95% CI)**	**P**
Model 1. Time-varying BMI (kg/m^2)						
<20	3.25 (1.17, 9.01)	0.02	3.07 (1.11, 8.53)	0.03	2.93 (1.28, 6.67)	0.01
20–25	*Referent*	-	*Referent*	-	*Referent*	-
25–30	0.86 (0.51, 1.46)	0.59	0.86 (0.49, 1.51)	0.59	0.93 (0.57, 1.52)	0.78
>30	0.53 (0.24, 1.17)	0.12	0.53 (0.23, 1.22)	0.14	0.50 (0.23, 1.11)	0.09
Model 2. Time-varying weight loss rate (kg/m^2/year)						
None	*Referent*	-	*Referent*	-	*Referent*	-
0–2	0.83 (0.52, 1.32)	0.43	0.80 (0.49, 1.32)	0.39	0.85 (0.50, 1.43)	0.53
2–3	1.05 (0.45, 2.42)	0.92	0.97 (0.43, 2.21)	0.95	0.92 (0.44, 1.96)	0.84
>3	2.01 (1.00, 4.03)	0.05	1.86 (0.93, 3.73)	0.08	1.30 (0.75, 2.26)	0.35
P trend		0.09		0.15		0.49
Model 3. Time-varying percent weight loss						
None	*Referent*	-	*Referent*	-	*Referent*	-
<5	1.15 (0.70, 1.89)	0.58	1.15 (0.73, 1.80)	0.55	1.18 (0.75, 1.88)	0.47
5–10	1.93 (1.12, 3.32)	0.02	1.92 (1.07, 3.47)	0.03	1.86 (1.07, 3.25)	0.03
>10	3.33 (2.15, 5.17)	<0.001	3.11 (1.97, 4.93)	<0.001	2.19 (1.30, 3.70)	0.003
P trend		<0.001		<0.001		0.001

* Bare model covariates: age and sex; Intermediate model: bare model + race, smoking status, respiratory disease; Full model: intermediate model + MDHAQ, DAS28

Abbreviations: BMI = body mass index; sHR = sub-hazard ratio; CI = confidence interval

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Table 5

Associations of weight loss and BMI (in the same model) with cause-specific mortality *

	Cardiovascular		Cancer		Respiratory	
	sHR (95% CI)	**P**	**sHR (95% CI)**	**P**	**sHR (95% CI)**	**P**
Model 1. Time-varying BMI and weight loss rate						
BMI (kg/m^2)						
<20	1.16 (0.26, 5.13)	0.84	1.27 (0.69, 2.31)	0.44	2.96 (1.29, 6.78)	0.01
20–25	*Referent*	-	*Referent*	-	*Referent*	-
25–30	0.58 (0.39, 0.87)	0.009	0.90 (0.39, 2.10)	0.69	0.91 (0.55, 1.52)	0.73
>30	0.76 (0.33, 1.77)	0.53	0.73 (0.37, 1.43)	0.36	0.49 (0.23, 1.02)	0.06
Weight loss rate (kg/m^2/year)						
None	*Referent*	-	*Referent*	-	*Referent*	-
0–2	0.97 (0.69, 1.37)	0.88	0.79 (0.52, 1.20)	0.27	0.76 (0.46, 1.24)	0.27
2–3	1.17 (0.63, 2.17)	0.62	1.16 (0.66, 2.04)	0.60	0.71 (0.34, 1.48)	0.36
>3	2.15 (1.50, 3.08)	<0.001	2.20 (1.02, 4.73)	0.04	1.06 (0.56, 1.98)	0.86
Model 2. Time-varying BMI and percent weight loss						
BMI (kg/m^2)						
<20	1.21 (0.29, 5.02)	0.80	1.28 (0.62, 2.66)	0.51	2.69 (1.09, 6.60)	0.03
20–25	*Referent*	-	*Referent*	-	*Referent*	-
25–30	0.63 (0.44, 0.90)	0.01	0.94 (0.42, 2.08)	0.87	1.00 (0.58, 1.74)	0.99
>30	0.86 (0.41, 1.80)	0.67	0.77 (0.41, 1.46)	0.42	0.56 (0.27, 1.16)	0.12
Weight loss percent						
None	*Referent*	-	*Referent*	-	*Referent*	-
<5	1.39 (1.08, 1.80)	0.01	0.89 (0.44, 1.82)	0.76	1.06 (0.67, 1.67)	0.80
5–10	1.31 (0.93, 1.86)	0.13	1.21 (0.77, 1.89)	0.40	1.50 (0.78, 2.86)	0.22
>10	2.09 (1.00, 4.39)	0.05	1.71 (0.88, 3.32)	0.11	1.54 (0.71, 3.32)	0.27

* Covariates: age, sex, race, smoking status, comorbidity, MDHAQ, DAS28

Abbreviations: BMI = body mass index; sHR = sub-hazard ratio; CI = confidence interval