**S1 Appendix. Causal mediation analysis**

**Methods**. Mediation may be measured by the difference in effects between a model that includes the mediator (regression direct effect) and one that does not include the mediator (total regression effect). This requires no interaction between the exposure and the mediator, which may not be the case here. Therefore we performed a causal mediation analysis similar to that of VanderWeele (48), modeling survival using an accelerated failure time model with a Weibull distribution. The assumptions for a causal mediation analysis with a proportional hazards model are only met if the outcome is rare (49). We fit the following models:

For low muscle mass as the mediator:

For the appendicular skeletal muscle mass index (ASMI) as the mediator:

where Ti is the follow-up time; εi is the residual variation in the log-transformed survival times; σ is a scale parameter; a1i – a4i are dummy variables, each taking the value of 1 for a BMI category (18.5 - <22, 22 - <25, 30 - <35, and 35-40 kg/m2, respectively) and 0 otherwise, with 25 - <30 kg/m2 as the reference category; mi is the mediator; and ci is a vector containing all other covariate values. When we examined mediation by low muscle mass, because of the small number of participants with obese BMI and low muscle mass, the two highest BMI categories were combined and only a1i – a3i were used for dummy variables.

For BMI 18.5 - <22 kg/m2, a1i, we estimated the following (50):

CDE1 = θ1

INTref1 = θint1(β0 + β’cci)a1i

INTmed1 = θint1β1

PIE1 = θmβ1

TE1 = CDE1 + INTref1 + INTmed1 + PIE1,

where the controlled direct effect (CDE) is the effect of BMI on all-cause mortality when the mediator is not present; INTref is the reference interaction between BMI and other predictors not including the mediator; INTmed is the interaction between BMI and the mediator; PIE is the pure indirect effect on mortality from the product effect of BMI through the mediator; and TE is the total effect of BMI on mortality. We similarly estimated the above parameters for the remaining BMI categories. INTref was estimated using the following covariate values: 51 year old (the mean age) non-Hispanic white woman, never smoker, without a high-school diploma, and reporting the lowest level of physical activity.

The appendicular skeletal muscle mass index was entered into the model as the sex-specific arithmetic distance from the low muscle mass threshold, as defined in the main text of the paper: ASMI - 5.45 for women; ASMI - 7.26 for men. We also performed causal mediation analyses for the appendicular skeletal muscle mass index in participants <60 and ≥60 years old, separately.

**Results**. There was a significant mediated effect (PIE) through muscle mass at all levels of BMI using either low muscle mass or the appendicular skeletal muscle mass index as the mediator (see Tables below). Significant mediated effects were also noted in both age subgroups. Interaction effects were not statistically significant.

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| **Causal mediation analysis examining low muscle mass as a mediator of the association of BMI with all-cause mortality** | | | | | | |
|  | Body Mass Index (kg/m2) | | | | | |
|  | 18.5-<22 | | 22-<25 | | 30-40 | |
|  | Estimate (95% CI) | p | Estimate (95% CI) | p | Estimate (95% CI) | p |
| **Causal mediation models** |  |  |  |  |  |  |
| Controlled direct effect | -0.29 (-0.51 to -0.07) | 0.01 | 0 (-.15 to .15) | 0.99 | -0.14 (-0.27 to -0.02) | 0.02 |
| Interaction in absence of mediator | -0.86 (-1.89 to 0.17) | 0.10 | -0.37 (-1.20 to 0.45) | 0.37 | 1.21 (-0.59 to 3.00) | 0.18 |
| Mediated interaction | 0.99 (-0.17 to 2.16) | 0.09 | 0.24 (-0.29 to 0.77) | 0.36 | 1.07 (-0.53 to 2.66) | 0.18 |
| Pure indirect effect | -1.05 (-1.63 to -0.47) | <0.001 | -0.59 (-0.91 to -0.28) | <0.001 | 0.80 (0.33 to 1.27) | 0.001 |
| Total effect | -1.21 (-1.78 to -0.63) | <0.001 | -0.72 (-1.38 to -0.06) | 0.03 | 2.93 (-0.42 to 6.29) | 0.08 |
|  |  |  |  |  |  |  |
| **Results from conventional models** |  |  |  |  |  |  |
| Regression direct effect | -0.14 (-0.26 to -0.02) | 0.03 | 0.03 (-0.08 to 0.14) | 0.55 | -0.13 (-0.26 to -0.01) | 0.03 |
| Total regression effect | -0.26 (-0.38 to -0.15) | <0.001 | -0.04 (-0.15 to 0.07) | 0.48 | -0.11 (-0.23 to 0.01) | 0.06 |

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| **Causal mediation analysis examining the appendicular skeletal muscle mass index as a mediator of the association of BMI with all-cause mortality** | | | | | | | | |
|  | Body Mass Index (kg/m2) | | | | | | | |
|  | 18.5-<22 | | 22-<25 | | 30-<35 | | 35-40 | |
|  | Estimate (95% CI) | p | Estimate (95% CI) | p | Estimate (95% CI) | p | Estimate (95% CI) | p |
| **Causal mediation models** |  |  |  |  |  |  |  |  |
| Controlled direct effect | -0.08 (-0.23 to 0.08) | 0.31 | 0.09 (-0.01 to 0.19) | 0.08 | -0.10 (-0.34 to 0.15) | 0.42 | -0.01 (-0.59 to 0.57) | 0.96 |
| Interaction in absence of mediator | -0.07 (-0.25 to 0.10) | 0.40 | 0.03 (-0.15 to 0.22) | 0.71 | -0.11 (-0.25 to 0.03) | 0.13 | -0.16 (-0.36 to 0.05) | 0.12 |
| Mediated interaction | 0.10 (-0.13 to 0.33) | 0.40 | -0.03 (-0.17 to 0.11) | 0.71 | -0.09 (-0.22 to 0.03) | 0.13 | -0.28 (-0.64 to 0.08) | 0.13 |
| Pure indirect effect | -0.24 (-0.37 to -0.10) | 0.001 | -0.14 (-0.22 to -0.06) | 0.001 | 0.16 (0.07 to 0.25) | 0.001 | 0.32 (0.14 to 0.50) | 0.001 |
| Total effect | -0.29 (-0.42 to -0.17) | <0.001 | -0.04 (-0.17 to 0.09) | 0.54 | -0.14 (-0.27 to -0.01) | 0.04 | -0.13 (-0.32 to 0.06) | 0.17 |
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| **Results from conventional models** |  |  |  |  |  |  |  |  |
| Regression direct effect | -0.10 (-0.24 to 0.04) | 0.16 | 0.05 (-0.05 to 0.16) | 0.31 | -0.23 (-0.39 to -0.07) | 0.006 | -0.33 (-0.57 to -0.09) | 0.008 |
| Total regression effect | -0.26 (-0.38 to -0.15) | <0.001 | -0.04 (-0.15 to 0.07) | 0.48 | -0.12 (-0.24 to 0.01) | 0.07 | -0.10 (-0.29 to 0.08) | 0.27 |

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| **Age-stratified causal mediation analysis examining the appendicular skeletal muscle mass index as a mediator of the association of BMI with all-cause mortality** | | | | | | | | |
|  | Body Mass Index (kg/m2) | | | | | | | |
|  | 18.5-<22 | | 22-<25 | | 30-<35 | | 35-40 | |
|  | Estimate (95% CI) | p | Estimate (95% CI) | p | Estimate (95% CI) | p | Estimate (95% CI) | p |
| *Age <60 (n=7,395)* |  |  |  |  |  |  |  |  |
| **Causal mediation models** |  |  |  |  |  |  |  |  |
| Controlled direct effect | 0.10 (-0.28 to 0.49) | 0.59 | 0.25 (-0.09 to 0.58) | 0.14 | -0.34 (-1.09 to 0.40) | 0.36 | -1.47 (-2.80 to -0.14) | 0.03 |
| Interaction in absence of mediator | -0.28 (-0.79 to 0.24) | 0.29 | 0.03 (-0.57 to 0.63) | 0.92 | -0.19 (-0.65 to 0.26) | 0.40 | 0.16 (-0.51 to 0.84) | 0.62 |
| Mediated interaction | 0.31 (-0.26 to 0.89) | 0.28 | -0.02 (-0.41 to 0.37) | 0.92 | -0.15 (-0.49 to 0.20) | 0.40 | 0.24 (-0.75 to 1.23) | 0.62 |
| Pure indirect effect | -0.52 (-0.92 to -0.12) | 0.01 | -0.30 (-0.54 to -0.07) | 0.01 | 0.35 (0.08 to 0.62) | 0.01 | 0.69 (0.17 to 1.20) | 0.01 |
| Total effect | -0.38 (-0.76 to 0.00) | 0.05 | -0.05 (-0.40 to 0.31) | 0.80 | -0.33 (-0.63 to -0.03) | 0.03 | -0.38 (-0.87 to 0.12) | 0.13 |
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| **Results from conventional models** |  |  |  |  |  |  |  |  |
| Regression direct effect | 0.10 (-0.29 to 0.48) | 0.62 | 0.22 (-0.06 to 0.50) | 0.12 | -0.62 (-1.02 to -0.23) | 0.003 | -1.02 (-1.63 to -0.41) | 0.002 |
| Total regression effect | -0.38 (-0.75 to -0.02) | 0.04 | -0.06 (-0.39 to 0.27) | 0.74 | -0.32 (-0.60 to -0.03) | 0.03 | -0.42 (-0.87 to 0.02) | 0.06 |
|  |  |  |  |  |  |  |  |  |
| *Age ≥60 (n=4,292)* |  |  |  |  |  |  |  |  |
| **Causal mediation models** |  |  |  |  |  |  |  |  |
| Controlled direct effect | -0.10 (-0.28 to 0.08) | 0.27 | 0.06 (-0.06 to 0.19) | 0.32 | -0.11 (-0.37 to 0.15) | 0.41 | 0.42 (-0.13 to 0.96) | 0.13 |
| Interaction in absence of mediator | 0.01 (-0.11 to 0.14) | 0.83 | 0.03 (-0.10 to 0.16) | 0.64 | -0.02 (-0.12 to 0.08) | 0.72 | -0.17 (-0.32 to -0.02) | 0.03 |
| Mediated interaction | -0.02 (-0.25 to 0.20) | 0.83 | -0.03 (-0.16 to 0.10) | 0.64 | -0.02 (-0.14 to 0.10) | 0.72 | -0.44 (-0.83 to -0.05) | 0.03 |
| Pure indirect effect | -0.12 (-0.22 to -0.01) | 0.04 | -0.07 (-0.13 to -0.01) | 0.03 | 0.08 (0.01 to 0.15) | 0.04 | 0.17 (0.01 to 0.33) | 0.04 |
| Total effect | -0.22 (-0.35 to -0.10) | <0.001 | 0 (-0.12 to 0.11) | 0.94 | -0.07 (-0.18 to 0.05) | 0.24 | -0.02 (-0.17 to 0.13) | 0.79 |
|  |  |  |  |  |  |  |  |  |
| **Results from conventional models** |  |  |  |  |  |  |  |  |
| Regression direct effect | -0.14 (-0.27 to -0.01) | 0.04 | 0.04 (-0.09 to 0.17) | 0.54 | -0.12 (-0.27 to 0.02) | 0.08 | -0.16 (-0.36 to 0.03) | 0.10 |
| Total regression effect | -0.22 (-0.34 to -0.10) | 0.001 | -0.01 (-0.12 to 0.11) | 0.89 | -0.06 (-0.18 to 0.05) | 0.28 | -0.04 (-0.18 to 0.11) | 0.63 |