 Annals of Internal Medicine

Relationship Among Body Fat Percentage, Body Mass Index, and All-Cause Mortality

A Cohort Study

Raj Padwal, MD, MSc; William D. Leslie, MD, MSc; Lisa M. Lix, PhD; and Sumit R. Majumdar, MD, MPH

Background: Prior mortality studies have concluded that elevated body mass index (BMI) may improve survival. These studies were limited because they did not measure adiposity directly.

Objective: To examine associations of BMI and body fat percentage (separately and together) with mortality.

Design: Observational study.

Setting: Manitoba, Canada.

Participants: Adults aged 40 years or older referred for bone mineral density (BMD) testing.

Measurements: Participants had dual-energy x-ray absorptiometry (DXA), entered a clinical BMD registry, and were followed using linked administrative databases. Adjusted, sex-stratified Cox models were constructed. Body mass index and DXA-derived body fat percentage were divided into quintiles, with quintile 1 as the lowest, quintile 5 as the highest, and quintile 3 as the reference.

Results: The final cohort included 49 476 women (mean age, 63.5 years; mean BMI, 27.0 kg/m^2; mean body fat, 32.1%) and 4944 men (mean age, 65.5 years; mean BMI, 27.4 kg/m^2; mean body fat, 29.5%). Death occurred in 4965 women over a median of 6.7 years and 984 men over a median of 4.5 years. In fully adjusted mortality models containing both BMI and body fat percentage, low BMI (hazard ratio [HR], 1.44 [95% CI, 1.30 to 1.59] for quintile 1 and 1.12 [CI, 1.02 to 1.23] for quintile 2) and high body fat percentage (HR, 1.19 [CI, 1.08 to 1.32] for quintile 5) were associated with higher mortality in women. In men, low BMI (HR, 1.45 [CI, 1.17 to 1.79] for quintile 1) and high body fat percentage (HR, 1.59 [CI, 1.28 to 1.96] for quintile 5) were associated with increased mortality.

Limitations: All participants were referred for BMD testing, which may limit generalizability. Serial measures of BMD and weight were not used. Some measures, such as physical activity and smoking, were unavailable.

Conclusion: Low BMI and high body fat percentage are independently associated with increased mortality. These findings may help explain the counterintuitive relationship between BMI and mortality.

Primary Funding Source: None.

Ann Intern Med. 2016;164:532-541. doi:10.7326/M15-1181 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 8 March 2016.

Many general population cohort studies over the past century have reported that excess adiposity (usually estimated with body mass index [BMI]) is associated with increased risk for all-cause death (1–3). However, not all of the published evidence agrees; a recent meta-analysis found that being overweight (BMI of 25.0 to 29.9 kg/m^2) was associated with a decreased mortality risk and that mild obesity (BMI of 30.0 to 34.5 kg/m^2) had a mortality risk similar to that of normal weight (BMI of 18.5 to 24.9 kg/m^2) (4). Population-based cohort studies performed in middle-aged and older adults and more focused studies in persons with chronic diseases (such as heart failure and chronic kidney disease) have reported lower mortality rates in overweight and mildly or moderately obese persons than in those with normal weight (5–11). This unexpected finding has been termed the "obesity paradox." These findings have generated considerable debate and discussion within and beyond the medical literature because they have obvious implications in terms of whether overweight and obese patients who are older or have chronic diseases should be counseled to lose weight to prolong their life (5, 9, 12–15).

Many explanations for the obesity paradox have been proposed. One commonly held view is that BMI, when used as a surrogate measure of body fat, confounds the relationship between excess adiposity and mortality risk (6, 16). Because it does not directly measure body fat, BMI is an imperfect measure of adiposity (6, 17, 18). Therefore, more sophisticated body fat measurements must be used in studies examining the relationship between adiposity and mortality so that this relationship can be more confidently and accurately assessed.

The purpose of this study was to assess the relationship of BMI and body fat percentage (separately and together) with all-cause mortality in a general population cohort of middle-aged and older adults. We hypothesized that greater body fat percentage (rather than greater BMI) would be independently associated with increased mortality in sex-stratified models containing both parameters and adjusted for other potential confounders. If confirmed, this hypothesis would support the need to use direct fat measures instead of BMI when examining the relationship between adiposity and mortality risk.

Methods

Study Design

We performed a population-based cohort study of all eligible residents of Manitoba, Canada, who were aged 40 years or older and who had initial dual-energy x-ray absorptiometry (DXA) of the spine and hip for bone mineral density (BMD) testing between 1999 and 2013. Participants were followed from the date of initial

BMD testing until death or the end of the study. Only the initial BMD test was examined in each participant. Manitoba, which has a population of 1.25 million, provides government-funded universal health care to all residents, regardless of age or income. The Health Research Ethics Board of the University of Manitoba approved the study, and the Manitoba Health Information Privacy Committee approved data access.

Data Sources

Population Health Research Data Repository

This registry contains multiple population-based, linked administrative health data sets provided by the provincial government and maintained by the Manitoba Centre for Health Policy of the University of Manitoba (19–21). Data include sociodemographic variables, physician claims and hospital separations (including primary diagnosis and up to 25 secondary diagnoses), prescription drugs (drug name and date, dose, and quantity dispensed), and vital statistics (including mortality). The data sets are linked through a deidentified personal health information number that facilitates linkage to external data sources, including the provincial clinical BMD registry. These data are well-validated and have been used extensively in previous research (20–23).

EDITORS' NOTES

Context

A lower mortality rate among overweight and mildly to moderately obese adults (the "obesity paradox") is unexplained. Studies documenting this paradox are limited because body mass index (BMI) is an imperfect and indirect measure of adiposity.

Contribution

In this population-based cohort study of middle-aged and older adults referred for bone mineral density testing, low BMI and high body fat percentage were independently associated with increased all-cause mortality among men and women.

Caution

Body fat percentage and BMI were measured only once at baseline.

Implication

The independent relationship between increased body fat percentage and mortality may help explain the obesity paradox.

Provincial Bone Mineral Density Registry

This validated population-based registry contains data on all BMD tests performed for clinical purposes in Manitoba (20–22). Uniform data collection standards are maintained, and data collection includes osteoporosis risk factors (including components of the World Health Organization [WHO] Fracture Risk Assessment [FRAX] risk calculator [24]), height and weight, testing indications, and reporting. The primary indication for testing is to assess bone density and fracture risk. All BMD test results have been captured since the program was established, with greater than 99% completeness and accuracy of registry data (20–22). Lumbar spine and hip DXA are performed and scans analyzed in accordance with manufacturer recommendations using one of the Manitoba Bone Density Program's cross-calibrated DXA instruments (Prodigy in 98% and iDXA in 2% [GE Healthcare Lunar]). All densitometers and personnel are subject to province-wide quality assurance programs under the direction of a medical physicist, including daily evaluation of densitometer stability using anthropometric spine phantoms.

Major Independent Variables: BMI and Body Fat Percentage

Height was assessed with a wall-mounted stadiometer, and weight (without shoes) was assessed using a standard floor scale. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Persons with BMI at either extreme (<10 or >60 kg/m^2) were excluded. Body fat percentages for the soft tissue regions included in the spine and hip scans were averaged to provide an index of total-body adiposity. A high correlation between body fat percentages from the regional DXA scan and the total-body DXA scan (the gold standard for total body fat measurement) was seen in a subgroup of participants with both measurements (r = 0.86 for 255 women and 0.87 for 46 men). Short-term precision error—calculated as the root mean square for measurements of body fat percentage in 30 participants having repeated scans on the same day, with repositioning between the scans—was 1.8% for the spine scans and 1.7% for the hip scans (25).

Body mass index and body fat percentage were divided into quintiles. In women, BMI quintiles were defined as follows: 22.52 kg/m^2 or lower (quintile 1), 22.53 to 24.99 kg/m^2 (quintile 2), 25.00 to 27.55 kg/m^2 (quintile 3), 27.56 to 31.12 kg/m^2 (quintile 4), and greater than 31.12 kg/m^2 (quintile 5). To facilitate clinical interpretability, in a sensitivity analysis we also characterized BMI according to the WHO classification scheme as follows: less than 18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25.0 to 29.9 kg/m^2 (overweight), 30.0 to 34.9 kg/m^2 (class I obesity), and 35.0 kg/m^2 or greater (class II or III obesity). Body fat percentage quintiles in women were 25.57% or lower (quintile 1), 25.58% to 30.40% (quintile 2), 30.41% to 34.41% (quintile 3), 34.42% to 38.68% (quintile 4), and greater than 38.68% (quintile 5). In men, BMI quintiles were 23.85 kg/m^2 or lower (quintile 1), 23.86 to 26.03 kg/m^2 (quintile 2), 26.04 to 28.13 kg/m^2 (quintile 3), 28.14 to 30.84 kg/m^2 (quintile 4), and greater than 30.84 kg/m^2 (quintile 5); the WHO BMI categories were the same as for women. Body fat percentage quintiles in men were 23.14% or lower (quintile 1), 23.15% to 27.98% (quintile 2), 27.99% to 31.72% (quintile 3), 31.73% to 36.14% (quintile 4), and greater than 36.14% (quintile 5).

Outcomes

The primary dependent variable of interest was all-cause mortality, ascertained from vital statistics data within the Population Health Research Data Repository.

Potential Confounders

Separate analyses were done a priori in men and women, with sequential adjustments. Potential confounders included age; Aggregated Diagnosis Groups (ADG) score; ethnicity (white vs. nonwhite); income quintile (lowest 2 vs. highest 3); residency (urban vs. nonurban); high alcohol use (yes vs. no); glucocorticoid use (yes vs. no); prior fracture; and presence of chronic obstructive pulmonary disease (COPD), diabetes, acute coronary syndrome, chronic kidney disease, or heart failure. The ADG score is an individualized comorbidity-based score consisting of 32 diagnostic clusters based on the Johns Hopkins Adjusted Clinical Groups Case-Mix System, version 10 (26). This score has been shown to accurately predict mortality in general ambulatory cohorts in Canada (27). Income data were at the neighborhood level and were sourced from the 2006 census.

No data were missing for any of the covariates, but we lacked data on smoking status. However, we have previously shown that a COPD diagnosis in our population represents a valid measure of "current smoking" and can be substituted for smoking in risk stratification tools, such as FRAX (28, 29). Thirteen percent of Canadian women who are similar in age to those in our sample are smokers, and COPD was present in 8% of the women in our cohort; among men, both proportions were 18% (28, 29).

Statistical Analysis

Descriptive analyses were conducted according to BMI quintile using parametric or nonparametric tests as appropriate to test between-group differences. Spearman correlations between BMI and mean body fat percentage were calculated separately in men and women. Multivariable Cox proportional hazards models were then constructed sequentially as described earlier. Proportional hazards assumptions were tested using log-minus-log survival plots and analysis of rescaled Schoenfeld residuals, and no violations were observed. Participants were censored at death, disenrollment from the provincial health plan, or the end of the study (31 March 2013).

Body mass index quintile was included as the major independent variable of interest in the first set of models, body fat percentage quintile was included in the second set, and both quintiles were included in the third set. Variance inflation factors were less than 3 when BMI and body fat percentage were simultaneously included, indicating absence of significant multicollinearity. Model 1 was adjusted for age, and model 2 was adjusted for age and ADG score. Model 3 was adjusted for the covariates in model 2 plus ethnicity, income quintile, and residency. Finally, model 4 (the "fully adjusted" model) added COPD, high alcohol use, glucocorticoid use, prior fracture, diabetes, acute coronary syndrome, chronic kidney disease, and heart failure to model 3.

To test various assumptions and demonstrate the robustness of our main results, we performed a pair of sensitivity analyses. First, we reanalyzed the data using the WHO clinical categories for BMI rather than quintiles. Second, because patients who had fractures before their BMD test may have differed clinically from the healthier majority who had never had an osteoporotic fracture, we repeated our analyses after excluding the 14.0% of patients whose records indicated a prior fracture. These analyses were conducted using STATISTICA, version 10.0 (StatSoft).

To generate figures, age-adjusted and fully adjusted Cox proportional hazards regression models (fitted to the central 95% of the observations and stratified by sex) were constructed to describe the association of BMI and mean body fat percentage (as continuous variables) with mortality. The models considered BMI and mean body fat percentage separately and together. Smoothed hazard ratio (HR) estimates with 95% CIs were obtained, using the sex-specific median values for BMI and mean body fat percentage as referents. Smoothing was performed using a penalized spline function, which selects the optimal number of degrees of freedom by using a penalized log-likelihood function (Akaike information criterion). Models were fitted in R, version 3.1.3 (R Foundation for Statistical Computing), using the SmoothHR package.

Role of the Funding Source

This study received no funding.

RESULTS

The final cohort comprised 49 476 women and 4944 men. Baseline characteristics, deaths, and death rates are summarized in Table 1. Among women, mean age was 63.5 years, mean BMI was 27.0 kg/m^2, 1011 (2.0%) were underweight, 18 933 (38.3%) had normal weight, 17 087 (34.5%) were overweight, 8358 (16.9%) had class I obesity, 4087 (8.3%) had class II or III obesity, and mean body fat percentage was 32.1%. Among men, mean age was 65.5 years, mean BMI was 27.4 kg/m^2, 62 (1.3%) were underweight, 1427 (28.9%) had normal weight, 2246 (45.4%) were overweight, 904 (18.3%) had class I obesity, 305 (6.2%) had class II or III obesity, and mean body fat percentage was 29.5%. The Pearson correlation between BMI and mean body fat percentage was 0.76 in women and 0.63 in men; the Appendix Figure (available at www.annals.org) shows a scatter plot of both variables, with the quintiles marked to provide a better graphical understanding of these associations. In both men and women, the proportion with diabetes, chronic kidney disease, low-income status, nonurban residency, and white ethnicity increased with increasing BMI quintile.

Death occurred in 4965 women over a median follow-up of 6.7 years (interquartile range, 3.5 to 10.0 years) and 984 men over a median follow-up of 4.5 years (interquartile range, 2.0 to 7.9 years). Mortality

Table 1. Baseline Demographic Characteristics, Deaths, and Death Rates*

Variable	Quintile of BMI					P Value for Trend
	Quintile 1 (≤22.52 kg/m²)	Quintile 2 (22.53–24.99 kg/m²)	Quintile 3 (25.00–27.55 kg/m²)	Quintile 4 (27.56–31.12 kg/m²)	Quintile 5 (>31.12 kg/m²)	
Women, *n*	9923	9951	9909	9897	9796	–
Mean age (SD), *y*	62.4 (11.7)	63.4 (11.1)	64.3 (10.6)	64.4 (10.3)	63 (10.1)	<0.001
Nonwhite ethnicity	409 (4.1)	327 (3.3)	249 (2.5)	221 (2.2)	126 (1.3)	<0.001
Prior fracture	1419 (14.3)	1355 (13.6)	1427 (14.4)	1351 (13.7)	1365 (13.9)	0.53
COPD	795 (8.0)	658 (6.6)	684 (6.9)	769 (7.8)	949 (9.7)	<0.001
Glucocorticoid use	301 (3.0)	325 (3.3)	296 (3.0)	359 (3.6)	495 (5.1)	<0.001
Rheumatoid arthritis	289 (2.9)	266 (2.7)	259 (2.6)	304 (3.1)	323 (3.3)	0.020
Alcohol/substance use	381 (3.8)	283 (2.8)	261 (2.6)	255 (2.6)	245 (2.5)	<0.001
Acute coronary syndrome	87 (0.9)	93 (0.9)	104 (1.0)	117 (1.2)	139 (1.4)	<0.001
Congestive heart failure	150 (1.5)	155 (1.6)	127 (1.3)	173 (1.7)	258 (2.6)	<0.001
Diabetes	416 (4.2)	491 (4.9)	699 (7.1)	1067 (10.8)	1852 (18.9)	<0.001
Chronic kidney disease	160 (1.6)	157 (1.6)	135 (1.4)	224 (2.3)	254 (2.6)	<0.001
Mean ADG score (SD)	4.5 (2.7)	4.4 (2.6)	4.5 (2.6)	4.8 (2.6)	5.1 (2.7)	<0.001
Nonurban residency	2858 (28.8)	3018 (30.3)	3244 (32.7)	3425 (34.6)	3704 (37.8)	<0.001
Low income	3291 (33.2)	3238 (32.5)	3381 (34.1)	3582 (36.2)	3851 (39.3)	<0.001
Mean BMI (SD), *kg/m²*	20.6 (1.5)	23.8 (0.7)	26.2 (0.7)	29.2 (1.0)	35.4 (4.0)	<0.001
Mean body fat (SD), *%*	23.5 (5.7)	28.8 (5.0)	32.3 (4.7)	35.6 (4.5)	40.2 (4.5)	<0.001
Deaths	1254 (12.6)	986 (9.9)	925 (9.3)	942 (9.5)	858 (8.8)	<0.001
Mean person-years (SD)	67 545 (6.8)	68 107 (6.8)	67 698 (6.8)	65 434 (6.6)	61 598 (6.3)	–
Crude death rate per 1000 person-years	18.6	14.5	13.7	14.4	13.9	–
	Quintile 1 (≤23.85 kg/m²)	Quintile 2 (23.86–26.03 kg/m²)	Quintile 3 (26.04–28.13 kg/m²)	Quintile 4 (28.14–30.84 kg/m²)	Quintile 5 (>30.84 kg/m²)	
Men, *n*	1001	991	998	981	973	–
Mean age (SD), *y*	67 (12.8)	66.5 (12.0)	66.2 (11.5)	65 (11.3)	62.7 (11.1)	<0.001
Nonwhite ethnicity	40 (4.0)	30 (3.0)	22 (2.2)	11 (1.1)	11 (1.1)	<0.001
Prior fracture	213 (21.3)	176 (17.8)	172 (17.2)	178 (18.1)	174 (17.9)	0.098
COPD	182 (18.2)	109 (11.0)	119 (11.9)	127 (12.9)	116 (11.9)	0.002
Glucocorticoid use	154 (15.4)	155 (15.6)	177 (17.7)	178 (18.1)	178 (18.3)	0.028
Rheumatoid arthritis	49 (4.9)	48 (4.8)	62 (6.2)	59 (6.0)	49 (5.0)	0.52
Alcohol/substance use	81 (8.1)	48 (4.8)	37 (3.7)	52 (5.3)	48 (4.9)	0.009
Acute coronary syndrome	21 (2.1)	34 (3.4)	40 (4.0)	30 (3.1)	34 (3.5)	0.169
Congestive heart failure	48 (4.8)	42 (4.2)	46 (4.6)	57 (5.8)	67 (6.9)	0.011
Diabetes	123 (12.3)	155 (15.6)	146 (14.6)	185 (18.9)	255 (26.2)	<0.001
Chronic kidney disease	90 (9.0)	96 (9.7)	75 (7.5)	90 (9.2)	107 (11.0)	0.24
Mean ADG score (SD)	5.6 (3.0)	5.6 (2.9)	5.5 (2.9)	5.6 (2.8)	5.7 (2.8)	0.56
Nonurban residency	280 (28.0)	299 (30.2)	344 (34.5)	371 (37.8)	408 (41.9)	<0.001
Low income	378 (37.8)	333 (33.6)	346 (34.7)	350 (35.7)	362 (37.2)	0.86
Mean BMI (SD), *kg/m²*	21.7 (1.7)	25.0 (0.6)	27.1 (0.6)	29.3 (0.8)	34.2 (3.1)	<0.001
Mean body fat (SD), *%*	22.5 (6.6)	27.2 (6.2)	29.7 (5.7)	32.4 (5.5)	36 (5.4)	<0.001
Deaths	2548 (25.7)	2069 (20.8)	1857 (18.7)	1745 (17.6)	1621 (16.5)	<0.001
Mean person-years (SD)	49 464 (5.0)	52 922 (5.3)	51 200 (5.2)	52 312 (5.3)	49 542 (5.1)	–
Crude death rate per 1000 person-years	51.5	39.1	36.3	33.4	32.7	–

ADG = Aggregated Diagnosis Groups; BMI = body mass index; COPD = chronic obstructive pulmonary disease.
* Values are numbers (percentages) unless otherwise indicated.

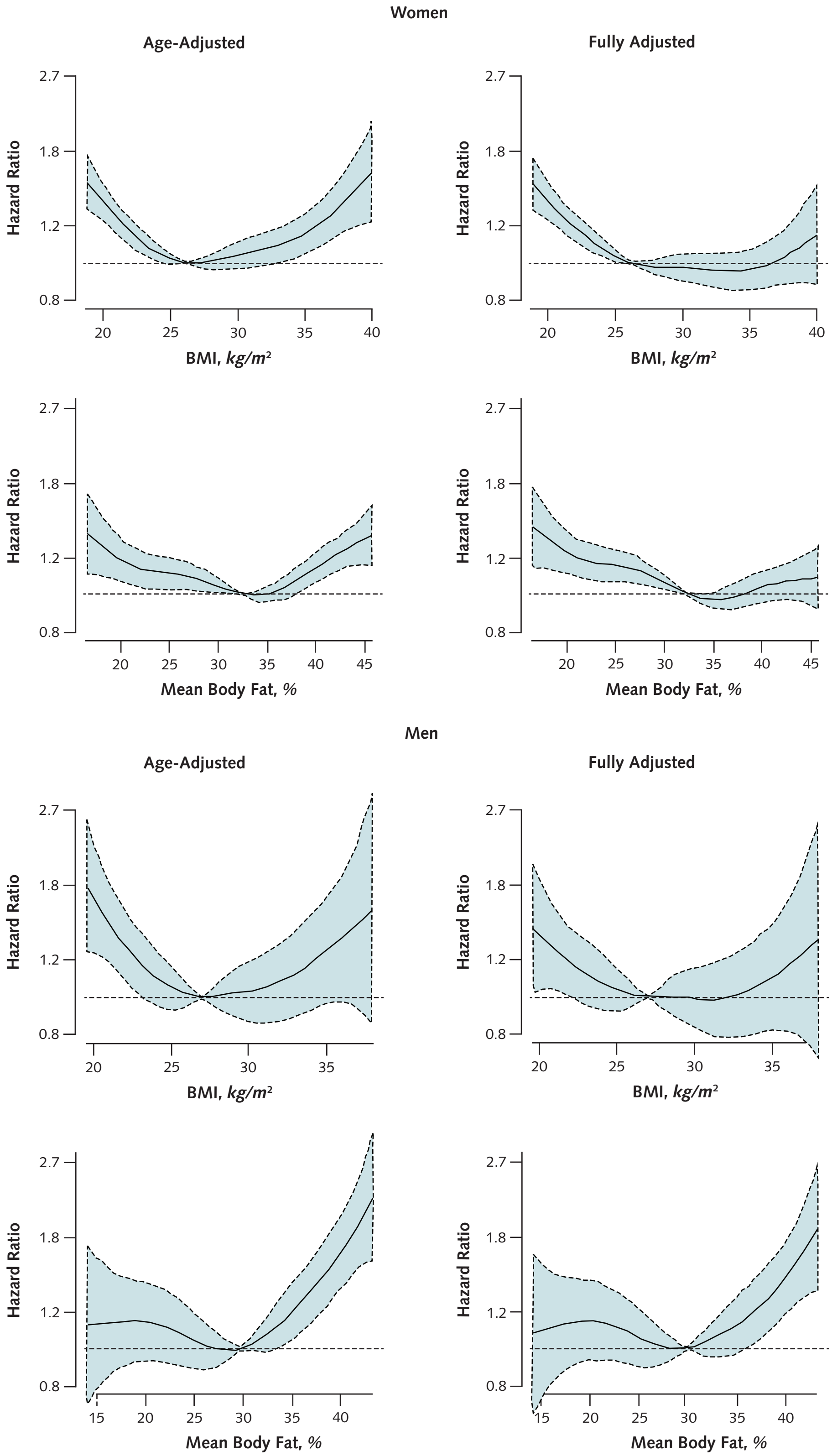
rates ranged from 4.6 (age 40 to 44 years) to 54.7 (age ≥85 years) deaths per 1000 women and from 7.0 (age 40 to 44 years) to 97.9 (age ≥85 years) deaths per 1000 men (**Appendix Table 1**, available at www.annals.org). Compared with the Manitoban and Canadian populations, age-stratified mortality rates were similar in women and slightly higher in men (**Appendix Table 1**) (30).

Higher BMI quintile was associated with lower risk for death (*P* for trend < 0.001 in both women and men). Crude death rates decreased from 18.6 per 1000 person-years for quintile 1 to 13.9 per 1000 person-years for quintile 5 in women and from 51.5 per 1000 person-years for quintile 1 to 32.7 per 1000 person-years for quintile 5 in men (**Table 1**).

Models Examining BMI and Body Fat Percentage Separately

Plots of the HRs for death in the sex-stratified, age-adjusted, and fully adjusted models that included BMI and body fat percentage separately are shown in **Figure 1**. Hazard ratios by BMI and body fat percentage quintiles (with quintile 3 as the reference) are shown in **Table 2**. Among women, low BMI and low body fat percentage were each associated with an increased risk for death (HR, 1.48 [95% CI, 1.36 to 1.61] for BMI quintile 1,

Figure 1. Hazard ratios for death in age-adjusted and fully adjusted models that included BMI and body fat percentage separately.



Reference median values for BMI and mean body fat were 26 kg/m^2 and 32% for women and 27 kg/m^2 and 30% for men. BMI = body mass index.

Table 2. Associations of BMI and Body Fat Percentage (Separately) With Mortality

Analysis	Hazard Ratio (95% CI)			
	Model 1*	Model 2†	Model 3‡	Model 4§
Women				
Quintile of BMI				
1 (≤22.52 kg/m^2)	1.49 (1.37–1.62)	1.48 (1.36–1.61)	1.49 (1.37–1.62)	1.48 (1.36–1.61)
2 (22.53–24.99 kg/m^2)	1.11 (1.01–1.21)	1.12 (1.02–1.22)	1.12 (1.02–1.22)	1.13 (1.03–1.23)
3 (25.00–27.55 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (27.56–31.12 kg/m^2)	1.07 (0.98–1.17)	1.05 (0.96–1.15)	1.05 (0.96–1.15)	1.01 (0.93–1.11)
5 (>31.12 kg/m^2)	1.24 (1.13–1.36)	1.18 (1.08–1.30)	1.17 (1.07–1.29)	1.03 (0.94–1.13)
Quintile of body fat percentage				
1 (≤25.57%)	1.33 (1.22–1.46)	1.34 (1.22–1.47)	1.35 (1.23–1.47)	1.36 (1.25–1.49)
2 (25.58%–30.40%)	1.12 (1.02–1.22)	1.14 (1.04–1.25)	1.15 (1.05–1.26)	1.17 (1.07–1.28)
3 (30.41%–34.41%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (34.42%–38.68%)	1.01 (0.92–1.11)	0.99 (0.91–1.09)	0.99 (0.91–1.08)	0.96 (0.88–1.06)
5 (>38.68%)	1.26 (1.16–1.38)	1.22 (1.12–1.33)	1.21 (1.11–1.32)	1.08 (0.99–1.18)
Men				
Quintile of BMI				
1 (≤23.85 kg/m^2)	1.35 (1.12–1.63)	1.34 (1.11–1.62)	1.33 (1.10–1.61)	1.26 (1.04–1.52)
2 (23.86–26.03 kg/m^2)	1.08 (0.88–1.31)	1.08 (0.89–1.32)	1.08 (0.88–1.32)	1.08 (0.89–1.32)
3 (26.04–28.13 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (28.14–30.84 kg/m^2)	1.05 (0.85–1.29)	1.04 (0.85–1.28)	1.04 (0.84–1.28)	1.01 (0.82–1.25)
5 (>30.84 kg/m^2)	1.24 (1.00–1.53)	1.21 (0.98–1.49)	1.20 (0.97–1.49)	1.13 (0.91–1.39)
Quintile of body fat percentage				
1 (≤23.14%)	1.16 (0.94–1.43)	1.16 (0.94–1.43)	1.14 (0.92–1.41)	1.19 (0.96–1.47)
2 (23.15%–27.98%)	1.01 (0.81–1.25)	1.00 (0.81–1.24)	1.00 (0.81–1.24)	1.04 (0.84–1.30)
3 (27.99%–31.72%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (31.73%–36.14%)	1.12 (0.91–1.37)	1.09 (0.89–1.34)	1.08 (0.88–1.33)	1.12 (0.91–1.38)
5 (>36.14%)	1.58 (1.30–1.92)	1.49 (1.23–1.81)	1.47 (1.21–1.78)	1.40 (1.16–1.71)

BMI = body mass index.
* Adjusted for age.
† Adjusted for age and Aggregated Diagnosis Groups score.
‡ Adjusted for covariates in model 2 plus ethnicity, income quintile, and residency.
§ Adjusted for covariates in model 3 plus high alcohol use; glucocorticoid use; prior fracture; and presence of chronic obstructive pulmonary disease, diabetes, acute coronary syndrome, chronic kidney disease, and congestive heart failure (fully adjusted model).

1.13 [CI, 1.03 to 1.23] for BMI quintile 2, 1.36 [CI, 1.25 to 1.49] for body fat percentage quintile 1, and 1.17 [CI, 1.07 to 1.28] for body fat percentage quintile 2) in the fully adjusted models. In contrast, women in the highest BMI or body fat percentage quintile did not have significantly increased mortality (**Table 2**). Among men, mortality was significantly higher for those in BMI quintile 1 (HR, 1.26 [CI, 1.04 to 1.52]) and those in body fat percentage quintile 5 (HR, 1.40 [CI, 1.16 to 1.71]). Otherwise, no significant increases in mortality were found.

Models Examining BMI and Body Fat Percentage Together

Plots of the HRs for death in the sex-stratified, age-adjusted, and fully adjusted models that included BMI and body fat percentage together are shown in **Figure 2**. Hazard ratios by BMI and body fat percentage quintiles (with quintile 3 as the reference) are shown in **Table 3**. Among women, low BMI was significantly associated with increased mortality (HR, 1.44 [CI, 1.30 to 1.59] for quintile 1 and 1.12 [CI, 1.02 to 1.23] for quintile 2) in the fully adjusted models. High body fat percentage was also independently associated with significantly higher mortality (HR, 1.19 [CI, 1.08 to 1.32] for quintile 5). Results were similar among men in the fully adjusted models; low BMI (HR, 1.45 [CI, 1.17 to 1.79] for quintile 1) and high body fat percentage (HR, 1.59 [CI, 1.28 to 1.96] for quintile 5) were still associated with increased mortality.

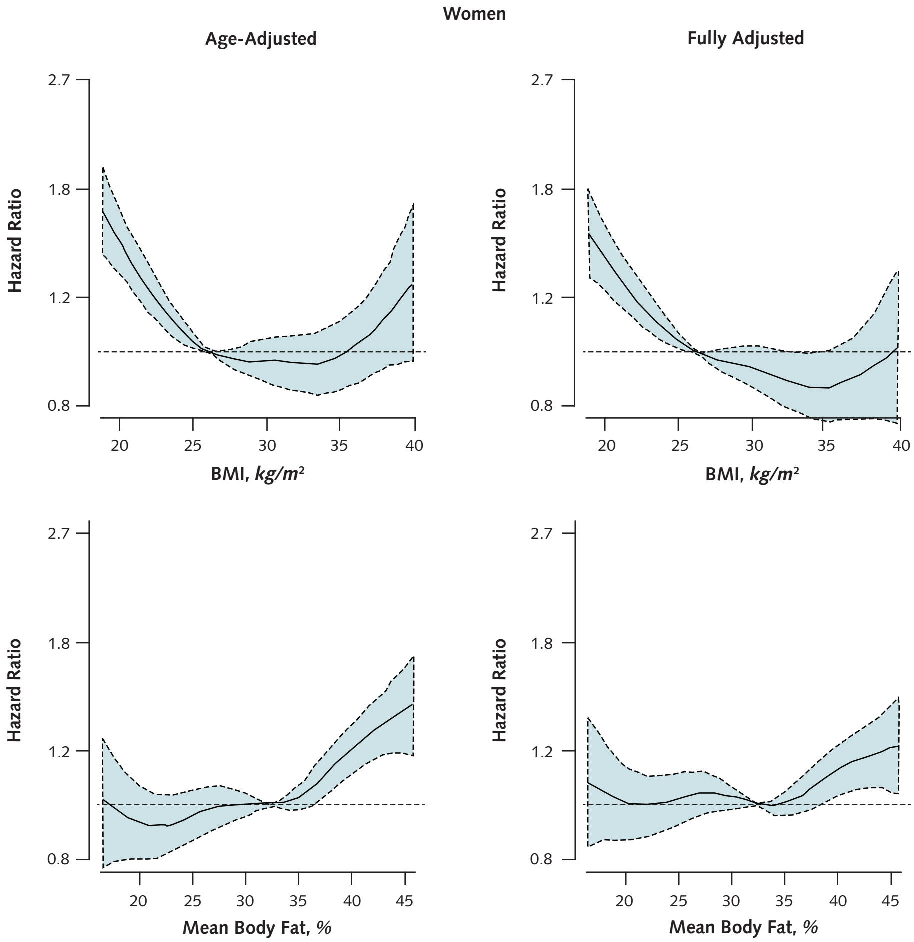
Sensitivity Analysis

Analyzing BMI according to the WHO clinical categories rather than quintiles did not affect our results, although we noted particularly adverse outcomes associated with being underweight or being in the highest quintile of body fat percentage, perhaps representing "sarcopenic obesity" (**Appendix Table 2**, available at www.annals.org). In addition, excluding patients with prevalent fracture did not affect the strength of association or statistical significance of any of our findings (data not shown).

Discussion

In this large population-based cohort study of more than 50 000 middle-aged and older adults undergoing BMD testing for clinical purposes, we examined associations among BMI, body fat percentage, and all-cause mortality. The major finding was that when BMI and body fat percentage were included in the same fully adjusted models, low BMI and high body fat percentage were both associated with increased all-cause mortality. Mortality increased as BMI decreased and body fat percentage increased. This suggests that after adjustment for BMI, higher adiposity may have a detrimental effect on survival and that after adjustment for body fat percentage, a lower BMI may likewise be associated with decreased survival.

Figure 2. Hazard ratios for death in age-adjusted and fully adjusted models that included BMI and body fat percentage together.

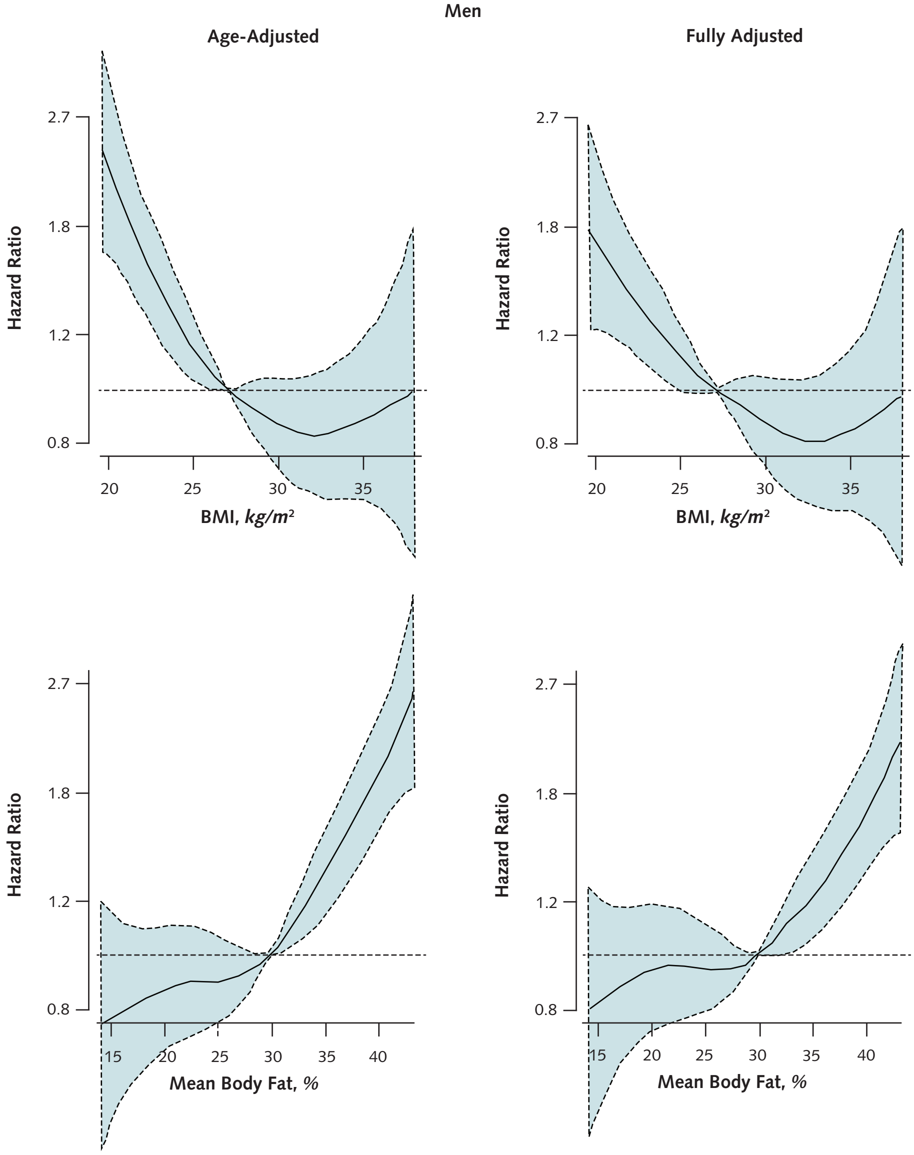


Reference median values for BMI and mean body fat were 26 kg/m² and 32% for women and 27 kg/m² and 30% for men. BMI = body mass index.

These findings show that increasing body fat percentage is independently associated with reduced survival, at least in our cohort of patients referred for BMD testing. Low BMI, a proxy for lean mass when body fat percentage is included in the model, is also predictive of increased mortality; this is potentially mediated through known associations among weight loss, chronic diseases, frailty, and cachexia (5, 31). Body mass index is widely used as a proxy for adiposity even though it more closely reflects lean mass than fat mass (18, 32). Increasing BMI may therefore reflect higher fitness levels, greater metabolic reserve, and less cachexia—factors that are associated with greater survival (6, 16, 18, 32–34)—rather than increasing fat. Thus, our results suggest that BMI may be an inappropriate surrogate for adiposity, and this limitation may explain the presence of the obesity paradox in many studies. Of note, other studies have shown an association between increased survival and increasing waist circumference or fat percentage as well as increased BMI (35, 36), but this has been an inconsistent finding (37).

Although our study reports on a large cohort that incorporates and links both clinical registry data and administrative databases, there are limitations. First, we assessed BMD and anthropometric indices at baseline only and were not able to assess repeated measures over time, and we did not have data on the presence of and reasons for recent weight changes. Second, the study sample was primarily female and white, which limits generalizability. In addition, our findings are not necessarily generalizable to persons with chronic diseases characterized by inflammation, malnutrition, and cachexia. Third, the cohort was restricted to participants undergoing BMD testing, who may have systematically differed from those who did not have or declined such testing. This may have resulted in enrollment of a healthier or more "health-seeking" population and a larger number of persons at the lower end of the weight spectrum (given that lower weight is associated with lower BMD) compared with the general population. Although this limits external generalizability, it should not affect the internal validity of our find-

Figure 2–Continued



ings. Fourth, we examined only all-cause mortality and can provide no data on cause-specific mortality or nonfatal events. Fifth, we lacked data on smoking and physical activity, which limited our ability to adjust for these factors, although previous work of ours suggests that adjustment for COPD accurately captures most current smokers (28). Finally, we lacked more mechanistic data that might have provided insights into the associations we observed, such as measures of visceral adiposity, inflammatory markers, or cardiovascular fitness.

In conclusion, our findings underscore that the risk for all-cause mortality increases with both increasing adiposity and decreasing BMI in a general population of middle-aged and older adults. These findings also suggest the importance of using direct measures of adiposity when building prognostic or even exploratory models.

From University of Alberta, Edmonton, Alberta, and University of Manitoba, Winnipeg, Manitoba, Canada.

Note: This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee.

Disclaimer: The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

Acknowledgment: The authors thank the Manitoba Centre for Health Policy for the use of data contained in the Population

Table 3. Associations of BMI and Body Fat Percentage (Together) With Mortality

Analysis	Hazard Ratio (95% CI)			
	Model 1*	Model 2†	Model 3‡	Model 4§
Women				
Quintile of BMI				
1 (≤22.52 kg/m^2)	1.52 (1.37–1.68)	1.49 (1.34–1.64)	1.49 (1.35–1.65)	1.44 (1.30–1.59)
2 (22.53–24.99 kg/m^2)	1.13 (1.03–1.24)	1.13 (1.03–1.24)	1.13 (1.03–1.24)	1.12 (1.02–1.23)
3 (25.00–27.55 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (27.56–31.12 kg/m^2)	1.01 (0.92–1.11)	1.01 (0.92–1.11)	1.00 (0.91–1.10)	0.99 (0.90–1.09)
5 (>31.12 kg/m^2)	1.06 (0.95–1.18)	1.03 (0.92–1.15)	1.02 (0.92–1.14)	0.95 (0.85–1.06)
Quintile of body fat percentage				
1 (≤25.57%)	1.05 (0.95–1.17)	1.07 (0.96–1.19)	1.07 (0.97–1.19)	1.10 (0.99–1.22)
2 (25.58%–30.40%)	1.03 (0.94–1.13)	1.05 (0.96–1.15)	1.06 (0.96–1.16)	1.08 (0.99–1.19)
3 (30.41%–34.41%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (34.42%–38.68%)	1.06 (0.96–1.16)	1.04 (0.95–1.14)	1.04 (0.95–1.14)	1.02 (0.93–1.12)
5 (>38.68%)	1.33 (1.20–1.47)	1.30 (1.18–1.44)	1.30 (1.17–1.44)	1.19 (1.08–1.32)
Men				
Quintile of BMI				
1 (≤23.85 kg/m^2)	1.63 (1.32–2.02)	1.62 (1.31–2.00)	1.61 (1.30–1.99)	1.45 (1.17–1.79)
2 (23.86–26.03 kg/m^2)	1.14 (0.94–1.40)	1.15 (0.94–1.40)	1.15 (0.94–1.40)	1.14 (0.93–1.39)
3 (26.04–28.13 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (28.14–30.84 kg/m^2)	0.92 (0.74–1.13)	0.93 (0.75–1.14)	0.93 (0.75–1.15)	0.92 (0.74–1.13)
5 (>30.84 kg/m^2)	0.92 (0.73–1.15)	0.93 (0.74–1.17)	0.93 (0.74–1.17)	0.91 (0.72–1.15)
Quintile of body fat percentage				
1 (≤23.14%)	0.89 (0.71–1.12)	0.89 (0.71–1.13)	0.89 (0.70–1.12)	0.98 (0.78–1.23)
2 (23.15%–27.98%)	0.91 (0.73–1.13)	0.91 (0.73–1.13)	0.91 (0.73–1.13)	0.96 (0.77–1.19)
3 (27.99%–31.72%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (31.73%–36.14%)	1.20 (0.97–1.47)	1.17 (0.95–1.45)	1.16 (0.94–1.43)	1.19 (0.97–1.47)
5 (>36.14%)	1.80 (1.46–2.22)	1.70 (1.38–2.10)	1.67 (1.35–2.06)	1.59 (1.28–1.96)

BMI = body mass index.
* Adjusted for age.
† Adjusted for age and Aggregated Diagnosis Groups score.
‡ Adjusted for covariates in model 2 plus ethnicity, income quintile, and residency.
§ Adjusted for covariates in model 3 plus high alcohol use; glucocorticoid use; prior fracture; and presence of chronic obstructive pulmonary disease, diabetes, acute coronary syndrome, chronic kidney disease, and congestive heart failure (fully adjusted model).

Health Research Data Repository (Health Information Privacy Committee project number 2011/2012-31). The authors also thank Dr. Shuman Yang for assisting with R programming and figure preparation. Dr. Majumdar holds the Endowed Chair in Patient Health Management from the Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences, University of Alberta. Dr. Lix is supported by a Manitoba Research Chair from Research Manitoba.

Disclosures: Dr. Leslie reports grants from Genzyme and Amgen and speaker fees from Amgen, Eli Lilly, and Novartis outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1181.

Reproducible Research Statement: *Study protocol, statistical code, and data set:* Not available.

Requests for Single Reprints: William D. Leslie, MD, Department of Medicine (C5121), University of Manitoba, 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada; e-mail, bleslie@sbgh.mb.ca.

Current author addresses and author contributions are available at www.annals.org.

References

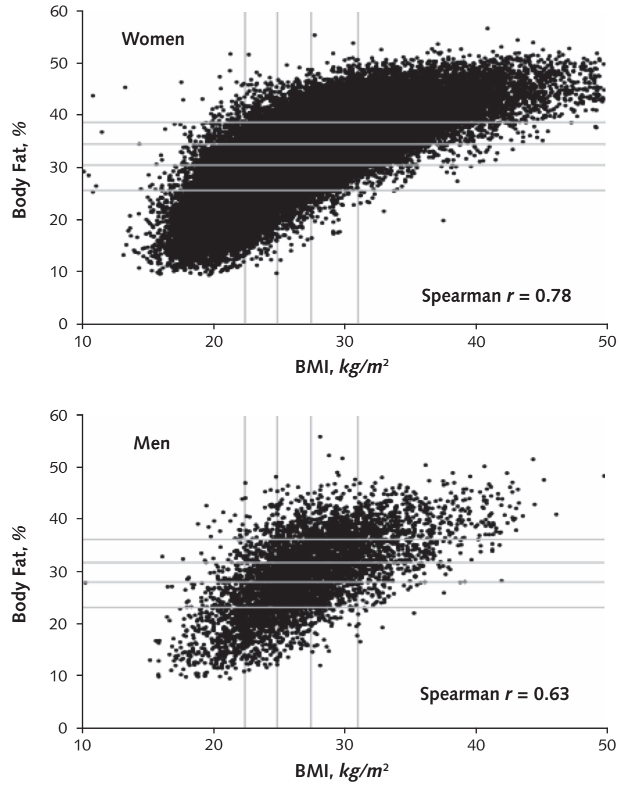
1. **Boggs DA, Rosenberg L, Cozier YC, Wise LA, Coogan PF, Ruiz-Narvaez EA, et al.** General and abdominal obesity and risk of death among black women. N Engl J Med. 2011;365:901-8. [PMID: 21899451] doi:10.1056/NEJMoa1104119
2. **Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al.** Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363:2211-9. [PMID: 21121834] doi:10.1056/NEJMoa1000367
3. **Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al; Prospective Studies Collaboration.** Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083-96. [PMID: 19299006] doi:10.1016/S0140-6736(09)60318-4
4. **Flegal KM, Kit BK, Orpana H, Graubard BI.** Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309:71-82. [PMID: 23280227] doi:10.1001/jama.2012.113905
5. **Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD, et al.** Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care. 2007;10:433-42. [PMID: 17563461]
6. **Oreopoulos A, Kalantar-Zadeh K, Sharma AM, Fonarow GC.** The obesity paradox in the elderly: potential mechanisms and clinical implications. Clin Geriatr Med. 2009;25:643-59, viii. [PMID: 19944265] doi:10.1016/j.cger.2009.07.005
7. **Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA.** Body mass index and mortality in heart failure: a meta-analysis. Am Heart J. 2008;156:13-22. [PMID: 18585492] doi:10.1016/j.ahj.2008.02.014

8. **Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO.** Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail. 2013;1:93-102. [PMID: 24621833] doi:10.1016/j.jchf.2013.01.006
9. **Greenberg JA.** The obesity paradox in the US population. Am J Clin Nutr. 2013;97:1195-200. [PMID: 23636238] doi:10.3945/ajcn.112.045815
10. **Vapattanawong P, Aekplakorn W, Rakchanyaban U, Prasartkul P, Porapakkham Y.** Obesity and mortality among older Thais: a four year follow up study. BMC Public Health. 2010;10:604. [PMID: 20942942] doi:10.1186/1471-2458-10-604
11. **Costanzo P, Cleland JG, Pellicori P, Clark AL, Hepburn D, Kilpatrick ES, et al.** The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. Ann Intern Med. 2015;162:610-8. [PMID: 25938991] doi:10.7326/M14-1551
12. **Flegal KM, Kalantar-Zadeh K.** Overweight, mortality and survival [Editorial]. Obesity (Silver Spring). 2013;21:1744-5. [PMID: 23929522] doi:10.1002/oby.20588
13. **Lavie CJ, Mehra MR, Milani RV.** Obesity and heart failure prognosis: paradox or reverse epidemiology? [Editorial]. Eur Heart J. 2005;26:5-7. [PMID: 15615792]
14. **Lavie CJ, Milani RV, Ventura HO, Romero-Corral A.** Body composition and heart failure prevalence and prognosis: getting to the fat of the matter in the "obesity paradox" [Editorial]. Mayo Clin Proc. 2010;85:605-8. [PMID: 20592168] doi:10.4065/mcp.2010.0333
15. **Habbu A, Lakkis NM, Dokainish H.** The obesity paradox: fact or fiction? Am J Cardiol. 2006;98:944-8. [PMID: 16996880]
16. **Lavie CJ, De Schutter A, Patel DA, Milani RV.** Body composition and fitness in the obesity paradox—body mass index alone does not tell the whole story [Editorial]. Prev Med. 2013;57:1-2. [PMID: 23545240] doi:10.1016/j.ypmed.2013.03.010
17. **Agarwal R, Bills JE, Light RP.** Diagnosing obesity by body mass index in chronic kidney disease: an explanation for the "obesity paradox?". Hypertension. 2010;56:893-900. [PMID: 20876448] doi:10.1161/HYPERTENSIONAHA.110.160747
18. **Oreopoulos A, Fonarow GC, Ezekowitz JA, McAlister FA, Sharma AM, Kalantar-Zadeh K, et al.** Do anthropometric indices accurately reflect directly measured body composition in men and women with chronic heart failure? Congest Heart Fail. 2011;17:90-2. [PMID: 21449998] doi:10.1111/j.1751-7133.2010.00204.x
19. **Roos NP, Shapiro E.** Revisiting the Manitoba Centre for Health Policy and Evaluation and its population-based health information system. Med Care. 1999;37:JS10-4. [PMID: 10409002]
20. **Leslie WD, Caetano PA, Macwilliam LR, Finlayson GS.** Construction and validation of a population-based bone densitometry database. J Clin Densitom. 2005;8:25-30. [PMID: 15722584]
21. **Leslie WD, Majumdar SR, Lix LM, Johansson H, Oden A, McCloskey E, et al; Manitoba Bone Density Program.** High fracture probability with FRAX usually indicates densitometric osteoporosis: implications for clinical practice. Osteoporos Int. 2012;23:391-7. [PMID: 21365460] doi:10.1007/s00198-011-1592-3
22. **Leslie WD, Lix LM, Tsang JF, Caetano PA; Manitoba Bone Density Program.** Single-site vs multisite bone density measurement for fracture prediction. Arch Intern Med. 2007;167:1641-7. [PMID: 17698687]
23. **Leslie WD, Orwoll ES, Nielson CM, Morin SN, Majumdar SR, Johansson H, et al.** Estimated lean mass and fat mass differentially affect femoral bone density and strength index but are not FRAX independent risk factors for fracture. J Bone Miner Res. 2014;29:2511-9. [PMID: 24825359] doi:10.1002/jbmr.2280
24. **Johansson H, Kanis JA, Odén A, McCloskey E, Chapurlat RD, Christiansen C, et al.** A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res. 2014;29:223-33. [PMID: 23775829] doi:10.1002/jbmr.2017
25. **Leslie WD, Ludwig SM, Morin S.** Abdominal fat from spine dual-energy x-ray absorptiometry and risk for subsequent diabetes. J Clin Endocrinol Metab. 2010;95:3272-6. [PMID: 20392865] doi:10.1210/jc.2009-2794
26. **Weiner JP, Starfield BH, Steinwachs DM, Mumford LM.** Development and application of a population-oriented measure of ambulatory care case-mix. Med Care. 1991;29:452-72. [PMID: 1902278]
27. **Austin PC, Walraven Cv.** The mortality risk score and the ADG score: two points-based scoring systems for the Johns Hopkins aggregated diagnosis groups to predict mortality in a general adult population cohort in Ontario, Canada. Med Care. 2011;49:940-7. [PMID: 21921849] doi:10.1097/MLR.0b013e318229360e
28. **Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, et al; CaMos Research Group.** Fracture prediction and calibration of a Canadian FRAX® tool: a population-based report from CaMos. Osteoporos Int. 2011;22:829-37. [PMID: 21161508] doi:10.1007/s00198-010-1465-1
29. **Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA; Manitoba Bone Density Program.** Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. J Bone Miner Res. 2010;25:2350-8. [PMID: 20499367] doi:10.1002/jbmr.123
30. **Statistics Canada.** CANSIM database. Table 102-0504: Deaths and Mortality Rates, by Age Group and Sex, Canada, Provinces and Territories. 2015. Accessed at http://www5.statcan.gc.ca/cansim/a05?lang=eng&id=1020504 on 2 August 2015.
31. **Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al.** Wasting as independent risk factor for mortality in chronic heart failure. Lancet. 1997;349:1050-3. [PMID: 9107242]
32. **Oreopoulos A, Ezekowitz JA, McAlister FA, Kalantar-Zadeh K, Fonarow GC, Norris CM, et al.** Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc. 2010;85:609-17. [PMID: 20592169] doi:10.4065/mcp.2010.0103
33. **Lavie CJ, Cahalin LP, Chase P, Myers J, Bensimhon D, Peberdy MA, et al.** Impact of cardiorespiratory fitness on the obesity paradox in patients with heart failure. Mayo Clin Proc. 2013;88:251-8. [PMID: 23489451] doi:10.1016/j.mayocp.2012.11.020
34. **McAuley PA, Artero EG, Sui X, Lee DC, Church TS, Lavie CJ, et al.** The obesity paradox, cardiorespiratory fitness, and coronary heart disease. Mayo Clin Proc. 2012;87:443-51. [PMID: 22503065] doi:10.1016/j.mayocp.2012.01.013
35. **Clark AL, Chyu J, Horwich TB.** The obesity paradox in men versus women with systolic heart failure. Am J Cardiol. 2012;110:77-82. [PMID: 22497678] doi:10.1016/j.amjcard.2012.02.050
36. **Lavie CJ, Osman AF, Milani RV, Mehra MR.** Body composition and prognosis in chronic systolic heart failure: the obesity paradox. Am J Cardiol. 2003;91:891-4. [PMID: 12667583]
37. **Coutinho T, Goel K, Corrêa de Sá D, Carter RE, Hodge DO, Kragelund C, et al.** Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of "normal weight central obesity." J Am Coll Cardiol. 2013;61:553-60. [PMID: 23369419] doi:10.1016/j.jacc.2012.10.035

Current Author Addresses: Drs. Padwal and Majumdar: General Internal Medicine, University of Alberta, 5-134 Clinical Sciences Building, 8440 112th Street, Edmonton, Alberta T6G 2G3, Canada.
Dr. Leslie: Department of Medicine (C5121), University of Manitoba, 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada.
Dr. Lix: Department of Community Health Sciences, University of Manitoba, S113-750 Bannatyne Avenue, Winnipeg, Manitoba R3P 2H5, Canada.

Author Contributions: Conception and design: R. Padwal, W.D. Leslie, S.R. Majumdar.
Analysis and interpretation of the data: R. Padwal, W.D. Leslie, L.M. Lix, S.R. Majumdar.
Drafting of the article: R. Padwal, W.D. Leslie.
Critical revision of the article for important intellectual content: R. Padwal, W.D. Leslie, L.M. Lix, S.R. Majumdar.
Final approval of the article: R. Padwal, W.D. Leslie, L.M. Lix, S.R. Majumdar.
Provision of study materials or patients: W.D. Leslie.
Statistical expertise: W.D. Leslie, L.M. Lix.
Administrative, technical, or logistic support: W.D. Leslie.
Collection and assembly of data: W.D. Leslie.

Appendix Figure. Scatter plot of quintiles of body fat percentage, by BMI.



Gray vertical and horizontal lines indicate the quintiles of body fat and BMI, respectively. BMI = body mass index.

Appendix Table 1. Cohort Mortality Rates Compared With National and Provincial Mortality Rates*

Age at Death, y	Mortality Rate per 1000 Persons					
	Women			Men		
	Canada	Manitoba	Study Cohort	Canada	Manitoba	Study Cohort
40–44	1.0	1.3	4.6	1.6	2.6	7.0
45–49	1.8	2.3	6.5	2.6	3.1	7.7
50–54	2.6	3.1	5.8	4.2	4.3	14.4
55–59	4.1	5.2	5.7	6.6	7.1	19.1
60–64	6.3	7.5	6.8	10.2	11.7	24.9
65–69	10.2	11.9	9.9	16.5	19.6	30.4
70–74	16.7	18.7	15.4	26.7	31.0	40.2
75–79	27.5	27.5	23.0	44.0	46.2	59.9
80–84	48.8	47.3	34.8	73.0	82.7	66.1
≥85	89.5	84.5	54.7	122.1	119.2	97.9

* National and Manitoba data are from the Statistics Canada Canadian Socio-Economic Information Management System Web site (www5.statcan.gc.ca/cansim/a05?lang=eng&id=1020504).

Appendix Table 2. Sensitivity Analysis Using World Health Organization Thresholds for BMI

Analysis	Hazard Ratio (95% CI)			
	Model 1*	**Model 2†**	**Model 3‡**	**Model 4§**
Women				
BMI classification				
Underweight (<18.5 kg/m²)	2.40 (2.10–2.75)	2.29 (2.00–2.62)	2.29 (2.00–2.63)	2.12 (1.85–2.43)
Normal weight (18.5–24.9 kg/m²)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25.0–29.9 kg/m²)	0.84 (0.79–0.90)	0.84 (0.79–0.90)	0.83 (0.78–0.89)	0.82 (0.77–0.87)
Class I obesity (30.0–34.9 kg/m²)	0.92 (0.85–1.00)	0.89 (0.82–0.97)	0.88 (0.81–0.96)	0.81 (0.74–0.88)
Class II or III obesity (≥35.0 kg/m²)	1.16 (1.04–1.30)	1.09 (0.97–1.22)	1.08 (0.96–1.21)	0.89 (0.79–1.00)
Quintile of body fat percentage				
1 (≤25.57%)	1.33 (1.22–1.46)	1.34 (1.22–1.47)	1.35 (1.23–1.47)	1.36 (1.25–1.49)
2 (25.58%–30.40%)	1.12 (1.02–1.22)	1.14 (1.04–1.25)	1.15 (1.05–1.26)	1.17 (1.07–1.28)
3 (30.41%–34.41%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (34.42%–38.68%)	1.01 (0.92–1.11)	0.99 (0.91–1.09)	0.99 (0.91–1.08)	0.96 (0.88–1.06)
5 (>38.68%)	1.26 (1.16–1.38)	1.22 (1.12–1.33)	1.21 (1.11–1.32)	1.08 (0.99–1.18)
Combined analysis				
BMI classification				
Underweight (<18.5 kg/m²)	2.40 (2.08–2.77)	2.28 (1.98–2.64)	2.28 (1.98–2.64)	2.09 (1.81–2.41)
Normal weight (18.5–24.9 kg/m²)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25.0–29.9 kg/m²)	0.82 (0.76–0.88)	0.82 (0.76–0.89)	0.82 (0.76–0.88)	0.82 (0.76–0.89)
Class I obesity (30.0–34.9 kg/m²)	0.81 (0.73–0.91)	0.80 (0.72–0.90)	0.80 (0.72–0.89)	0.78 (0.70–0.87)
Class II or III obesity (≥35.0 kg/m²)	0.95 (0.82–1.09)	0.92 (0.80–1.06)	0.91 (0.79–1.05)	0.82 (0.71–0.94)
Quintile of body fat percentage				
1 (≤25.57%)	1.05 (0.95–1.16)	1.06 (0.96–1.17)	1.06 (0.96–1.18)	1.09 (0.98–1.21)
2 (25.58%–30.40%)	1.05 (0.96–1.15)	1.07 (0.98–1.17)	1.08 (0.98–1.18)	1.10 (1.00–1.20)
3 (30.41%–34.41%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (34.42%–38.68%)	1.06 (0.96–1.16)	1.04 (0.95–1.14)	1.04 (0.95–1.14)	1.02 (0.93–1.11)
5 (>38.68%)	1.32 (1.19–1.46)	1.29 (1.17–1.43)	1.29 (1.16–1.42)	1.19 (1.07–1.32)
Men				
BMI classification				
Underweight (<18.5 kg/m²)	2.61 (1.71–3.98)	2.66 (1.74–4.06)	2.64 (1.73–4.05)	2.44 (1.59–3.76)
Normal weight (18.5–24.9 kg/m²)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25.0–29.9 kg/m²)	0.77 (0.67–0.89)	0.78 (0.67–0.90)	0.78 (0.68–0.90)	0.81 (0.70–0.93)
Class I obesity (30.0–34.9 kg/m²)	0.85 (0.70–1.04)	0.83 (0.69–1.01)	0.83 (0.68–1.01)	0.83 (0.68–1.01)
Class II or III obesity (≥35.0 kg/m²)	1.16 (0.85–1.59)	1.13 (0.82–1.54)	1.13 (0.82–1.54)	1.03 (0.75–1.41)
Quintile of body fat percentage				
1 (≤23.14%)	1.16 (0.94–1.43)	1.16 (0.94–1.43)	1.14 (0.92–1.41)	1.19 (0.96–1.47)
2 (23.15%–27.98%)	1.01 (0.81–1.25)	1.00 (0.81–1.24)	1.00 (0.81–1.24)	1.04 (0.84–1.30)
3 (27.99%–31.72%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (31.73%–36.14%)	1.12 (0.91–1.37)	1.09 (0.89–1.34)	1.08 (0.88–1.33)	1.12 (0.91–1.38)
5 (>36.14%)	1.58 (1.30–1.92)	1.49 (1.23–1.81)	1.47 (1.21–1.78)	1.40 (1.16–1.71)
Combined analysis				
BMI classification				
Underweight (<18.5 kg/m²)	2.86 (1.86–4.40)	2.89 (1.88–4.45)	2.88 (1.86–4.45)	2.61 (1.69–4.04)
Normal weight (18.5–24.9 kg/m²)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight (25.0–29.9 kg/m²)	0.62 (0.53–0.73)	0.63 (0.53–0.74)	0.63 (0.53–0.74)	0.68 (0.57–0.80)
Class I obesity (30.0–34.9 kg/m²)	0.55 (0.43–0.69)	0.55 (0.44–0.70)	0.55 (0.44–0.70)	0.59 (0.47–0.75)
Class II or III obesity (≥35.0 kg/m²)	0.64 (0.45–0.91)	0.65 (0.46–0.92)	0.65 (0.46–0.93)	0.65 (0.46–0.93)
Quintile of body fat percentage				
1 (≤23.14%)	0.84 (0.67–1.05)	0.84 (0.67–1.06)	0.84 (0.67–1.05)	0.92 (0.73–1.15)
2 (23.15%–27.98%)	0.91 (0.74–1.14)	0.91 (0.73–1.13)	0.91 (0.73–1.13)	0.96 (0.77–1.19)
3 (27.99%–31.72%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
4 (31.73%–36.14%)	1.23 (1.00–1.51)	1.21 (0.98–1.49)	1.20 (0.97–1.47)	1.23 (0.99–1.51)
5 (>36.14%)	1.84 (1.49–2.27)	1.75 (1.42–2.15)	1.72 (1.39–2.12)	1.65 (1.33–2.03)

BMI = body mass index.
* Adjusted for age.
† Adjusted for age and Aggregated Diagnosis Groups score.
‡ Adjusted for covariates in model 2 plus ethnicity, income quintile, and residency.
§ Adjusted for covariates in model 3 plus high alcohol use; glucocorticoid use; prior fracture; and presence of chronic obstructive pulmonary disease, diabetes, acute coronary syndrome, chronic kidney disease, and congestive heart failure (fully adjusted model).