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Impact of body composition changes and risk of all-cause mortality in persons 65 years old and above

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ABSTRACT

Purpose: This study evaluates the relationship between body mass index (BMI), fat mass index (FMI) and fat-free mass index (FFMI) changes and mortality in persons ≥65 years.

Methods: Adults ≥65 years with at least two body composition measurements (BCM) between 1990 and 2011 were included. We excluded persons who died within one month of the second BCM and who had two single BCM in a one-month timeframe. Mortality data was retrieved until December 2012. For each person, we calculated the regression slopes for BMI, FMI and FFMI changes. Significant positive slopes were categorized as "gain", negative slopes as "loss" and the others as "maintenance". The impact of body composition changes was evaluated by Cox regression models while adjusting for sex, age, co-morbidities and body composition at the last measurement.

Results: We included 791 persons with 3049 BCM. After adjustment for sex, and age and co-morbidities, a loss of FFMI, but not of FMI or BMI, increased the risk of mortality (HR 2.02, 95%CI 1.28-3.19). The prediction of mortality with FFMI loss remained significant when further adjusting for FMI loss and the last available body composition (HR 1.68, 95%CI 1.04-2.70).

Conclusions: FFMI loss increases the risk of mortality in older persons.

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INTRODUCTION

In older persons, body mass index (BMI), corresponding to height-adjusted weight, is associated to mortality through a U-shaped or J-shaped curve (1-3). Considering that BMI consists of fat mass (FM) and fat-free mass (FFM), several cohort studies tried to identify whether FM or FFM predicted mortality. They reported either no impact (4, 5) or an increased mortality with low FFM (6-8) and high FM (8-10). These discrepancies may be due to methodological issues, but could also indicate that mortality is better predicted by changes in weight and body composition than absolute values.

Weight loss has been associated with increased risk of mortality in patients with chronic heart failure (11), cancer (12, 13), Alzheimer's disease (14), chronic kidney failure (15), chronic obstructive pulmonary disease (16) and amyotrophic lateral sclerosis (17). In older persons specifically, weight loss predicts mortality, even though the studies differ regarding the amount and the considered timeframe of weight loss, and the time of follow-up between weight loss assessment and mortality (18-21). One study has evaluated the relation between body composition changes and mortality in older persons and was performed in ambulatory US residents. It showed an increased risk of death in men who had lost ≥ 5% body weight, lean body mass, appendicular lean mass or fat mass over an average of 4.6 years (22). Since the study included only men, it is not clear whether these findings also apply to women.

The question whether loss of FM or FFM in older persons increases the risk of mortality is important in order to target therapeutic strategies. The loss of FM can theoretically be prevented by hypercaloric diets, while the loss of FFM can be limited by appropriate calorie and protein intakes (23) and the addition of physical activity (13, 24). Furthermore, if the loss of both FM and FFM increases the risk of mortality in older persons, it would suggest that any hypocaloric diet, even voluntary, should be avoided in these persons.

This study aimed at exploring the relationship between weight and body composition (BC)

changes and all-cause mortality in men and women aged over 65 years.

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METHODS

Subjects and design

This historical cohort study includes all subjects aged ≥ 65 years, who had at least two measurements of body composition by 50-kHz bioimpedance analysis (BIA), performed between January 1990 and December 2011, at the Geneva University Hospitals (HUG). Persons were measured in clinical routine or in a research setting.

Persons were excluded if 1) they were living outside of Switzerland, because we could not obtain mortality data, 2) they had undergone only two BIA measurements in a timeframe < 1 month, because small differences in such a short time may reflect changes in hydration status rather than body composition, and 3) they had undergone only two BIA measurements, with the second measurement within one month of death, because the latter measurement could be affected by the terminal phase of life *per se,* 4) they had negative FM, probably due to fluid and electrolyte abnormalities not identified by the nutrition team and which limit the accuracy of BIA measurements, and 5) their co-morbidities and lifestyle habits at the time of the last body composition measurement were not known, precluding the calculation of a co-morbidity score. This protocol was approved by the Ethical Committee of the HUG who waived the requirement for a signed informed consent. It was registered under clinicaltrials.gov (NCT01472679).

Body composition and co-morbidities

We retrieved the BIA parameters (50-kHz resistance, reactance), anthropometric data, co-morbidities and lifestyle habits at the time of body composition measurements, from two sources: 1) the computer database of the HUG for measurements performed in clinical routine since 2000 and 2) the database of the nutrition unit of the HUG for measurements performed in clinical routine from 1990 to 1999 and in research setting from 1990 to 2011 (7). As detailed elsewhere (7), BIA measurements are performed in our institution, in hospitalized and

ambulatory patients at nutritional risk, in order to follow their nutritional state and potentially adapt their nutritional support. The BIA measurements in the research setting were performed mostly in healthy persons in order to create a population-specific BIA formula and normative values according to age and physical activity.

Measurements of weight, height and resistance and reactance by 50-kHz BIA are standardized in the HUG, and have been described previously (25). These parameters were introduced into the Geneva formula , developed (26) and validated against dual-energy x-ray absorptiometry (27) in older persons living in the Geneva area, in order to obtain FFM. FM was calculated as body weight (kg) minus FFM (kg). FM and FFM were divided by height (m^2) to obtain fat-free mass index (FFMI) and fat mass index (FMI).

We used several BIA devices over the 21 years: RJL-109 and RJL-101 (RJL Systems, Inc., Clinton Towhnship MI, USA), Xitron 4000 B (Xitron Technologies, San Diego, CA, USA), Bio-Z2 (Spengler, Paris, France), and Nutriguard (Data Input GmbH, Darmstadt, Germany). All BIA devices were calibrated using a calibration jig, setting a limit of tolerance, at 50 kHz, of 5 Ω for impedance and 2 degrees for the phase angle. For FFM, the method agreement in vivo, calculated from 53 paired measurements, was 0.03 kg (95% confidence interval (CI): -1.7 to 2.1 kg), and the inter-observer agreement, determined in 51 persons, was 0.02 kg (95% CI -1.3 to 1.3) (25).

We relied on the letters of admission or discharge, or the consultations reports to determine co-morbidities and lifestyle habits at the time of body composition measurements. This data was translated into a score, using the modified Cumulative Illness Rating Scale (CIRS) (28). CIRS evaluates 14 organs and systems, and assigns each of them a score from 0 (no disease) to 4 (severe disease) points. CIRS has been positively associated with mortality (29). In our study, the Spearman correlation between the two raters who determined retrospectively the CIRS was 0.92, based on the CIRS of 20 randomly selected persons.

Mortality

Mortality data was retrieved until December 2012 from the computer database of the HUG, the Geneva population register of deaths (30), and the Swiss National Cohort (SNC) (31), as explained elsewhere (7). The latter is a national data platform which associates anonymously all-cause and cause-specific mortality to national censuses.

Statistical analyses

Characteristics of the included persons at the last BIA measurement are presented as means ± standard deviation. We checked the normality of the distribution of continuous data by Shapiro-Wilks tests. Data between women and men and between included persons and those excluded on the basis of missing CIRS were compared by unpaired t-tests for continuous variables and Mann-Whitney u tests for categorical variables. Significance, set originally at $p < 0.05$, was corrected to $p < 0.04$ for multiple analysis according to the Benjamini-Hochberg method (32).

The BMI at the last body composition measurement was categorized as < 18.5 kg/m^2, 18.5-24.9 kg/m^2 and > 25 kg/m^2, because the association between BMI and mortality is U-shaped or J-shaped. The category > 25 kg/m^2 included patients of the WHO categories 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2 (33). The FFMI at the last body composition measurement was dichotomized into absence or presence of sarcopenia (FFMI < 15.1 kg/m^2 for women and < 17.5 kg/m^2 for men) and the last FMI into absence or presence of obesity (FMI > 8.2 kg/m^2 for women and > 5.2 kg/m^2 for men) (34). The choice of categorization of last BMI, FFMI and FMI data, as compared to the use of continuous values, quadratic (BMI + BMI^2) or cubic splines (BMI + BMI^2 + BMI^3), relies on two elements. First, the explained variation of mortality (R^2) (35) in unadjusted cox regression models is best with BMI and FFMI categories (**supplemental**

table 1). Second, the categorizations provide more explicit data for the clinician than quadratic or cubic splines. Thus, although, the quadratic spline provides the best R^2 for FMI, we preferred categorizing the last BMI and body composition.

To evaluate the impact of body composition changes on mortality using all available measurements, we calculated, for each person, the regression slopes for BMI, FMI and FFMI changes over time and its significance. We categorized significantly positive ($p<0.05$) slopes as “gain”, significantly negative slopes ($p<0.05$) as “loss” and the others as “maintenance”. The characteristics of our study population at the last BIA measurement were compared between categories of BMI, FMI and FFMI changes by Kruskall-Wallis tests or Chi-squared tests, as appropriate. These models including the last assessment values and the changes which occurs before, explain what is the future mortality risk of the patient we see today according to his/her current body composition and how is this risk modified by our knowledge about the 'history' of the preceding changes in body composition.

We performed univariate Cox regressions, using days as time axis and counting deaths from one month after the last BIA measurement, to evaluate whether body composition changes predicted mortality, followed by 5 models of multiple Cox regressions. Model 1, 2 and 3 evaluated the impact of BMI, FFMI and FMI changes separately, with adjustments for age and CIRS at last BIA measurement and sex. Model 4 incorporated BMI changes and BMI at the last BIA measurement, with the same adjustments as before, while Model 5 incorporated FMI and FFMI changes and the body composition at the last BIA measurement. For each model, we reported hazard ratios (HR), 95% CI and the level of significance. For each covariable, we plotted ln [-ln(survival probality] vs. ln (time) to verify the proportional hazard assumptions. To evaluate collinearity among covariates, we examined the variance inflation factor (VIF) for the covariates in the five multiple Cox regression models. As the VIF was below 5 for all

covariates, there was no collinearity in any model. Interactions between sex and BMI or body composition changes were calculated in the Cox regression Models 4 and 5. Finally, we reported Kaplan-Meier curves for the categories of BMI, FFMI and FMI changes, calculated lot rank tests to compare the curves and determined mortality trends throughout the categories of BMI, FFMI and FMI changes.

Significance was set at $p<0.05$. Statistical analyses were run with Stata software version 13.1 (TX, USA).

RESULTS

We included 791 persons (318 women and 473 men) totalizing 3049 BIA measurements. The trial flow-chart is shown on **supplemental figure 1**. Two hospitalized women were excluded because of negative FMI probably linked with hydro-electrolytic disturbances as one suffered from aggravation of chronic renal failure, and the other one of severe malnutrition. Persons excluded because of missing CIRS (n = 94) were younger and had a lower BMI and FMI at last BIA measurement than included persons (**supplemental table 2**).

The characteristics of the included persons at the last BIA measurement are shown on **table 1**. They had a median number of 3 BIA measurements in both gender (range: 2 to 24 in women; 2 to 27 in men). Expressed as median (range), the median duration between the first and last BIA measurement was 1.5 (0.1 to 12.9) and 1.0 (0.1 to 11.0) years in women and men, respectively, and the median time interval between BIA measurements was 0.5 years (1 day to 15.4 years) and 0.3 years (1 day to 14.3 years) in women and men, respectively. Categorization into BMI, FMI and FFMI changes highlight that BMI and body composition did not change significantly over time for the majority of the persons (**table 2**). Persons who had lost FMI were mostly non obese at the last BIA measurement, while those who had lost FFMI were mostly sarcopenic at the last BIA measurement **(supplemental table 3)**.

Of the 791 persons, 425 persons (58%) died. Causes of mortality, available in 382 persons, were cancer (29%), cardiovascular diseases (22%) and respiratory diseases (11%). Univariate Cox regressions demonstrated that a loss of FFMI predicted an increased risk of mortality compared to a stable FFMI, while changes of FMI had no impact on mortality (**supplemental table 4**).

When adjusting for age and CIRS at last BIA measurement and sex, a loss of FFMI doubled the risk of mortality, but changes of FMI and BMI had no significant impact on mortality (**table 3**). The inclusion of BMI changes and last BMI into a single Cox regression model adjusted for

sex, last age and last CIRS highlights that BMI changes still do not predict mortality (Model 4). However, when considering body composition changes and the last body composition instead of BMI changes and the last BMI (Model 5), a loss of FFMI increased the risk of mortality by 68%, while changes of FMI had no impact on mortality.

In Model 4, sex interacted significantly with BMI gain (p=0.001) but in Model 5, no significant interactions could be highlighted between sex and FFMI or FMI changes. Kaplan-Meier survival curves (**figure 1)** and mortality trends (**supplemental table 5)** for categories of BMI, FMI and FFMI changes were performed by sex. Kaplan-Meier curves showed that loss of BMI and FFMI were both associated with a worse survival.

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DISCUSSION

This study demonstrates that the majority of the studied older persons have a stable BMI, FMI and FFMI over time. However, those who are losing FFMI have a higher risk of mortality than those who are maintaining it, even when adjusting for co-morbidities and body composition at the last BIA measurement. In contrast, a loss of BMI or FMI has no impact on mortality in this older study population.

One study has evaluated the relationship between body composition changes and mortality in older persons. The authors measured body composition by dual-energy x-ray absorptiometry in 4331 ambulatory US men over 65 years, on two occasions, at a mean time interval of 4.6 years. Three years after the second visit, 433 men had died. Mortality was higher in men who had lost ≥ 5% body weight, lean body mass, appendicular lean mass or FM between both visits (22). Regarding lean body mass, this represented a median loss of - 0.07 kg /month (range -0.09 to -0.06), as compared to a median loss of -0.15 kg of FFM/month (range -0.69 to -0.01) in the men of this study. Although the extent of FFM loss predicting an increased risk of mortality varies, both studies agree that a loss of FFMI negatively affects survival.

However, our study does not support the negative impact of FMI loss. This difference may be due to several issues. First, we have included men and women in the same Cox regression model. This raises the question whether FMI loss has a different impact on mortality in men and women, but sex did not interact significantly with FMI loss. Second, the persons who have lost FMI may have started with a different baseline body composition. A lower baseline FFMI or FMI may have increased the risk of mortality. This data could not be retrieved in the study of Lee et al, precluding any comparison with our study. Third, our persons probably suffered from more co-morbidities than those in the study of Lee et al, who underwent measurements only in the ambulatory setting. These co-morbidities may have obscured the impact of FMI loss alone. Fourth, differences may be due to methodological issues. Indeed, in our study we took

into account more than 2 BIA measurements when available. Also, our methodology used for categorization of body composition changes resulted in a more severe threshold for the categorization in the group "FMI loss" than in the study by Lee et al. (median loss of FM: -0.17 vs. -0.05 kg/month in men) and in a smaller proportion of persons categorized in this group (6 vs. 31% of the study population). Finally, the adjustments performed in the Cox regressions differed. Thus, the impact of FMI loss on mortality needs further investigations and should probably include longitudinal measurements in the hospital and ambulatory setting to better capture body composition variations.

Several articles have evaluated the impact of weight loss in persons > 60 years at baseline on mortality. In outpatients, mortality was predicted by a weight loss over 1 kg per year (18), over 1 kg in one year (19) or over 5% of initial body weight within 3 years (20). The reason why we could not confirm this finding in our study is unclear. It may be related to the consideration of body composition changes during a longer timeframe in our study, to the adjustment for baseline co-morbidities through the CIRS and to the evaluation of weight changes through ≥ 2 measurements. The afore-mentioned studies have excluded patients with cancer, myocardial infarction, diabetes or stroke at baseline (18), or adjusted their results only for a very limited number of co-morbidities (19, 20). Also, in these studies, weight change relied only on two time-points in contrast with our study, which may be misleading as a persont could be weight-stable using two time-points but still have gained or lost weight in between. Furthermore, none of these studies have evaluated whether the impact of weight loss differed according to baseline weight. Recent studies found no benefit of intentional weight loss on mortality in older overweight or obese persons, whether old (36) or young (36) (37) (38). In our study, 80% of the persons who had lost weight still had a BMI ≥ 25 kg/m^2 at last follow-up. Finally, as explained elsewhere (39), the consideration of weight changes does not capture the changes in regional body composition, which may be as important for prediction of

mortality.

The originality of this study is to take into account BMI and body composition changes in older persons by considering more than two measurements, if available, which may better take into account intra-individual variations than two measurements. We have adjusted our regressions for the CIRS, which takes into account co-morbidities and lifestyle habits as smoking and alcohol at the last observation of the patients. Regarding the study limitations, our population was too small in some sub-categories (like BMI or body composition changes) for separated Cox regressions by sex and required pooling of men and women. This is due to the fact that Cox regressions are parametrical statistical tests, whereas the log rank tests used to compare Kaplan-Meyer curves are non parametric tests. However, the pooling had the advantage to highlight that body composition changes affected men and women differently. Furthermore, we have no indication on voluntary vs. involuntary weight loss. This information could be important as involuntary weight loss is associated with an increased risk of mortality. In contrast, voluntary weight loss has no impact on mortality risk overall, but subgroup analysis highlighted an increased risk in healthy obese persons and a decreased risk in unhealthy obese persons (40). However, this information cannot be integrated in our study design including several measurement as many people undergo over years episodes of involuntary weight loss, as for instance during episodes of hospitalization, and voluntary weight loss. Furthermore, we have not reported physical activity, which may be a confounding factor.

CONCLUSION

This study highlights the negative impact of FFMI loss on mortality in persons ≥ 65 years, irrespective of sex, and age, co-morbidities, and body composition at the last follow-up. It could not confirm that loss of BMI or FMI increased the risk of mortality. Future clinical and epidemiological studies should evaluate the impact of body composition and weight changes

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based on several measurements, and not on only two measurements, on mortality and evaluate whether maintaining FFMI over time with physical exercise or anabolic strategies may improve survival.

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ABSTRACT PRESENTATION

Part of this work has been submitted as an abstract to the congress of the European Society for Clinical Nutrition and Metabolism (ESPEN), which will be held in Lisbon in September 2015.

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FIGURE

Figure 1: Kaplan-Meier curves showing the probability of survival according to categories of BMI (A), FFMI (B) and FMI changes (C) in women and men. "···· " indicates maintenance, " — " indicates gain and "—" indicates loss. The log rank tests were p=0.131 for BMI changes, 0.191 for FFMI changes and p=0.051 for FMI changes for women and p=0.025 for BMI changes, 0.019 for FFMI changes and p=0.123 for FMI change for men.

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Table 1: Characteristics of the study population at the last BIA measurement

	All				Women				Men				
	n	**%**	**mean**	**SD**	**n**	**%**	**mean**	**SD**	**n**	**%**	**mean**	**SD**	***p****
Continuous variables													
Last age [yrs]	791	100	75.3	6.8	318	100	76.0	7.1	473	100	74.8	6.5	0.022
Last CIRS score	791	100	14.1	7.4	318	100	12.1	7.1	473	100	15.5	7.3	<0.001
Last height [cm]	791	100	166.2	9.5	318	100	158.7	7.1	473	100	171.2	7.5	<0.001
Last weight [kg]	791	100	68.2	17.3	318	100	62.4	18.3	473	100	72.1	15.5	<0.001
Last BMI [kg/m^2]	791	100	24.6	6.0	318	100	24.8	7.1	473	100	24.6	5.0	0.674
Last FFMI [kg/m^2]	791	100	16.9	3.1	318	100	15.4	3.1	473	100	17.9	2.8	<0.001
Last FMI [kg/m^2]	791	100	7.8	3.9	318	100	9.4	4.6	473	100	6.7	3.0	<0.001
Follow-up since last BIA until censored [yrs]	791	100	3.0	3.0	364	100	3.6	3.1	473	100	2.6	2.8	<0.001
Age at death [yrs]	425	58	77.8	7.8	159	44	79.2	8.5	266	56	77.0	7.3	0.007
Follow-up since last BIA until death [yrs]	425	58	2.0	2.2	159	44	2.5	2.6	266	56	1.6	1.9	<0.001
Baseline age [yrs]	791	100	72.5	6.2	318	100	76.0	7.1	473	100	72.1	6.0	0.082
Baseline CIRS score	784	99	12.0	7.1	314	99	12.1	7.1	470	99	13.1	7.0	<0.001
Baseline height [cm]	791	100	166.8	9.4	318	100	158.7	7.1	473	100	171.7	7.4	<0.001
Baseline weight [kg]	791	100	69.7	17.9	318	100	62.4	18.3	473	100	73.8	16.0	<0.001
Baseline BMI [kg/m^2]	791	100	25.0	6.0	318	100	24.8	7.1	473	100	25.0	5.1	0.967
Baseline FFMI [kg/m^2]	791	100	17.0	3.2	318	100	15.4	3.1	473	100	18.1	2.8	<0.001
Baseline FMI [kg/m^2]	791	100	8.0	4.0	318	100	9.4	4.6	473	100	6.9	3.0	<0.001
Categorical variables													
Last BMI [kg/m^2]													0.066
< 18.5	97	12	16.6	1.3	50	16	16.5	1.3	47	10	16.6	1.4	
18.5-24.9	353	45	21.9	1.8	139	44	21.8	1.7	214	45	22.0	1.9	
> 25	341	43	29.8	5.1	129	41	31.1	6.7	212	45	29.0	3.5	

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Last FFMI [kg/m^2] [1]													0.283
No sarcopenia	399	50	19.1	2.5	153	48	17.7	2.7	246	52	19.9	1.9	
Sarcopenia	392	50	14.6	1.8	165	52	13.2	1.4	227	48	15.6	1.5	
Last FMI [kg/m^2] [2]													0.001
No obesity	308	39	4.8	1.8	146	46	6.0	1.7	162	34	3.7	1.1	
Obesity	483	61	9.7	3.7	172	54	12.3	4.2	311	66	8.3	2.4	

BIA: bioimpedance analysis, CIRS: Cumulative Illness Rating Scale, BMI: body mass index, FM: fat mass, FMI: fat mass index, FFMI: fat-free mass index

* *p*: unpaired t-test for continuous data between men and women and Mann-Whitney U test for categorical data comparison between men and women

[1] Sarcopenia was defined as FFMI < 15.1 kg/m^2 for women and <17.5 kg/m^2 for men (34)

[2] Obesity was defined as FMI > 8.2 kg/m^2 for women and >5.2 kg/m^2 in men (34)

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Table 2: Categories of body mass index, fat mass index and fat-free mass index changes, calculated for one month

	All (n=791)					Women (n=318)					Men (n=473)					
	n	**%**	**mean**	**SD**	**min, max**	**n**	**%**	**mean**	**SD**	**min, max**	**n**	**%**	**mean**	**SD**	**min, max**	***p****
BMI change [kg/m^2/month]																0.081
Maintenance	695	88	-0.1	0.5	-3.4, 2.1	282	89	-0.1	0.5	-3.2, 1.7	413	87	-0.1	0.5	-3.4, 2.1	
Gain	50	6	0.3	0.4	0.1, 1.9	23	7	0.3	0.3	0.1, 1.1	27	6	0.3	0.5	0.1, 1.9	
Loss	46	6	-0.3	0.3	-1.2, -0.1	13	4	-0.3	0.3	-1.1, -0.1	33	7	-0.3	4.0	-0.3, -0.1	
FFMI change [kg/m^2/month]																0.350
Maintenance	719	91	-0.1	0.5	-6.1, 2.9	294	92	-0.1	0.5	-6.1, 2.9	425	90	-0.1	0.4	-4.3, 2.2	
Gain	46	6	0.3	0.7	0.1, -4.5	18	6	0.3	1.0	0.1, 4.5	28	6	0.2	0.4	0.1, 1.6	
Loss	26	3	-0.3	0.4	-1.8, -0.1	6	2	-0.5	0.7	-1.8, -0.1	20	4	-0.2	0.2	-0.7, -0.1	
FMI change [kg/m^2/month]																0.936
Maintenance	697	88	-0.1	0.4	-2.9, 4.4	284	89	-0.1	0.4	-2.4, 4.4	413	87	-0.1	0.4	-2.9, 3.2	
Gain	49	6	0.2	0.2	0.1, 0.9	18	6	0.2	0.2	0.1, 0.9	31	7	0.2	0.2	0.1, 0.9	
Loss	45	6	-0.2	0.6	-4.2, -0.1	16	5	-0.4	1.0	-4.2, -0.1	29	6	-0.2	0.2	-0.7, -0.1	

BMI: body mass index, FMI: fat mass index, FFMI: fat-free mass index

* *p*: unpaired t-test for continuous data between men and women and Mann-Whitney U test for categorical data comparison between men and women

[1] Sarcopenia was defined as FFMI < 15.1 kg/m^2 for women and <17.5 kg/m^2 for men (34)

[2] Obesity was defined as FMI > 8.2 kg/m^2 for women and >5.2 kg/m^2 in men (34)

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Table 3: Multiple Cox regressions evaluating the association between body composition changes and mortality (n = 791)

	Model 1			Model 2			Model 3			Model 4			Model 5		
Variables	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**P**
			<0.001			<0.001			<0.001			<0.001			<0.001
BMI change [kg/m^2/year]															
Maintenance	1.00									1.00					
Gain	0.89	0.59, 1.36	0.612							0.95	0.62, 1.45	0.814			
Loss	1.12	0.76, 1.64	0.562							1.10	0.75, 1.61	0.627			
FFMI change [kg/m^2/year]															
Maintenance				1.00									1.00		
Gain				1.17	0.79, 1.75	0.438							1.17	0.77, 1.77	0.455
Loss				2.02	1.28, 3.19	0.002							1.68	1.04, 2.70	0.032
FMI change [kg/m^2/year]															
Maintenance							1.00						1.00		
Gain							1.05	0.70, 1.58	0.805				0.90	0.59, 1.39	0.645
Loss							0.87	0.57, 1.34	0.536				0.82	0.53, 1.28	0.379
Sex															
Women	1.00			1.00			1.00			1.00			1.00		
Men	1.19	0.97, 1.46	0.091	1.18	0.97, 1.45	0.106	1.20	0.98, 1.46	0.085	1.29	1.04, 1.58	0.018	1.27	1.04, 1.57	0.022
Last age [yrs]	1.01	1.00, 1.03	0.140	1.01	1.00, 1.03	0.110	1.01	1.00, 1.03	0.113	1.01	1.00, 1.03	<0.001	1.01	1.00, 1.03	0.001
Last CIRS [score]	1.08	1.06, 1.09	<0.001	1.08	1.06, 1.09	<0.001	1.08	1.06, 1.09	<0.001	1.08	1.06, 1.09	<0.001	1.07	1.06, 1.09	<0.001
Last BMI [kg/m^2]															
<18.5										1.10	0.75, 1.61				
18.5-24.9										1.00					
≥25.0										0.95	0.62, 1.45				
Last FFMI [kg/m^2]															
No sarcopenia													1.00		
Sarcopenia													1.68	1.35, 2.11	<0.001
Last FMI [kg/m^2]															
No obesity													1.00		
Obesity													0.80	0.64, 0.99	0.045

BMI: body mass index, FFMI: fat free mass index, FMI: fat mass index, CIRS: Cumulative Illness Rating Scale

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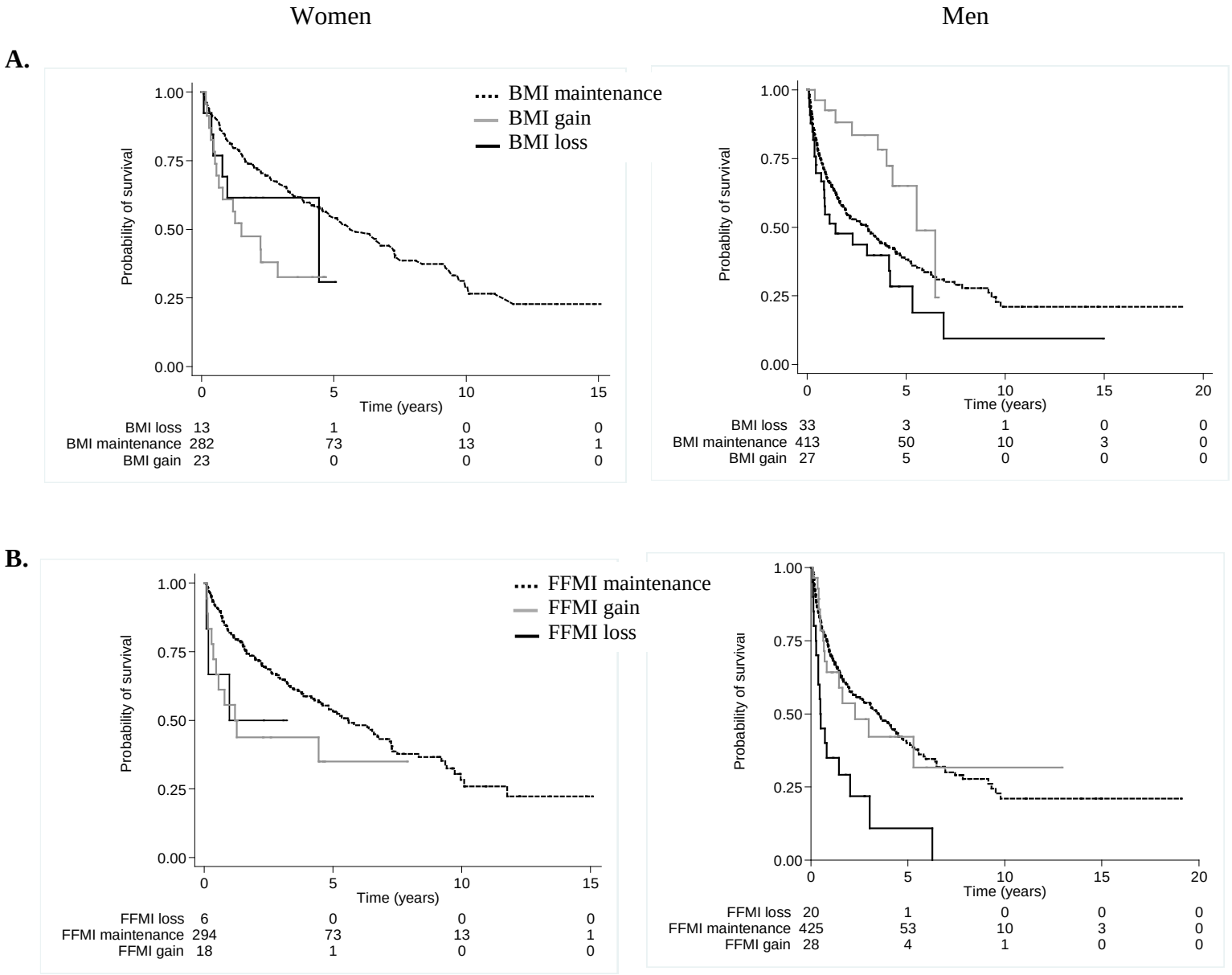
Figure 1



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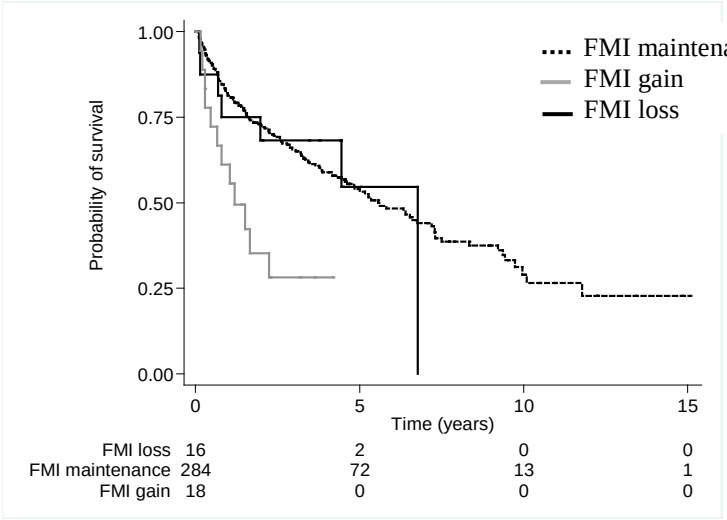
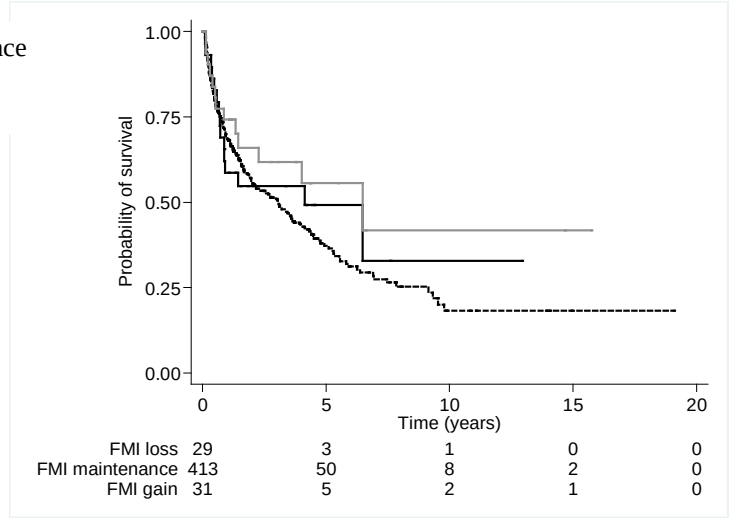
C.





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SUPPLEMENTAL ONLINE MATERIAL

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Supplemental table 1: Explained variation of mortality (R^2) in unadjusted cox regression according to types of data for the last BMI, FFMI and FMI

Variables	HR	95% CI	p	R^2*
Last BMI [kg/m^2]				
Categorization				0.066
<18.5	1.75	1.34, 2.30	<0.001	
18.5-24.9	1			
>25	0.64	0.52, 0.79	<0.001	
Continous value	0.95	0.93, 0.96	<0.001	0.043
Quadratic spline				0.061
BMI	0.84	0.79, 0.90	<0.001	
BMI^2	1.00	1.00, 1.00	<0.001	
Cubic spline				0.070
BMI	0.57	0.43, 0.76	<0.001	
BMI^2	1.02	1.01, 1.02	0.002	
BMI^3	1.00	0.99, 1.00	0.009	
Last FFMI [kg/m^2]				
Categorization				
No sarcopenia	1			
Sarcopenia	2.17	1.78, 2.63	<0.001	0.087
Continous value	0.92	0.89, 0.95	<0.001	0.037
Quadratic spline				0.047
FFMI	0.68	0.55, 0.83	<0.001	
FFMI^2	1.00	1.00, 1.02	0.003	
Cubic spline				0.053
FFMI	1.88	0.62, 5.74	0.266	
FFMI^2	0.95	0.90, 1.01	0.121	

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$FFMI^3$	1.00	0.99, 1.00	0.063	
Last FMI [kg/m^2]				
Categorization				0.015
No obesity	1			
Obesity	0.72	0.59, 0.87	0.001	
Continous value	0.94	0.92, 0.97	<0.001	0.023
Quadratic spline				0.031
FMI	0.88	0.83, 0.94	<0.001	
FMI^2	1.00	1.00, 1.01	0.007	
Cubic spline				0.044
FMI	0.71	0.61, 0.83	<0.001	
FMI^2	1.02	1.00, 1.04	0.001	
FMI^3	1.00	0.99, 1.00	0.008	

BMI: body mass index, FM: fat mass, FMI: fat mass index, FFMI: fat-free mass index

*str2ph command from Stata, which "computes Royston's modification of O'Quigley, Xu & Stare's (2005) modification of Nagelkerke's (1991) R^2 statistic (a.k.a., coefficient of determination, proportion of explained variation) for proportional-hazards (PH) models for censored survival data. " (35).

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Supplemental table 2: Characteristics of the persons excluded because of missing Cumulative Illness Rating Scale at the last BIA measurement compared to included persons

	Excluded subjects				Included subjects				
	n	**%**	**mean**	**SD**	**n**	**%**	**mean**	**SD**	**p***
Continuous variables									
Last age [yrs]	94	100	73.2	5.5	791	100	75.3	6.8	<0.001
Last BMI [kg/m^2]	94	100	23.6	3.1	791	100	24.6	6.0	0.003
Last FFMI [kg/m^2]	94	100	17.3	2.1	791	100	16.9	3.1	0.106
Last FMI [kg/m^2]	94	100	6.4	2.5	791	100	7.8	3.9	<0.001
Follow-up since last BIA until censored [yrs]	94	100	5.1	5.0	791	100	3.0	3.0	<0.001
Number of BIA measurements	94	100	3.6	2.1	791	100	3.8	2.7	0.262
Age at death [yrs]	8	9	82.7	7.7	425	58	77.8	7.8	0.119
Follow-up since last BIA until death [yrs]	8	9	2.1	1.6	425	58	2.0	2.2	0.818
Baseline age [yrs]	94	100	68.4	4.9	791	100	72.5	6.2	<0.001
Baseline BMI [kg/m^2]	94	100	23.5	2.9	791	100	25.0	6.0	0.003
Baseline FFMI [kg/m^2]	94	100	17.2	2.0	791	100	17.0	3.2	0.512
Baseline FMI [kg/m^2]	94	100	6.3	2.5	791	100	8.0	4.0	<0.001
Categorical variables									
Sex									0.104
Women	46	50	-	-	318	40	-	-	
Men	48	50	-	-	473	60	-	-	
Last BMI [kg/m^2]									0.311
< 18.5	4	4	17.0	0.6	97	12	16.6	1.3	
18.5-24.9	58	62	22.4	1.5	353	45	21.9	1.8	
> 25	32	34	27.0	1.6	341	43	29.8	5.1	
Last FFMI [kg/m^2] [1]									<0.001
No sarcopenia	71	76	17.9	1.7	399	50	19.1	2.5	
Sarcopenia	23	24	15.2	1.4	392	50	14.6	1.8	
Last FMI [kg/m^2] [2]									<0.001
No obesity	55	59	5.2	2.0	308	39	4.8	1.8	
Obesity	39	41	8.1	2.0	483	61	9.7	3.7	
Changes since baseline									
BMI change [kg/m^2/year]									0.201
Maintenance	85	90	0.1	0.3	695	88	-0.1	0.5	
Gain	7	8	0.1	0.1	50	6	0.3	0.4	
Loss	2	2	-0.3	0.3	46	6	-0.3	0.3	
FFMI change [kg/m^2/year]									0.855
Maintenance	91	97	0.1	0.2	719	91	-0.1	0.5	
Gain	3	3	0.1	0.1	46	6	0.3	0.7	
Loss	0	0	-	-	26	3	-0.3	0.4	
FMI change [kg/m^2/year]									0.016

Maintenance	83	88	-0.1	0.2	697	88	-0.1	0.4
Gain	10	11	0.1	1.1	49	6	0.2	0.2
Loss	1	1	-0.4	-	45	6	-0.2	0.6

BMI: body mass index, FM: fat mass, FMI: fat mass index, FFMI: fat-free mass index

* *p*: unpaired t-test or Mann-Whitney U test, as appropriate, for comparison with the included persons (n=791)

[1] Sarcopenia was defined as FFMI < 15.1 kg/m^2 for women and <17.5 kg/m^2 for men (34)

[2] Obesity was defined as FMI > 8.2 kg/m^2 for women and >5.2 kg/m^2 in men (34)

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Supplemental table 3: Characteristics of the persons according to categories of body mass index, fat mass index and fat-free mass index changes

		BMI change [kg/m²/year]				FFMI change [kg/m²/year]				FMI change [kg/m²/year]			
		Maintenance n=695	Gain n=50	Loss n=46	p*	Maintenance n=719	Gain n=46	Loss n=26	p*	Maintenance n=697	Gain n=49	Loss n=45	p*
Continuous variables													
Last age [yrs]	mean [SD]	75.5 [6.9]	75.4 [6.7]	76.2 [7.2]	0.825	75.6 [6.9]	75.2 [7.0]	74.4 [6.8]	0.534	75.6 [6.8]	74.7 [6.8]	75.7 [7.7]	0.671
Last CIRS [score]	mean [SD]	13.8 [7.5]	14.8 [6.5]	18.1 [6.3]	<0.001	13.8 [7.4]	16.3 [7.2]	19.5 [5.9]	<0.001	13.9 [7.4]	15.6 [7.3]	15.4 [7.7]	0.137
Last BMI [kg/m²]	mean [SD]	24.8 [6.1]	23.2 [5.4]	22.3 [4.6]	0.022	24.8 [6.0]	24.2 [6.0]	21.8 [5.2]	0.023	24.8 [6.1]	24.4 [4.3]	22.8 [5.4]	0.006
Last FFMI [kg/m²]	mean [SD]	16.9 [3.2]	16.0 [2.8]	15.9 [2.4]	0.154	16.9 [3.1]	17.3 [3.1]	15.5 [2.8]	0.042	16.9 [3.1]	16.0 [2.5]	17.0 [3.4]	0.200
Last FMI [kg/m²]	mean [SD]	7.9 [4.0]	7.2 [3.8]	6.4 [3.0]	0.027	7.9 [3.9]	7.0 [4.2]	6.3 [3.2]	0.025	7.9 [4.0]	8.5 [3.5]	5.8 [2.9]	<0.001
Baseline age [yrs]	mean [SD]	72.5 [6.2]	71.7 [6.4]	75.4 [6.7]	0.278	72.5 [6.2]	72.0 [6.6]	71.6 [5.8]	0.544	72.6 [6.3]	71.6 [6.2]	71.7 [6.1]	0.244
Baseline CIRS [score][1]	mean [SD]	11.8 [7.1]	12.1 [7.2]	14.6 [5.6]	0.019	11.7 [7.0]	13.7 [7.4]	15.0 [6.8]	0.012	11.9 [7.1]	12.8 [6.9]	12.8 [7.0]	0.440
Baseline BMI [kg/m²]	mean [SD]	25.2 [6.1]	21.5 [5.1]	25.5 [4.7]	<0.001	25.2 [6.0]	22.5 [6.0]	24.2 [5.1]	0.012	25.2 [6.0]	21.8 [4.8]	25.3 [5.5]	<0.001
Baseline FFMI [kg/m²]	mean [SD]	17.1 [3.2]	15.2 [2.8]	17.3 [2.7]	<0.001	17.1 [3.2]	15.4 [3.0]	17.6 [3.1]	0.002	17.1 [3.2]	15.8 [3.3]	16.8 [3.1]	0.054
Baseline FMI [kg/m²]	mean [SD]	8.1 [4.0]	6.3 [3.6]	8.3 [3.1]	<0.001	8.1 [4.0]	7.2 [4.2]	6.6 [2.7]	0.039	8.1 [4.0]	6.1 [3.2]	8.5 [3.4]	<0.001
Number of BIA measurements	median [min, max]	3 [2, 22]	5 [3, 18]	5 [3, 27]	<0.001	2 [2, 24]	3 [3, 18]	5 [3, 27]	<0.001	2 [2, 27]	5 [3, 18]	2 [3, 24]	<0.001
Time between first and last BIA measurement [yrs]	median [range]	1.1 [0.1, 15.3]	1.9 [0.1, 13.4]	1.4 [0.1, 12.4]		1.1 [0.1, 15.3]	1.4 [0.1, 13.0]	1.2 [0.1, 12.4]		1.1 [0.1, 15.3]	1.6 [0.1, 13.3]	2.8 [0.1, 9.9]	
Categorical variables													
Last BMI [kg/m²]				0.127				0.010				0.323	
< 18.5	n [%]	85 [12]	3 [6]	9 [20]		83 [12]	5 [11]	9 [35]		87 [13]	3 [6]	7 [16]	
18.5-24.9	n [%]	307 [44]	22 [44]	24 [52]		320 [45]	23 [50]	10 [39]		307 [44]	22 [45]	24 [53]	
≥25.0	n [%]	303 [44]	25 [50]	13 [28]		316 [44]	18 [39]	7 [27]		303 [43]	24 [49]	14 [31]	
Last FFMI [kg/m²]				0.008				0.001				0.229	
No sarcopenia	n [%]	360 [52]	26 [52]	13 [28]		372 [52]	23 [50]	4 [15]		358 [51]	19 [39]	22 [49]	
Sarcopenia[2]	n [%]	335 [48]	24 [48]	33 [72]		347 [48]	23 [50]	22 [85]		339 [49]	30 [61]	23 [51]	
Last FMI [kg/m²]				0.280				0.453				0.011	
No obesity	n [%]	270 [39]	16 [32]	22 [48]		275 [38]	21 [46]	12 [46]		268 [38]	14 [29]	26 [58]	
Obesity[3]	n [%]	425 [61]	34 [68]	24 [52]		444 [62]	25 [54]	14 [54]		429 [62]	35 [71]	19 [42]	

BMI: body mass index, FFMI: fat free mass index, FMI: fat mass index, CIRS: cumulative illness rating scale

[1]For the baseline CIRS score, n= 689, 49 and 46 for the categories of BMI maintenance, gain and loss, respectivels, n= 713, 45, and 26 for the categories of FFMI maintenance, gain and loss, respectively, and n = 691, 49 and 44 for the categories of FMI maintenance.

[2] Sarcopenia was defined as FFMI < 15.1 kg/m² for women and <17.5 kg/m² for men

[3] Obesity was defined as FMI > 8.2 kg/m² for women and >5.2 kg/m² in men

*Comparisons within categories of BMI, FFMI or FFMI changes (Kruskall-Wallis test for continuous data, Chi-squared test for categorical data)

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Supplemental table 4: Univariate Cox regressions (n=791)

	All (n=791)			Women (n=318)			Men (n=473)		
Variables	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
BMI change			0.112			0.017			0.008
Stable	1			1			1		
Gain	0.95	0.63, 1.43		2.31	1.34, 3.97		0.46	0.23, 0.89	
Loss	1.52	1.04, 2.23		1.52	0.67, 3.47		1.40	0.91, 2.16	
FFMI change			<0.001			0.070			0.001
Stable	1			1			1		
Gain	1.37	0.92, 2.04		2.01	0.64, 6.34		1.06	0.63, 1.79	
Loss	2.88	1.83, 4.52		2.05	1.11, 3.80		2.82	1.72, 4.63	
FMI change			0.868			0.012			0.297
Stable	1			1			1		
Gain	1.11	0.74, 1.66		2.83	1.55, 5.16		0.67	0.38, 1.16	
Loss	0.96	0.63, 1.48		1.08	0.50, 2.31		0.89	0.53, 1.50	
Sex			<0.001						
Women	1								
Men	1.45	1.19, 1.76							
Last age [yrs]	1.00	0.98, 1.01	0.516	0.99	0.97, 1.01	0.401	1.00	0.98, 1.02	0.785
Last CIRS [score]	1.08	1.06, 1.09	<0.001	1.08	1.06, 1.11	<0.001	1.07	1.05, 1.09	<0.001
Last BMI [kg/m^2]			<0.001			<0.001			<0.001
<18.5	1.75	1.34, 2.30		1.63	1.08, 2.47		2.15	1.50, 3.08	
18.5-24.9	1			1			1		
>25	0.64	0.52, 0.79		0.62	0.43, 0.88		0.64	0.49, 0.83	
Last FFMI [kg/m^2]			<0.001			<0.001			<0.001
No sarcopenia	1			1			1		
Sarcopenia	2.17	1.78, 2.64		2.24	1.61, 3.10		2.22	1.74, 2.85	
Last FMI [kg/m^2]			<0.001			<0.001			<0.001
No obesity	1			1			1		
Obesity	0.72	0.59, 0.87		0.75	0.55, 1.03		0.63	0.49, 0.81	

BMI: body mass index, FFMI: fat free mass index, FMI: fat mass index, CIRS: cumulative illness rating scale

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Supplemental table 5: Trends of mortality throughout categories of body mass index, fat mass index and fat-free mass index changes

		Loss	Maintenance	Gain	p
Changes of BMI					
Women	Total (n)	6	138	15	0.181
	Deceased (%)	46.2	48.9	65.2	
Men	Total	23	234	9	0.006
	Deceased (%)	69.7	56.7	33.3	
Changes of FFMI					
Women	Total (n)	3	145	11	0.411
	Deceased (%)	50.0	49.3	61.1	
Men	Total (n)	17	234	15	0.059
	Deceased (%)	85.0	55.1	53.6	
Changes of FMI					
Women	Total (n)	7	140	12	0.171
	Deceased (%)	43.8	49.3	66.7	
Men	Total (n)	15	238	13	0.417
	Deceased (%)	51.7	57.6	41.9	

BMI: body mass index, FFMI: fat free mass index, FMI: fat mass index

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Supplemental figure 1