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The Association of Anthropometric Measures With Long-Term Survival Among Frail Older Women: Observations From the Women’s Health Initiative Study

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Abstract

Objectives—This study evaluated the association between currently recommended guidelines and commonly used clinical criteria for body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) and all-cause mortality in frail older women.

Design—Longitudinal, prospective, cohort study.

Setting—Women’s Health Initiative – Observational Study.

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Author Contributions

Drs. Zaslavsky, Rillamas-Sun, LaCroix and Zelber-Sagi had full access to all of the data used in the study and take responsibility for the integrity of the data and accuracy of data analysis. Zaslavsky, Rillamas-Sun, Woods, LaCroix, Zelber-Sagi: study concept, design, interpretation of data, and preparation of manuscript. Zaslavsky, Zelber-Sagi, Rillamas-Sun: data analysis and visualization. Zisberg, Shadmi, Woods, Cochrane, Edwards, Kritchevsky, Stefanick, Tinker, Vitolins, Wactawski-Wende: preparation of manuscript.

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Participants—A sample of 11,070 women aged 65–84 years with complete data to characterize frailty in the 3rd year of WHI study follow-up.

Measurements—Frailty phenotype was determined using modified Fried’s criteria. Anthropometric measures, (BMI, WC, and WHR) were collected by clinical examination. Cox proportional hazard models were used to estimate the effect of BMI, WC, and WHR on the rate of mortality adjusted for demographic and health behaviors.

Results—Over a mean follow-up of 11.5 years, there were 2,911 (26%) deaths in the sample. The hazard rate ratio (HR) for deaths in participants with BMI from 25–<30 kg/m² and 30–<35 kg/m² was 0.80 (95% confidence interval (CI) 0.73–0.88) and 0.79 (95% CI 0.71–0.88), respectively, compared with participants whose BMI was from 18.5–<25 kg/m². Women with WHR >0.8 had a higher rate of mortality (HR 1.16, 95% CI 1.07–1.26) compared to women with WHR ≤ 0.8. No differences in mortality rates were observed by WC. Stratifying by chronic morbidity or smoking status or excluding women with early death and unintentional weight loss did not substantially change these findings.

Conclusion—In frail, older women, having a BMI between 25 and <35 kg/m² or a WHR ≤ 0.8 was associated with lower rates of death. Currently recommended healthy BMI guidelines should be re-evaluated for older women with frailty.

Keywords

frailty; mortality; women’s health; obesity; body mass index

INTRODUCTION

Recent research has raised doubts about the role of obesity on mortality among older adults.¹ Updated guidelines recommend using a body mass index (BMI) of at least 30 kg/m² to identify adults of all ages at elevated risk of mortality from all causes.² However, a meta-analysis of 97 studies with a combined sample size of almost three million adults failed to demonstrate a higher risk of death for adults 65 years of age and older with a BMI above 30 kg/m² relative to those with a BMI of 18.5 to 24.9 kg/m².³

In contrast to BMI, which represents total body fat, indexes of fat distribution such as waist circumference (WC) and waist-to-hip ratio (WHR) might be more pertinent to negative health outcomes associated with excessive adiposity in the general population.^{4,5} Persons with higher WC or WHR have a higher risk of obesity-related morbidity and mortality.^{6–9} Although evidence suggests that higher anthropometric measures were associated with worse health in older persons, the relationship between adiposity indexes and mortality has not been well examined in older adults with physical frailty.

Frailty is a distinct geriatric syndrome with phenotypical representation and etiology of multisystem dysregulation.¹⁰ Frail older adults are at increased risk of disability, morbidity, and mortality compared with non-frail older adults.^{10–12} Yet, it is unclear whether current guidelines and commonly used clinical criteria for BMI, WC and WHR are applicable to these individuals. Studies that investigated the relationship between BMI, frailty and mortality used non-frail participants as a reference category^{11,13}, limiting, thus, the capacity

to understand the impact of BMI and other anthropometric measures among persons with frailty.

To address this gap, we evaluated the association between BMI, WC, and WHR and all-cause mortality in a large cohort of frail only, older women. We hypothesized that overall mortality would be associated with adiposity in frail persons. Because BMI, WC and WHR are indirect indicators of metabolic health, we expected that the rates of mortality would be lower for frail older women with normal adiposity and higher for those with increased adiposity.

METHODS

Study population

The Women's Health Initiative Observational Study (OS) comprised of 93,676 women age 50 to 79 years at baseline (1993–1998) from 40 U.S. clinical centers. Details of the WHI study design and baseline characteristics have been reported elsewhere.¹⁴ The WHI study was approved by the institutional review boards at all 40 clinic sites and all participants provided written informed consent. At baseline and the first follow-up clinic visit, which occurred three years after baseline (1997–2001), OS participants completed questionnaires on medical and psychosocial characteristics and provided anthropometric measures, including BMI, WC, and WHR, which were clinically-assessed by trained medical staff. Because the sample was limited to those characterized as frail, the first follow-up visit was required to define the weight-loss component of frailty phenotype. Thus, the eligible sample were participants aged 65 years and older with a Year 3 clinic visit (n=55,654). Participants with missing data on at least one of the frailty criteria were further excluded (n=12,464). Among those remaining, 11,070 (26%) were characterized as frail and comprised the analytical sample for this study.

Frailty criteria

Frailty was operationally defined congruently with Fried's definition¹⁰ as the presence of three or more of the following five criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss (shrinking). This operationalization was adapted and validated in the WHI¹² and has been extensively used in the WHI OS cohort.^{12,15,16} For each criterion, one or two points were assigned if the participant's assessment was below a criterion-specific cut-point. Points were summed to provide a score ranging from zero to five. A score of three or more was used to characterize a woman as frail.¹⁰ Criteria-specific cut-points were based on the WHI frailty index¹² and were described as follows:

Frailty Criterion	WHI Measure (Point Assignment)
Muscle weakness Slow walking speed	RAND SF-36 Physical Function ¹⁷ score below 75 (2 points)
Exhaustion	RAND SF-36 Vitality ¹⁷ score below 55 (1 point)

Frailty Criterion	WHI Measure (Point Assignment)
Low physical activity	Lowest quartile on the WHI physical activity questionnaire (1 point)
Unintentional weight loss / shrinking	Weight loss >5% at Year 3 from weight at baseline and self-report of non intention to lose five or more pounds in the past 2 years (1 point)

Anthropometric measures

At the Year 3 follow-up visit, trained staff clinically collected anthropometric measurements. Weight to the nearest 0.1 kilogram (kg) and height to the nearest 0.1 centimeter (cm) were measured and used to compute BMI. WC at the natural waist or narrowest part of the torso was measured to the nearest 0.1 cm. Hip measurements were obtained to the nearest 0.5 cm over nonbinding undergarments at the level of the fullest hip circumference. BMI categories were defined according to the NIH/NHLBI¹⁸ classification: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), class I obesity (30–34.9 kg/m²), class II obesity (35–39.9 kg/m²), and class III obesity (>40 kg/m²). A standard clinical definition for central adiposity, defined as WC >88 cm and WHR >0.8 for women, was used.^{2,6,7}

All-cause mortality—Medical updates were collected annually by mail. Participants' deaths were adjudicated by study physicians using hospital records, autopsy or coroner reports, and/or death certificates. Periodic checks of the National Death Index (NDI) for all participants, including those lost to follow-up, were performed. At the time of this analysis, the latest WHI data on mortality were available through December 1, 2013.

Covariates—Baseline data on demographic and health variables, including age, race/ethnicity, family income, highest level of education completed, smoking status (*Never, Past, or Current*), and history of common diseases related to body weight and mortality, such as cancer (excluding non-melanoma skin cancer), diabetes, emphysema, and cardiovascular disease were obtained by self-report. Previous studies have indicated smoking and the abovementioned preexisting conditions confound the relationship between obesity and mortality^{19,20} and were found to be associated with prevalent and incident frailty.¹² Physical activity was assessed at the first follow-up clinical visit by self-report of frequency and duration of walking and mild, moderate, and strenuous activities, with total expenditure of energy calculated in metabolic equivalents (METs).²¹

Statistical approach

The demographic and health behavior characteristics of participants with incomplete criteria to classify frailty were compared with those who had complete data in order to address the possibility of selection bias. For participants with complete frailty data, descriptive characteristics were examined by six BMI categories. Frequencies and means and standard deviations (SD) were estimated for categorical and continuous variables, respectively, and Chi square tests and analysis of variance (ANOVA) and were used to compare distributions across BMI categories. Crude rates of mortality per 1000 person-years by anthropometric indexes were calculated to express a number of deaths. Cox proportional hazards models were used to estimate the association of BMI categories and WC and WHR indexes on the

all-cause mortality rate. Models are reported adjusted for baseline age only and then for baseline age, race/ethnicity, education, income, smoking status, number of frailty criteria, and physical activity. The time-to-event was defined as number of years from WHI Year 3 follow-up visit to death from any cause, with censoring at the last known contact or the date of last available NDI search, whichever occurred later. Because the relationship of BMI on mortality might be distorted by reverse causality of weight loss due to prodromal disease symptoms and inadequate adjustment for the effects of smoking and chronic morbidity,^{22,23} regression models that stratified by the presence or absence of chronic conditions and by smoking status were also performed. A sensitivity analysis that excluded women who died within three years after the Year 3 follow up period was also completed. Since the frailty criteria includes a body-weight-change component, models that excluded participants with unintentional weight loss were also evaluated. Finally, to account for collinearity between central adiposity and BMI, *post hoc* analyses were conducted that examined the association of WHR and WC on mortality at different levels of BMI. WC and WHR indexes were categorized by using currently recommended guidelines and commonly used clinical cutpoints. Shoenfeld residuals were used to test proportionality across BMI and anthropometric measures. Reported *p*-values were two-tailed. Statistical analysis was completed using STATA, version 11.2 (StataCorp, College Station, TX).

RESULTS

Among the eligible sample of WHI-OS participants, 22.4% (n=12,464) had missing data on at least one of the frailty criteria. Compared with participants who had all frailty criteria available, those with missing data were older, less likely to be White, less educated, and more likely to smoke, have diabetes, and be obese (Table S1).

The mean (SD) age at baseline was 72.6 (4.6) years (range: 65–82) among the 11,070 frail women in the sample. At the Year 3 follow-up, one-third of the participants were overweight and 40.1% were obese. (Table 1). Women obese at Year 3 tended to be younger, non-White, have lower family incomes, and have a history of diabetes.

Over a mean follow-up of 11.5 years (range 2.6–18.8), there were 2,911 (26%) deaths from all causes. The mean (SD) age at death was 83.7 (5.9) years. In general, crude rates of death, expressed in number of deaths per 1000 person-years, demonstrated a decrease in mortality with above-normal BMI. The adjusted HR (95% CI) for frail women who were overweight and class I obese was 0.80 (0.73–0.88) and 0.79 (0.71–0.88), respectively, compared to frail women with normal weight. Frail women with a WHR >0.8 had an adjusted HR of 1.16 (95% CI 1.07–1.26) relative to those who had a WHI 0.8. The rate of mortality did not differ between those with WC >0.88 and those with lower WC (Table 2).

Frail underweight women with chronic morbidity had a 2.4-fold higher rate (95% CI 1.78–3.03) of death relative to frail normal weight women. In contrast, the relative rate ratio was 1.16 (95% CI 0.68–1.98) for underweight women without chronic morbidity. When chronic morbidity was present, women with class I obesity had an HR (95% CI) of 0.85 (0.74–0.98) relative to normal weight women, but this rate was lowered further when chronic morbidity was absent (HR 0.69, 95% CI 0.58–0.83). Relative to normal weight women, overweight

and class I and class II obese women had lower rates of death if they were ever smokers (Table 3), but among never smokers, this protection only remained for overweight and class I obese women. In our sensitivity analysis, we found that excluding those who died within 3 years after the Year 3 follow-up visit or those who experienced unintentional weight loss did not substantially change the estimates.

Figure 1 A illustrates that frail overweight and class I obese women with WC >88 cm had a higher rate of mortality compared with overweight and women with class I obesity who had WC ≤ 88 cm (HR 1.24, 95% CI 1.08–1.41 and HR 1.55, 95% CI 1.11–2.15, respectively). Frail normal and overweight women with WHR >0.8 had higher rates of death (HR 1.27, 95% CI 1.10–1.41 and HR 1.36, 95% CI 1.16–1.58, respectively) compared with the counterpart women who had WHR ≤ 0.8.

DISCUSSION

Over an average 11.5 years of study follow-up, frail older women who were overweight or class I obese had a lower rate of all-cause mortality compared with frail women of normal weight. Differences in mortality rates in women with class II and class III obesity were not observed, likely because of lower power in these subgroups, and those analyses should be repeated in a larger population of frail older women with morbid obesity. In contrast, frail women with higher WHR (>0.8) had higher rates of death compared to those with lower WHR (≤ 0.8), while mortality rates did not differ when comparing women with higher WC (>0.88 cm) to those with lower WC (≤ 0.88 cm).

To our knowledge, this is the first study to evaluate the association of a variety of anthropometric measures on all-cause mortality in a sample of only frail, older adults. Most studies have examined these relationships in non-frail, older adults. A study using WHI data reported that obese women had higher odds of dying before reaching age 85 years compared to normal weight women.²⁴ A meta-analysis of 32 studies examining adults aged 65 years and older reported a U-shaped relationship between BMI and mortality, with the lowest hazard rates among those whose BMI was between 24 and 31 kg/m² and with rates progressively rising for those with BMI >33 kg/m².¹ A few studies that examined the relationship of BMI and mortality compared frail to non-frail older adults. The Study of Osteoporotic Fractures in older women showed that frailty impacts mortality across all categories of BMI. However examination of the tables reported in the manuscript indicated that the impact of frailty on mortality tends to be less pronounced for overweight and obese women.¹¹ Another study by Lee and colleagues (2014) showed that obesity in persons with frailty was associated with increased rates of death when compared with non-frail individuals of normal weight. These findings however should be interpreted in light of the type of reference group used. Both studies used non-frail participants as the comparison category, which allowed for testing of effect modification by frailty status, rather than examining impact of BMI on mortality in those with frailty.

Consistent with our results, most studies in community-dwelling adults reported that WHR was a sensitive indicator of increased central adiposity and was associated with higher mortality risks.^{4,5} In a meta-analysis that included more than 58,000 older adults higher

rates of death among overweight and obese women with WC > 88 cm⁸ were also observed. Likewise, several reports indicated an association between WC > 88 cm and higher mortality in a subset of older and younger participants with normal BMI.^{8, 25} Pending further research one caution interpretation is that an increased visceral adiposity or body shape with, to a some extent, lower trunk adiposity, may confer additional risk for mortality in those with frailty.

Stratifying by chronic morbidity, smoking status or excluding women with early death and unintentional weight loss did not substantially change our results. Although some suggested that the relationship of BMI on mortality might be influenced by reverse causality of weight loss due to pre-clinical symptoms and inadequate adjustment for the effects of smoking and chronic morbidity,^{22,23} our sensitivity analyses were consistent with primary models further reinforcing the validity of the findings.

Excessive central adiposity increased the rates of all-cause mortality across most of the BMI categories, although the magnitude of the effect varied by BMI category. This suggests that body shape and fat distribution might have a different pathology for normal weight, overweight and obese women. This conclusion resonated in other studies that showed increased mortality risk for older adults with an increased WC or WHR measures across normal weight, overweight and obese BMI categories.^{8,25}

There are several possible methodological explanations for our findings. The first is misclassification of BMI cut-points as the best weight-for-height indicator. In older populations, BMI cut-points may be less sensitive to predict future morbidity and mortality than those seen in younger adults.²⁶ As older adults' body composition changes toward a decrease in lean tissue and height and an increase in fat tissue, the use of BMI may be an inherently biased proxy of overall obesity.²⁷ Older adults have, on average, more fat than younger adults at any BMI, due to a loss of muscle mass with age. As a result, the sensitivity of BMI cut-points with respect to body fatness decreases with age, and the use of a fixed cut-point for all ages results in misclassification bias.²⁸ The combination of increased fat mass and decreased lean body mass in frail older adults is especially pronounced,²⁹ rendering the frail population more susceptible to this misclassification bias. Importantly, this non-differential misclassification bias can only lead to underestimation of the true strength of the associations.

A second explanation may be "survival effect." Individuals who are susceptible to the complications of obesity may have died at a younger age, and overweight and obese individuals who survive to old age may have characteristics that protect them from the adverse effects of being overweight or obese.²⁷

A third explanation is reverse causation.²² Unintentional weight loss caused by unrecognized systemic illness can lead to a misclassification of the mortality risk of the "healthy" weight reference group, thereby making the obese group seemingly protected.²⁷ To address this potential concern, we repeated the analysis excluding frail women who died within 3 years of follow-up and the results did not change. Thus, reverse causation is less likely to explain our findings.

Finally, confounding factors, most importantly smoking status, were also considered in our multivariate models. Since smokers are thinner³⁰ and have increased risk for mortality, residual confounding of smoking may make obese groups seem protected. However, restricting the analysis to never-smokers did not reverse the lower risks observed among those with class I obesity.

Others researchers have hypothesized a causal protective association between excessive weight and lower mortality^{31–33}. Specifically, overweight and obesity may benefit older adults by exerting a favorable effect on cognitive function,³¹ protecting against osteoporotic fractures,³² and serving as an energy reserve against protein-energy malnutrition.³³ The last assertion might be particularly pertinent to frail, older adults because higher protein consumption, as a fraction of total energy, has been associated with a strong, independent, dose-responsive favorable effect on functioning in older women.¹⁵ Thus, pending further research, a cautious interpretation of these results is that salutary effects of overweight and obesity on long-term mortality in older frail female populations might be channeled through anabolic processes.

The strengths of this study include the large sample size of frail older women, the use of well-validated frailty criteria, the use of objectively assessed anthropometric measures, and a long study follow-up with adjudicated mortality protocols. The long follow-up is important since many years of obesity are required to induce harmful effects on health, and studies with a short follow-up may not sufficiently demonstrate an association between obesity and mortality.³⁴ We were also able to adjust for important potential confounders including a measure of physical activity, which has been demonstrated to moderate the relationship between body mass and functional impairment³⁵ and adiposity and mortality.³⁶

Our study has limitations. Lack of objective physical performance measures in the operationalization of frailty is a likely weakness of the WHI frailty index. Although the RAND-36 physical function scores is a valid measure¹⁷, it has been shown to have low to moderate correlation compared with objectively measured values.¹² As with any observational study, there exists the possibility of residual and unmeasured confounding. Given a preponderance of White women participants, our results may not be widely generalizable. We were unable to classify frailty in nearly a quarter of our eligible sample. Women with these missing data were older, had poorer health, and were more likely to be obese. While it is unclear how many of these women would have been regarded as frail, in light of these differences, the results should be interpreted conservatively since they might represent an overestimation of the associations. Furthermore, although our results might provide preliminary insights into the association of total and central adiposity indexes with mortality, biological validity of the findings in the context of direct measures of body composition and their effects on health outcomes in frail population have not been thoroughly examined. In the general population, body adiposity indexes and percentage body fat are highly related³⁷ and show consistency in the context of attributable fractions of death,³⁸ but these associations have not been established in those with frailty. Finally, change in adiposity over time rather than single occasion measures might provide more nuanced information on whether the risk of developing adverse outcomes is greater or less for frail persons with distinct longitudinal dynamics in body composition measures.

In conclusion, overweight and obesity may be associated with lower rates of all-cause mortality in frail, older women. Currently recommended guidelines for a healthy BMI range might not be suitable for older women with frailty and weight management recommendations should account for older adults' functional and physiological status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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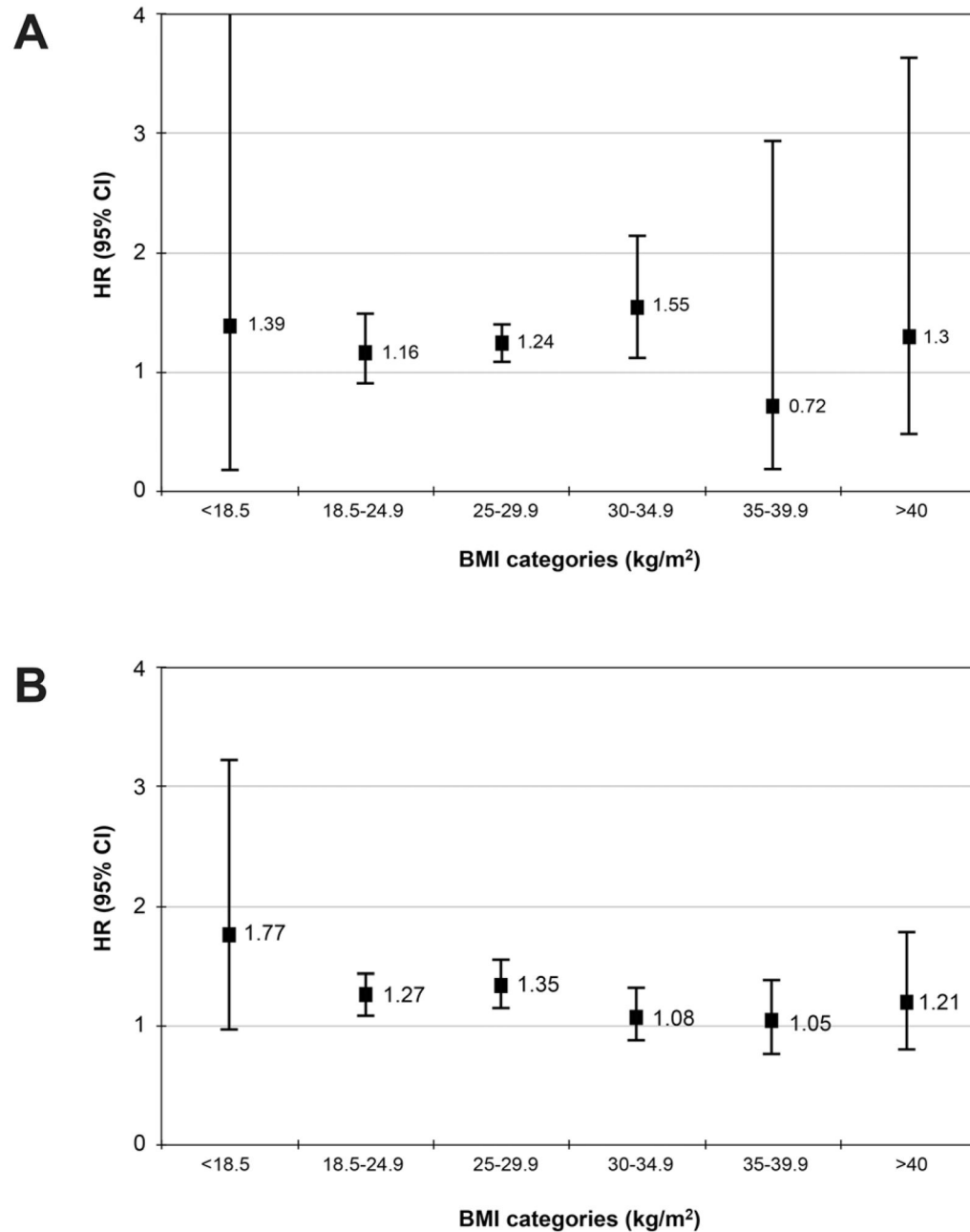


Figure 1.

Hazard ratios and 95% confidence intervals for all-cause mortality among frail Women's Health Initiative Observational Study participants by body mass index category and according to (A) waist circumference 88cm (reference) vs. > 88 cm; (B) waist-to-hip ratio 0.8 (reference) vs. > 0.8. Models adjusted for age, race/ethnicity, education, income, number of frailty criteria, smoking status and physical activity. Frailty was operationally defined as the presence of three or more of the following five criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss.

Table 1

Baseline and Year 3 Characteristics of Frail WHI OS Participants (N = 11,070), by Body Mass Index (BMI in kg/m²) Category

Characteristic	BMI category ^a					
	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0
No. of participants	143	2,714	3,702	2,581	1,163	690
Age, in y ^{a,h}	74.1 (4.3)	73.5 (4.6)	72.9 (4.5)	72.1 (4.4)	71.4 (4.3)	70.1 (4.1)
BMI, kg/m ² ^a	17.2 (1.1)	22.6 (1.6)	27.4 (1.4)	32.2 (1.4)	37.2 (1.4)	44.8 (4.9)
White, n (%) ^{b,h}	115 (80.4)	2,402 (89.0)	3,177 (86.1)	2,183 (84.7)	972 (84.0)	548 (79.5)
Education, n (%) ^{b,h}						
Some School	46 (32.2)	992 (36.7)	1,488 (40.5)	1,119 (43.7)	518 (44.9)	341 (49.6)
Some College	61 (42.7)	1,026 (38.0)	1,358 (37.0)	908 (35.4)	387 (33.6)	220 (32.0)
Some Graduate	36 (25.2)	683 (25.3)	828 (22.5)	536 (20.9)	248 (21.5)	126 (18.3)
Income, n (%) ^{b,h}						
<\$20,000	46 (34.1)	585 (22.5)	901 (25.5)	686 (27.6)	323 (28.7)	210 (31.3)
\$20,000–\$50,000	56 (41.5)	1,283 (49.3)	1,734 (49.0)	1,248 (50.2)	596 (53.0)	330 (49.1)
>\$50,000	33 (24.4)	733 (28.2)	902 (25.5)	552 (22.2)	205 (18.2)	132 (19.6)
No. of frailty criteria, n (%) ^{a,c,h}						
3	57 (39.9)	1,590 (58.6)	2,293 (61.9)	1,498 (58.0)	629 (54.1)	332 (48.1)
4	57 (39.9)	907 (33.4)	1,249 (33.7)	1,011 (39.2)	490 (42.1)	346 (50.1)
5	29 (20.3)	217 (8.0)	160 (4.3)	72 (2.8)	44 (3.8)	12 (1.7)
Smoking status, n (%) ^{a,h}						
Never	66 (47.5)	1,393 (52.2)	1,885 (51.6)	1,307 (51.3)	620 (54.1)	347 (51.0)
Past	51 (36.7)	1,037 (38.8)	1,538 (42.1)	1,107 (43.4)	489 (42.7)	301 (44.2)
Current	22 (15.8)	241 (9.0)	228 (6.2)	136 (5.3)	37 (3.2)	33 (4.9)
Physical activity, MET ^{a,h}	6.0 (11.9)	6.7 (9.6)	6.1 (9.5)	5.0 (8.0)	4.4 (8.2)	3.8 (7.7)
Cancer, n (%) ^b	29 (20.4)	477 (17.7)	599 (16.3)	445 (17.4)	186 (16.2)	106 (15.5)
Cardiovascular disease, n (%) ^b	59 (42.8)	867 (32.7)	1,163 (32.3)	772 (30.6)	366 (32.2)	212 (31.7)
Diabetes, n (%) ^{b,h}	4 (2.8)	106 (3.9)	225 (6.1)	223 (8.7)	152 (13.1)	110 (15.9)
Emphysema, n (%) ^{b,h}	28 (20.1)	256 (9.6)	235 (6.5)	171 (6.8)	83 (7.3)	50 (7.5)

Characteristic	BMI category ^a					
	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0
WC, cm ^{g,h}	65.7 (5.8)	76.7 (6.9)	87.8 (7.2)	97.7 (8.0)	107 (8.7)	117.0 (12.3)
WC >88 cm, n (%) ^{a,h}	2 (1.4)	177 (6.6)	1,773 (48.4)	2,306 (90.2)	1,138 (99.3)	959 (98.0)
WHR ^{g,h}	0.77 (0.1)	0.80 (0.1)	0.84 (0.1)	0.86 (0.1)	0.86 (0.1)	0.86 (0.1)
WHR > 0.8, n (%) ^{a,h}	38 (27.5)	1,257 (47.0)	2,511 (68.7)	1,996 (78.2)	913 (80.0)	524 (78.3)
Frailty criteria ^{a,c}						
Poor physical function ^{d,h} , n (%)	137 (95.8)	2,671 (98.4)	3,666 (99.0)	2,567 (99.5)	1,160 (99.7)	689 (99.9)
Exhaustion ^e , n (%)	102 (71.3)	2,059 (75.9)	2,762 (74.6)	1,947 (75.4)	878 (75.5)	524 (75.9)
Low physical activity ^{f,h} , n (%)	86 (60.1)	1,373 (50.6)	2,045 (55.2)	1,584 (61.4)	770 (66.2)	500 (72.5)
Weight loss ^{g,h} , n (%)	82 (57.3)	709 (26.1)	536 (14.5)	233 (9.0)	99 (8.5)	38 (5.5)

Notes: BMI = body mass index; CI = confident interval; WC = Waist circumference; WHI OS = Women's Health Initiative Observation Study; MET = metabolic equivalent task; WHR = waist-to-hip ratio.

^a Measured at Year 3 WHI OS follow up

^b Measured at WHI OS baseline

^c Frailty was operationally defined as the presence of three or more of the following five criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss. To align the scoring with conventional frailty measure, poor physical function was scored as 2 points because the scale indicated both muscle strength and walking ability components

^d The RAND-36 Physical Function scale scores below 75.

^e The RAND-36 Vitality scale below 55.

^f The lowest quartile on the WHI physical activity questionnaire.

^g Weight loss > 5% between Year 3 and baseline, and "yes" to the question "in the past two years, did you lose five or more pounds not on purpose at any time?"

^h $p < 0.001$ based on ANOVA analysis for continuous measures and chi square for categorical

Table 2

Association of BMI with All-Cause Mortality in Frail^d WHI OS Participants

Characteristic	Crude rates per 1000 pr-yr	Model 1 ^a HR (95% CI)	p value	Model 2 ^b HR (95% CI)	p value
N = 10,977					
BMI category, n (%)					
Underweight (<18.5 kg/m ²)	51.24	2.17 (1.69–2.78)	<0.001	1.91 (1.48–2.47)	<0.001
Normal weight (18.5–24.9 kg/m ²)	27.82	1.00		1.00	
Overweight (25.0–29.9 kg/m ²)	21.12	0.75 (0.69–0.83)	<0.001	0.80 (0.73–0.88)	<0.001
Class I Obesity (30.0–34.9 kg/m ²)	19.21	0.73 (0.66–0.81)	<0.001	0.79 (0.71–0.88)	<0.001
Class II Obesity (35.0–39.9 kg/m ²)	21.38	0.88 (0.76–1.00)	0.05	0.93 (0.81–1.07)	0.28
Class III Obesity (>40.0 kg/m ²)	20.59	0.96 (0.81–1.13)	0.87	1.01 (0.85–1.21)	0.86
N = 10,910					
Waist categories					
88 cm	24.10	Ref	Ref	Ref	Ref
>88 cm	21.42	0.98 (0.91–1.06)	0.63	1.02 (0.94–1.09)	0.69
N = 10,885					
Waist-to-hip ratio					
0.8	20.83	Ref	Ref	Ref	Ref
>0.8	23.45	1.18 (1.09–1.28)	<0.001	1.16 (1.07–1.26)	<0.001

Notes: pr-yr= person years; BMI = body mass index; CI = confident interval; HR = hazard ratio; Ref = Reference.

^a Adjusted for age.

^b Adjusted for age, race, education, income, number of frailty criteria, smoking status, and physical activity

^c Hazard ratios per standard deviation increase.

^d Frailty was operationally defined as the presence of three or more of the following five criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss.

Table 3
Subgroup analysis of the Association of BMI with All-Cause Mortality in Frail^e WHI OS Participants ^a

Characteristic	BMI category (in kg/m ²) HR (95% CI)					
	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40
Free of selected chronic conditions ^b (n = 4,981)	1.16 (0.68–1.98)	Ref	0.79 (0.68–0.92)	0.69 (0.58–0.83)	0.95 (0.75–1.19)	1.09 (0.83–1.43)
Not free of selected chronic conditions ^b (n = 4,961)	2.42 (1.78–3.03)	Ref	0.79 (0.69–0.90)	0.85 (0.74–0.98)	0.84 (0.70–1.01)	0.95 (0.76–1.19)
Never smoker (n = 5,330)	1.60 (1.05–2.44)	Ref	0.83 (0.72–0.96)	0.80 (0.68–0.94)	1.01 (0.83–1.23)	1.12 (0.87–1.44)
Ever smoker (n = 4,965)	2.23 (1.61–3.08)	Ref	0.75 (0.66–0.86)	0.74 (0.64–0.86)	0.79 (0.65–0.96)	0.86 (0.68–1.09)
Excluding early death ^c (n = 10,064)	1.73 (1.28–2.32)	Ref	0.78 (0.71–0.87)	0.80 (0.71–0.89)	0.87 (0.75–1.01)	1.04 (0.87–1.25)
Frailty without weight loss criteria ^d (n = 8,698)	1.35 (0.86–2.15)	Ref	0.79 (0.70–0.88)	0.77 (0.67–0.87)	0.95 (0.82–1.11)	1.02 (0.85–1.23)

Notes: BMI = body mass index; CI = confident interval; WHI OS = Women's Health Initiative Observation Study.

^a Adjusted for age, race/ethnicity, education, income, number of frailty criteria, smoking status and physical activity

^b Cancer, emphysema, cardiovascular disease, diabetes.

^c Death within 3 years of this study follow up

^d Excluding those who screened positively for weight loss.

^e Frailty was operationally defined as the presence of three or more of the following five criteria: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss.