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Relation of body fat mass and fat-free mass to total mortality: results from 7 prospective cohort studies

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ABSTRACT

Background: Fat mass and fat-free mass may play independent roles in mortality risk but available studies on body composition have yielded inconsistent results.

Objective: The aim was to determine the relations of body fat mass and fat-free mass to risk of mortality.

Methods: In pooled data from 7 prospective cohorts encompassing 16,155 individuals aged 20 to 93 y (median, 44 y), we used Cox regression and restricted cubic splines to estimate HRs and 95% CIs for the relation of body composition, measured by bioelectrical impedance analysis, to total mortality. We adjusted for age, study, sex, ethnicity, history of diabetes mellitus, education, smoking, physical activity, and alcohol consumption.

Results: During a median follow-up period of 14 y (range, 3–21 y), 1347 deaths were identified. After mutual adjustment for fat mass and fat-free mass, fat mass showed a J-shaped association with mortality (overall P value < 0.001; P for nonlinearity $= 0.003$). Using a fat mass index of 7.3 kg/m^2 as the reference, a high fat mass index of 13.0 kg/m^2 was associated with an HR of 1.56 (95% CI: 1.30, 1.87). In contrast, fat-free mass showed an inverse association with mortality (overall P value < 0.001; P for nonlinearity $= 0.001$). Compared with a low fat-free mass index of 16.1 kg/m^2, a high fat-free mass of 21.9 kg/m^2 was associated with an HR of 0.70 (95% CI: 0.56, 0.87).

Conclusions: Fat mass and fat-free mass show opposing associations with mortality. Excess fat mass is related to increased mortality risk, whereas fat-free mass protects against risk of mortality. These findings suggest that body composition provides important prognostic information on an individual's mortality risk not provided by traditional proxies of adiposity such as BMI. *Am J Clin Nutr* 2021;113:639–646.

Keywords: obesity, body composition, fat mass, fat-free mass, mortality

Introduction

The association between BMI and mortality has been extensively examined, and most studies show that people with high or low BMI die earlier than participants with intermediate levels of relative weight (1). The main limitation of BMI as a predictor of mortality is that it cannot differentiate between fat mass and fat-free mass. In fact, several studies have shown that the association between BMI and total mortality could be disentangled into a J-shaped association between fat mass index (fat mass/height^2)

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The Cooperative Health Research in the Region Augsburg (KORA) was initiated and financed by the Helmholtz Zentrum München (German Research Center for Environmental Health), which is funded by the German Federal Ministry of Education and Research (BMBF) and by the state of Bavaria. The Study of Health in Pomerania (SHIP) is part of the Community Medicine Net (http://www.medizin.uni-greifswald.de/cm) of the University of Greifswald, which is funded by grants from the German Federal Ministry of Education and Research (BMBF; grant 01ZZ0403); the Ministry for Education, Research, and Cultural Affairs; and the Ministry for Social Affairs of the Federal State of Mecklenburg, West Pomerania.

Supplemental Figures 1–4 and Supplemental Tables 1–10 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

The NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is part of the US CDC.

Abbreviations used: AIC, Akaike's Information Criterion; BIA, bioelectrical impedance analysis; ICD, International Classification of Diseases; KORA, Cooperative Health Research in the Region Augsburg; SHIP, Study of Health in Pomerania.

Received July 15, 2020. Accepted for publication October 22, 2020.

First published online January 12, 2021; doi: https://doi.org/10.1093/ajcn/nqaa339.

and mortality and a reverse J-shaped association between fat-free mass index (fat-free mass/height^2) and mortality, with a tendency to level off for high fat-free mass values (2–7). Although these findings were first demonstrated >20 y ago (5, 7), body composition is still of great clinical and public health relevance because excess fat mass and inadequate fat-free mass represent important risk factors for the development of major chronic diseases (8, 9). Identifying the aspect of body composition relevant to mortality is essential to developing targeted and effective interventions. For example, fat mass can be decreased by energy restriction and endurance exercise, while loss of fat-free mass can be prevented by resistance exercise.

A number of epidemiologic studies investigated the relation of body composition to mortality in the general population, but the overall evidence is mixed (10). Potential explanations for inconsistent findings across previous studies include variation in follow-up periods, heterogeneity in the level of control for confounding, and divergence in the precision of determining the shape of the body composition and mortality relation due to differences in the number of mortality cases.

We therefore comprehensively examined the relation of body composition to total mortality in an individual-level pooled analysis of 7 prospective cohort studies. We assessed whether body fat mass improves the ability of BMI to predict the risk of mortality. We also systematically addressed potential selection bias, reverse causation, and confounding. We used bioelectrical impedance analysis (BIA) as a valid, simple, and noninvasive method to measure fat mass and fat-free mass (11).

Methods

Study population

We utilized data from 3 population-based studies encompassing 7 prospective cohorts. The Cooperative Health Research in the Region Augsburg (KORA) study was established in Germany in 1996 as an expansion of the WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) project (12). BIA was conducted in individuals aged 25 to 74 y in 2 independent cohorts in 1994–1995 (n = 4856; response: 75%) and 1999–2001 (n = 4261; response: 67%) (13). The Study of Health in Pomerania (SHIP) was established in Germany in 1997 (14). BIA was carried out in persons aged 20 to 79 y in 2 independent cohorts in 2008 (n = 2333; response: 63%; and n = 4420; response: 50%). The NHANES examines an independent sample of ~5000 US individuals annually (15). BIA was administered to eligible participants aged 8 to 49 y in 3 cohorts in 1999–2000 (n = 9282; response: 76%), 2001–2002 (n = 10,477; response: 80%), and 2003–2004 (n = 9643; response: 76%).

All studies were approved by local ethics committees and all study participants provided written informed consent.

For the current analysis, participants were excluded if they were under 20 y of age; had incomplete data on anthropometric exposure, outcome, or covariate data; had implausible follow-up time values; withdrew their consent; or had prevalent cardiovascular disease or cancer. The final analytic sample comprised 16,155 individuals (8033 men, 8122 women; **Supplemental Figure 1**).

Assessment of fat mass and fat-free mass

In all 7 cohorts, certified study personnel conducted standardized computer-assisted face-to-face interviews, during which information was collected on sociodemographic variables, lifestyle factors, personal and family history of chronic diseases, and medication use (12–15). Participants also underwent clinical examinations, during which anthropometric measures were assessed. In KORA, BIA was conducted using the Body Composition Analyzer TVI-10 (Danziger Medical Technology) and the B.I.A.-2000-S Analyzer (Data Input). SHIP used the Nutriguard-M Analyzer (Data Input) and NUTRI4 software (Data Input). NHANES utilized the HYDRA ECF/ICF Bio-Impedance Spectrum Analyzer (model 4200; Xitron Technologies, Inc.). In all cohorts, fat-free mass was calculated as follows:

$$FFM(kg) = A \cdot \left(\frac{height^2}{resistance}\right) + (B \cdot weight) - (C \cdot age) + (D \cdot sex) \quad (1)$$

where A, B, C, and D are constants specific to manufacturers and devices (16). This equation best reflects the influences of age and sex in each study population and was modified where necessary. In all cohorts, tetrapolar BIA was performed while participants lay in a supine position. Although a study showed that BIA overestimated fat-free mass from 3.4 to 8.3 kg and underestimated fat mass from 2.5 to 5.7 kg in comparison to reference methods such as DXA (17), it provides more detailed information on body composition in large-scale studies than do simple anthropometric measures.

Fat mass was calculated by subtracting fat-free mass (kg) from weight (kg). Fat mass index was calculated as fat mass (kg) divided by height in meters squared (kg/m^2). Fat-free mass index was calculated as fat-free mass (kg) divided by height in meters squared (kg/m^2). BMI was calculated as body weight (kg) divided by height in meters squared (kg/m^2). Body weight was measured in light clothing to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm.

Ascertainment of mortality cases

In KORA, mortality was ascertained by regularly checking the vital status of study participants through population registries, and information on cause of death was provided by death certificates obtained from the local health authorities until 31 December 2016. The underlying cause of death was coded using the International Classification of Diseases (ICD), 9th revision (ICD-9). In SHIP, information on vital status was collected from population registries at annual intervals from time of enrollment into the study through 31 December 2015. Death certificates were requested from local health authorities and were coded according to the International Classification of Diseases, 10th revision (ICD-10). In NHANES, verification of vital status was provided by regular linkage of the cohorts to the National Death Index, a centralized database of US death records gathered from states' vital statistics offices (18). Mortality follow-up data were available from the date of survey participation through 31 December 2015. Coding for deaths followed ICD-10 guidelines.

Statistical analysis

Data preparation for all variables was performed consistently in all cohorts. Age-adjusted baseline characteristics of the combined study sample across sex-specific quartiles of fat mass and fat-free mass were calculated by direct standardization to the baseline age distribution of the study population. Pearson's correlation coefficient was used to determine the strength of associations between the main anthropometric variables.

HRs and 95% CIs were estimated using Cox proportional hazards regression with age as the underlying time metric. Follow-up time was calculated from the date of the baseline examination until death from any cause, the end of follow-up (31 December 2015 for SHIP and NHANES; 31 December 2016 for KORA), or loss to follow-up, whichever came first. Covariates were chosen using the disjunctive cause criterion (19). The final model included terms for sex (men/women), cohort (1/2/3/4/5/6/7), ethnicity (non-Hispanic White/Mexican American/non-Hispanic Black/other Hispanic/other ethnicity), baseline history of diabetes (yes/no), educational attainment (low/high), smoking (never/former/current), physical activity (yes/no), and alcohol intake (continuous). We mutually adjusted for fat mass and fat-free mass to estimate the independent effects of those variables.

To assess potential nonlinear associations between body composition and mortality and to capture variation in risk across the entire continuum of the relations, we used restricted cubic splines with 4 knots placed at the 5th, 35th, 65th and 95th quantiles. As suggested by Harrell (20), 4 knots offer an adequate fit of the model and represent a good compromise between flexibility and loss of precision. Reference points for fat mass index were set at 7.3 kg/m^2 and for fat-free mass index at 16.1 kg/m^2 using the mean values of sex-specific quartiles. In addition, data were winsorized at 1% and 99% to reduce the potential impact of outliers. We calculated overall *P* values across fat mass and fat-free mass values using a Wald test. Effect modification of the body composition and mortality relation by sex was evaluated using a likelihood ratio test. In a separate analysis, we disregarded the first 4 y of follow-up to address potential reverse causation.

To examine whether a particular cohort may have influenced the pooled risk estimates, we calculated HRs for each cohort separately and performed a fixed-effects meta-analysis of the individual studies. Heterogeneity across the study-specific estimates was quantified using the I^2 statistic (21). We also tested whether the associations of fat mass and fat-free mass with mortality varied by age or smoking status. To verify the robustness of our assumptions, in a sensitivity analysis we applied chained-equation multiple imputation to covariables with missing values (22). We repeated the procedure for 5 cycles to produce a single imputed dataset, and the whole procedure was repeated 10 times. Non–normally distributed continuous variables were imputed with predictive mean matching (23).

In a sensitivity analysis, we estimated the E-value, a measure that quantifies the minimum strength of association that an unmeasured confounder would need to have with the exposure and the outcome to explain the observed relation (24). For a better visual comparison of the results, all body composition indices and their relations to mortality were placed simultaneously in one figure. We created *z*-scores by subtracting the mean of all values from each individual data point and then dividing those data points by the SD of all values. Akaike's Information Criterion (AIC), the likelihood ratio test, and Harrell's Concordance Index were used to determine whether body fat mass adds to the prediction of mortality after considering BMI (20). The baseline model included BMI, sex, ethnicity, study, history of diabetes mellitus at baseline, education, smoking, physical activity, and alcohol consumption and was extended by fat mass in a second step.

All statistical tests were 2-sided and *P* values <0.05 were considered statistically significant. Analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, 2020).

Results

During a median follow-up time of 14.3 y (192,557 person-years), we documented 1347 deaths. Participants with low fat mass tended to have higher educational levels, be more physically active, and be less likely to have a history of diabetes than those with high fat mass (**Table 1**). In contrast, participants with low fat-free mass were more likely to currently smoke, consume higher amounts of alcohol, and be physically inactive than those with high fat-free mass. Additional information about baseline characteristics in the individual cohorts is available in **Supplemental Tables 1–8**.

Fat mass index and fat-free mass index were only weakly correlated with one another ($r = 0.171$). By comparison, BMI was highly correlated with both fat mass index ($r = 0.813$) and fat-free mass index ($r = 0.710$). AIC ($AIC_{model\ 1} = 19{,}313.64$; $AIC_{model\ 2} = 19{,}306.11$), the likelihood ratio test ($P = 0.002$), and Harrell's Concordance Index (C-$index_{model\ 1} = 0.414$; C-$index_{model\ 2} = 0.439$) indicated that fat mass showed prognostic values exceeding that of BMI (**Supplemental Table 9**).

We detected no differences in the relations of fat mass and fat-free mass to mortality between sexes (*P* values for interaction by sex = 0.337 for fat mass and 0.301 for fat-free mass). Therefore, all analyses are presented using sexes combined. We observed a J-shaped association between fat mass and mortality, with the greatest hazard seen for the highest fat mass level (overall $P < 0.001$; *P* for nonlinearity = 0.003). Using the mean of the second quartile of 7.3 kg/m^2 as the fat mass index reference value, participants with a high fat mass index of 13.0 kg/m^2 showed an HR of 1.56 (95% CI: 1.30, 1.87). By comparison, a low fat mass index of 5.2 kg/m^2 was associated with an HR of 1.08 (95% CI: 0.96, 1.20) (**Table 2** and **Figure 1**).

In contrast, mortality risk decreased with increasing fat-free mass levels, with a slight weakening of the association at the highest fat-free mass levels (overall $P < 0.001$; *P* for nonlinearity = 0.001). Compared with a low fat-free mass index of 16.1 kg/m^2, participants with a high fat-free mass index of 21.9 kg/m^2 showed a decreased HR of 0.70 (95% CI: 0.56, 0.87) (Table 2 and Figure 1).

When we repeated our main analyses after excluding the initial 4 y of follow-up, point estimates and risk functions were largely unchanged. Compared with the reference point of 7.3 kg/m^2, a high fat mass index of 13.0 kg/m^2 showed an HR of 1.52 (95% CI: 1.24, 1.86) (Table 2). In contrast, compared with a low fat-free mass index of 16.1 kg/m^2, a

TABLE 1 Age-standardized baseline characteristics of participants according to sex-specific quartiles of fat mass index and fat-free mass index in KORA 1994/1995, KORA 1999/2001, NHANES 1999/2000, NHANES 2001/2002, NHANES 2003/2004, SHIP-2 2008/2012, and SHIP-Trend 2008/2012[1]

	Fat mass index				Fat-free mass index			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
n (%)	4133 (25.6)	4004 (24.8)	4034 (25.0)	3984 (24.7)	4108 (25.4)	3970 (24.6)	4063 (25.2)	4014 (24.8)
Age, mean ± SD, y	39.7 ± 13.1	45.0 ± 14.0	48.6 ± 14.1	49.2 ± 14.5	40.5 ± 13.5	45.4 ± 14.0	48.1 ± 14.4	48.3 ± 14.4
Sex, %								
Men	49.3	50.0	49.9	48.9	50.1	50.7	50.3	50.6
Women	50.7	50.0	50.1	51.1	49.9	49.3	49.7	49.4
Anthropometric variables, mean ± SD								
Fat mass index, kg/m^2	5.2 ± 1.2	7.3 ± 1.2	9.2 ± 1.7	13.0 ± 3.2	6.8 ± 2.2	7.7 ± 2.4	8.8 ± 2.9	11.2 ± 4.4
Fat-free mass index, kg/m^2	17.5 ± 2.7	18.0 ± 2.6	18.8 ± 2.6	20.5 ± 2.6	16.1 ± 1.8	17.8 ± 1.7	19.2 ± 1.8	21.9 ± 2.3
BMI, kg/m^2	22.7 ± 2.4	25.3 ± 2.2	28.0 ± 2.2	33.6 ± 4.0	22.9 ± 2.4	25.5 ± 2.4	28.0 ± 2.7	33.1 ± 4.4
Body fat mass, kg	14.6 ± 3.3	20.7 ± 2.7	26.1 ± 3.6	36.8 ± 8.5	19.6 ± 6.1	21.8 ± 6.5	24.7 ± 7.8	31.4 ± 12.0
Body weight, kg	65.4 ± 11.0	72.8 ± 11.1	80.4 ± 11.4	95.6 ± 14.5	66.4 ± 11.0	73.3 ± 11.3	80.1 ± 12.2	94.2 ± 15.6
Ethnicity, %								
Mexican-American	4.1	5.8	8.1	9.9	6.6	5.0	6.0	9.0
Other Hispanic	1.0	1.0	1.4	1.6	1.3	0.7	1.2	1.9
Non-Hispanic White	89.5	88.8	84.5	78.1	85.1	90.4	88.2	78.7
Non-Hispanic Black	4.2	3.4	5.1	9.4	5.4	3.3	3.9	9.3
Other ethnicity	1.2	0.9	0.9	1.0	1.7	0.6	0.6	1.0
Education,[2] %								
Low	31.0	37.8	44.1	48.7	40.3	40.0	42.0	42.2
High	69.0	62.2	55.9	51.3	59.7	60.0	58.0	57.8
Physical activity, %								
No physical activity	32.3	38.0	42.7	50.1	43.3	41.1	40.9	40.6
Physical activity	67.7	62.0	57.3	49.9	56.7	58.9	59.1	59.4
Smoking, %								
Never	42.0	43.8	45.6	46.7	42.9	43.4	44.3	45.8
Former	25.6	27.9	27.6	29.3	25.4	28.5	28.2	29.0
Current	32.4	28.2	26.8	24.1	31.7	28.1	27.5	25.2
Alcohol intake, mean ± SD, g/d	8.7 ± 16.3	9.9 ± 16.9	11.2 ± 19.8	9.6 ± 18.5	12.4 ± 19.6	11.7 ± 19.0	9.7 ± 17.8	7.1 ± 15.9
Diabetes mellitus, %	3.6	3.8	4.3	8.8	2.3	3.1	4.3	10.0

[1] Age-standardization was obtained via direct standardization to the baseline age distribution of the analytic cohort. Sex-specific quartiles of fat mass index were defined by their distribution (25th quantile, median, 75th quantile); for men: 25th quantile = 5.40 kg/m^2, median = 6.90 kg/m^2, 75th quantile = 8.60 kg/m^2; for women: 25th quantile = 7.30 kg/m^2, median = 9.40 kg/m^2, 75th quantile = 12.20 kg/m^2. Sex-specific quartiles of fat-free mass index were defined by their distribution (25th quantile, median, 75th quantile); for men: 25th quantile = 18.77 kg/m^2, median = 20.18 kg/m^2, 75th quantile = 21.80 kg/m^2; for women: 25th quantile = 15.50 kg/m^2, median = 16.75 kg/m^2, 75th quantile = 18.30 kg/m^2. KORA, Cooperative Health Research in the Region Augsburg; Q, quartile; SHIP, Study of Health in Pomerania.

[2] Low education is defined as ≤10 y of education for KORA and SHIP or "<9th grade/9–11th grade/high school graduate/GED or equivalent" for NHANES. High education is defined as >10 y of education for KORA and SHIP or "Some college or AA degree/college graduate or above" for NHANES.

high fat-free mass index of 21.9 kg/m^2 was associated with an HR of 0.75 (95% CI: 0.59, 0.96). In additional analyses, we ran separate Cox models for each cohort and subsequently combined the cohort-specific risk estimates using fixed-effects meta-analysis. The pooled HR of mortality comparing high versus intermediate with low fat mass was 1.37 (95% CI: 1.13, 1.65; I^2 = 0.0%; *P*-heterogeneity = 0.0012) (**Supplemental Figure 2**). An HR of 0.68 was seen for high versus low fat-free mass in relation to mortality risk (95% CI: 0.53, 0.87; I^2 = 0.0%; *P*-heterogeneity = 0.0023) (**Supplemental Figure 3**).

The interactions between body-composition measures and age were not statistically significant in the overall dataset (*P* values for interaction by age = 0.721 for fat mass and 0.495 for fat-free mass). However, differences in the shapes of associations emerged when we restricted the analysis to participants aged ≥65 y. Specifically, the previously observed J-shaped relation between fat mass and mortality flattened and became linearly positive (*P* for nonlinearity = 0.18), whereas fat-free mass showed a linear inverse association with mortality (*P* for nonlinearity = 0.12). By comparison, the mortality relation among individuals <65 y of age remained J-shaped for fat mass and was inversely J-shaped for fat-free mass (*P* values for interaction by age strata = 0.531 for fat mass and 0.100 for fat-free mass) (**Figure 2**). Results for smokers and nonsmokers were not significantly different from one another (*P* values for interaction by smoking status = 0.950 for fat mass and 0.214 for fat-free mass).

Figure 3 shows that the left-hand portion of the BMI and mortality curve is predominantly determined by the relation of fat-free mass index to mortality, whereas the right-hand portion of the BMI and mortality curve mainly reflects the association between fat mass and mortality.

The chained-equation multiple imputation procedure yielded slightly stronger relations of fat mass and fat-free mass to mortality than the primary analysis (**Supplemental Table 10** and **Supplemental Figure 4**).

TABLE 2 Relations of fat mass index and fat-free mass index to total mortality in the complete case dataset ($n = 16,155$) and after further excluding the initial 4 y of follow-up[1]

	Total mortality			
	Complete case dataset		Sensitivity analysis: follow-up >4 y	
	HR (95% CI)	*n*	HR (95% CI)	*n*
Fat mass index (kg/m^2)				
5.2	1.08 (0.96, 1.20)	162	1.09 (0.96, 1.24)	130
7.3[2]	1	266	1	227
9.2	1.18 (1.07, 1.29)	378	1.16 (1.05, 1.28)	332
13.0	1.56 (1.30, 1.87)	541	1.52 (1.24, 1.86)	480
Overall *P* value	<0.001		<0.001	
Fat-free mass index (kg/m^2)				
16.1[2]	1	338	1	290
17.8	0.83 (0.76, 0.91)	384	0.84 (0.77, 0.93)	338
19.2	0.73 (0.63, 0.85)	356	0.77 (0.65, 0.92)	322
21.9	0.70 (0.56, 0.87)	269	0.75 (0.59, 0.96)	219
Overall *P* value	<0.001		<0.001	

[1] $n = 12,095$. HRs from Cox proportional hazards regression using age as the underlying time metric. Adjusted for sex, ethnicity, study, history of diabetes mellitus at baseline, education, smoking, physical activity, and alcohol intake. Fat mass index and fat-free mass index were mutually adjusted. *n*, number of total mortality cases in each sex-specific quartile.

[2] Reference groups for fat mass index = 7.3 kg/m^2 and for fat-free mass index = 16.1 kg/m^2 were set according to predicted cubic spline functions. Fat mass index and fat-free mass index measurement points were selected using means of sex-specific quartiles.

We calculated the E-value for a fat mass index of 13.0 kg/m^2 and a fat-free mass index of 21.9 kg/m^2. An unmeasured confounder would need to be related to fat mass and mortality with an HR of 2.49 to explain away the observed HR of 1.56 regarding the fat mass and mortality relation, and an unmeasured confounder would need to be related to fat mass and mortality with an HR of 1.92 to move the lower CI limit to include the null. Likewise, an unmeasured confounder would need to be associated with both fat-free mass and mortality with an HR of 2.21 to explain away the observed HR of 0.70 regarding the fat-free mass and mortality relation, and an unmeasured confounder would need to be related to fat-free mass and mortality with

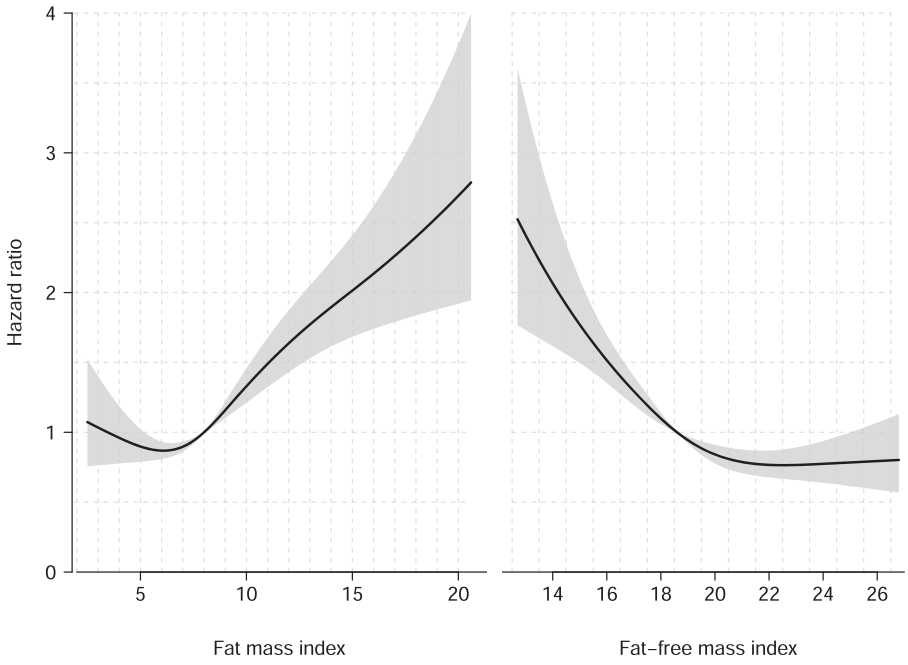

FIGURE 1 Spline functions with corresponding 95% CIs from Cox proportional hazards regression for the relations of fat mass index (kg/m^2) and fat-free mass index (kg/m^2) to total mortality ($n = 16,155$).

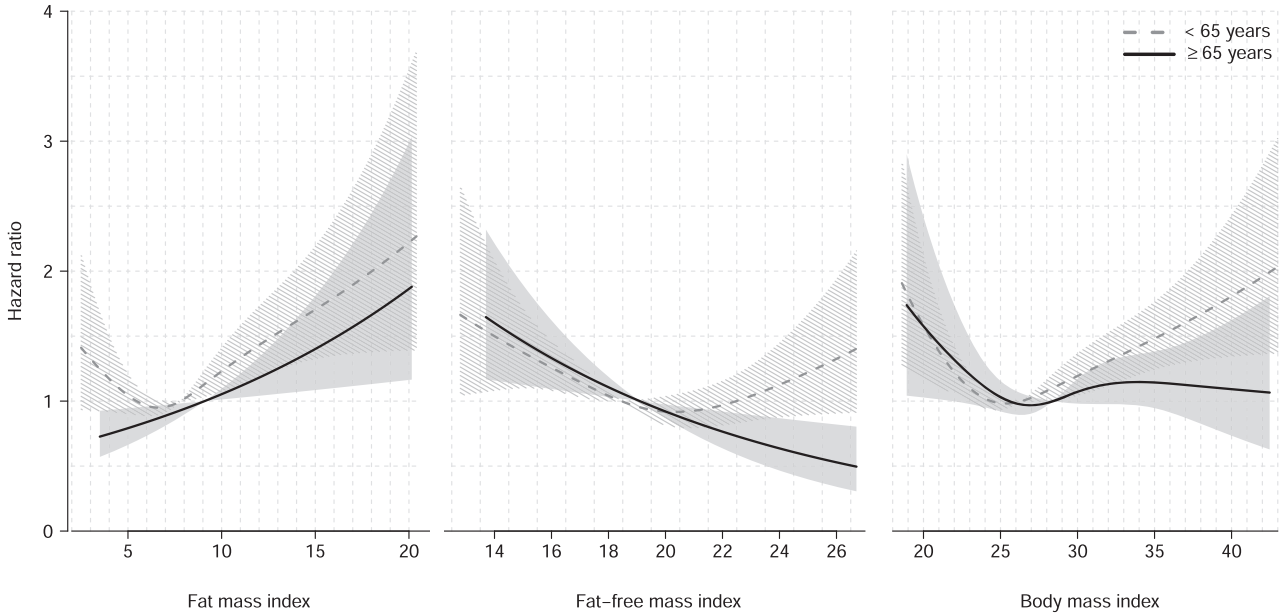

FIGURE 2 Linear and spline functions with corresponding 95% CIs from Cox proportional hazards regression for the relations of fat mass index (kg/m^2), fat-free mass index (kg/m^2), and BMI (kg/m^2) to total mortality in participants <65 y (n = 14,087; 95% CI with shaded lines) and ≥65 y (n = 2068; 95% CI with gray filling).

an HR of 1.56 to move the upper CI limit to include the null.

Discussion

In this pooled analysis involving 7 prospective cohorts, we found a J-shaped association between fat mass and mortality, with a 50% increased mortality risk observed for a high versus low level of fat mass. In contrast, a high versus low level of fat-free mass showed a 30% decreased mortality risk. Supplemental analyses among individuals aged ≥65 y revealed a strong linear positive relation of fat mass and a clear graded inverse association of fat-free mass to mortality. This suggests that preventing excess adiposity and maintaining muscle mass represent relevant protective measures against mortality, particularly among the elderly. Further, we confirmed previous work (2, 7) demonstrating that the relation of BMI to mortality reflects a combination of the individual effects of fat mass and fat-free mass on total mortality and that BMI showed less value for predicting mortality risk than did body composition. These results lend strong support to consider body composition as a means of providing important prognostic information on an individual's mortality risk not delivered by BMI.

A number of epidemiologic studies examined the association between body composition and mortality, but results are inconsistent. Approximately one-quarter of previous studies support a positive relation (4, 25–28) or are consistent with a J- or U-shaped association between fat mass and mortality (2), whereas the remaining studies show an inverse relation (29, 30) or no association (31–34). Data regarding the relation of fat-free mass to mortality have also varied. Approximately one-third of studies found an inverse association between fat-free mass and mortality (4, 27, 32, 34–36) or are consistent with an inverse J- or U-shaped relation (2, 28), while the remaining studies found no association (26, 29–31, 33, 37). Approximately one-quarter of studies showed heterogeneous relations of fat mass or fat-free mass to mortality by sex (38–43). Thus, the evidence regarding body composition in relation to mortality is divergent.

Possible reasons for the observed inconsistencies in the literature include certain methodologic shortcomings of previous investigations, such as restriction to elderly individuals (4, 29–34, 36–38, 41–43); short follow-up periods (2, 25, 26, 29, 31–33, 35, 37, 38, 40, 41); lack of mutual adjustment for fat mass and fat-free mass (34, 38, 39); failure to adjust for important confounders such as smoking (25, 29, 31, 32, 34, 36, 38), physical activity (2, 25, 29, 32, 38, 41–43), and chronic disease (29, 32, 38); and inability to determine the shape of the body-composition and mortality relation due to small numbers of participants and deaths (4, 29, 31, 34, 36–38, 41).

We systematically addressed potential methodologic limitations by encompassing a large sample size and long-term follow-up, which yielded statistically precise estimates of the shape of the association between body composition and mortality across a wide range of fat mass and fat-free mass values. We mutually adjusted for fat mass and fat-free mass to tease out the independent mortality relations. We included smoking and physical activity in our models, variables that are strongly related both to changes in body composition and to mortality. Residual confounding is still possible but would have needed to be associated with body composition and mortality with a more than 2-fold increase in risk, above and beyond the measured confounders, to explain away observed associations. For example, smoking is a strong confounder of the adiposity–mortality relation and showed a similar HR of 2.4 with mortality in our pooled dataset. Thus, it is unlikely that our findings

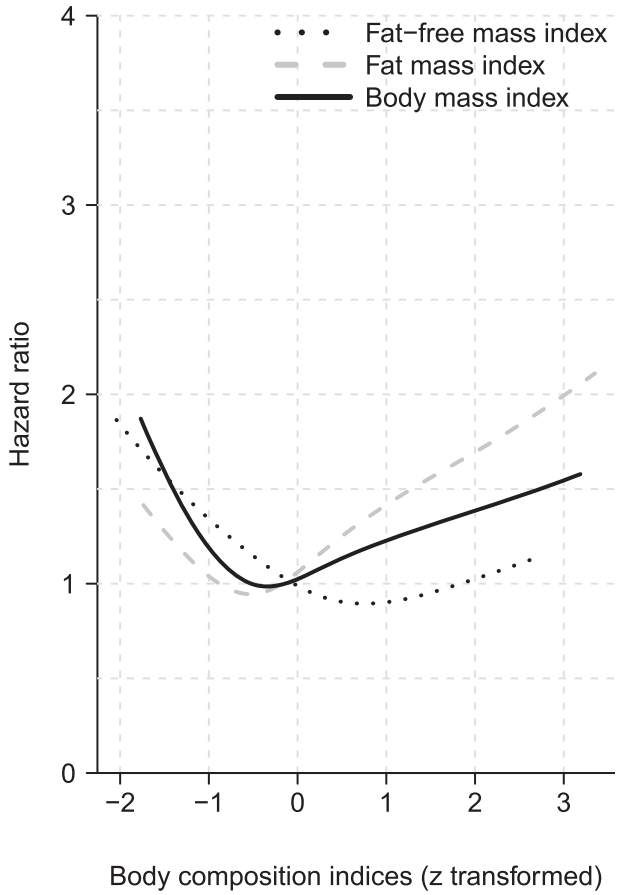

FIGURE 3 Spline functions from Cox proportional hazards regression for the relations of body mass index (kg/m^2), fat mass index (kg/m^2), and fat-free mass index (kg/m^2) to total mortality (n = 16,155). All values were z transformed.

are substantially affected by residual confounding. We excluded subjects with major chronic diseases at baseline to reduce the influence of chronic illness on body composition at study entry. In secondary analyses, we further minimized the potential for reverse causation due to undiagnosed chronic disease by excluding the first 4 y of follow-up and found that conclusions remained unchanged.

One potential limitation of our study is the use of different BIA devices and prediction equations across cohorts. However, cohort-specific results were comparable to those seen in our pooled dataset, making it improbable that differences in assessments of body composition across studies accounted for our findings. An additional shortcoming is our lack of data on changes in body composition. A recent study showed that changes in body composition during the preceding 6 y were not significantly associated with total mortality (6), suggesting that changes in body composition beyond a 6-y time period may be needed to detect a relation, if one existed. We also did not address potential confounding by the distribution of subcutaneous and visceral adipose tissue, the latter of which can be approximated by waist circumference and is positively associated with mortality (44). Our study was further limited by lack of data on smoking intensity and duration, although we detected no significant differences in the results between smokers and nonsmokers.

The pathophysiologic basis for a relation between excess fat mass and increased mortality risk is well established. Potentially fatal long-term medical complications of obesity include hypertension, type 2 diabetes, cardiovascular disease, pulmonary disease, and cancer (45). Possible etiologic pathways include insulin resistance, lipid abnormalities, hormonal perturbations, and chronic inflammation (46). In contrast, biological mechanisms that plausibly mediate the apparent protective effect of high fat-free mass on mortality risk include the ability of skeletal muscle cells to produce, express, and release myokines, such as myostatin, IL-6, IL-7, IL-15, insulin-like growth factor-1, or irisin (47). Myokines stimulate muscle growth, upregulate fat oxidation and the browning of white adipose tissue, improve insulin sensitivity via the activation of AMP-activated protein kinase, and induce anti-inflammatory activity (48).

In conclusion, our findings show opposing relations of fat mass and fat-free mass to mortality. Excess fat mass is related to increased mortality risk, whereas high fat-free mass protects against the risk of mortality. Our results have significant clinical and public health implications because they confirm and extend previous research (7) showing that body composition provides important prognostic information on an individual's mortality risk not provided by BMI. Thus, considering both fat mass and fat-free mass and highlighting the importance of a healthy body composition should be of primary interest instead of focusing on weight alone. People should be encouraged to adopt a healthy diet and to engage in light to moderate physical activity, including resistance exercise, to reduce fat mass and to prevent loss of muscle mass.

The authors' responsibilities were as follows—AMS: conducted the data preparation and analysis and drafted the manuscript with support from MFL and SEB; MFL and SEB: conceived the original idea and supervised the project; AW, BF, BT, TI, MD, SBF, HV, and AP: directly participated in interpretation of the results, provided critical comments to the manuscript, and revised the text; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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