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Low appendicular skeletal muscle mass is associated with the risk of mortality among adults in the United States

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Low skeletal muscle mass has been shown to be a predictor of mortality, but very few studies have focused on the association between appendicular skeletal muscle mass and mortality risk in a large sample. This study aimed to determine the associations of low appendicular skeletal muscle mass with all-cause and cause-specific mortality in an adult population in the United States. Data were retrieved from 21,938 participants aged 20–85 years from the National Health and Nutrition Examination Survey (NHANES) (1999–2006 and 2011–2018) and merged with the Public-use Linked Mortality File of 2018. The appendicular skeletal muscle mass index (kg/m^2) was determined by the skeletal muscle mass in the arms and legs (in kg) and divided by the square of the height (in meters) ^{2} (kg/m^2). Sex-specific quintiles were then used to categorize the appendicular skeletal muscle mass index. The major outcome in this study was mortality from all causes, and the secondary outcome was mortality from heart disease or cancer. Cox proportional hazards models were used to calculate hazard ratios, and 95% confidence intervals for all-cause and competing risk regression analyses were performed to analyze heart disease mortality and cancer mortality. During a 10.9-year median follow-up, 1632 males and 1253 females died. Compared with those of the 5th quintile of the skeletal muscle index, the fully adjusted HRs (95% CIs) of all-cause mortality were 0.81 (0.72–0.92), 0.63 (0.52–0.76), 0.52 (0.43–0.63), and 0.65 (0.52–0.81) for the 1st, 2nd, 3rd, and 4th quintiles of the skeletal muscle index, respectively. A 20-percentile increase in the appendicular skeletal muscle index was associated with a lower risk of all-cause mortality (HR, 0.86; 95% CI, 0.81–0.91) ($P < 0.001$ for trend) and a lower risk of cancer mortality (HR, 0.87; 95% CI, 0.78–0.96) ($P = 0.009$ for trend). High appendicular skeletal muscle mass was associated with decreased all-cause mortality and cancer mortality in adults, and interventions aimed at maintaining appropriate appendicular skeletal muscle mass may help prevent premature death.

Keywords Skeletal muscle mass, All-cause mortality, Cancer mortality, NHANES

Skeletal muscle mass is a dominant part of lean body mass, which is an important component of the human body[1]. A low level of skeletal muscle mass is associated with weak physical function[2] and an unhealthy overall status, such as weakness, disability and morbidity[3]. Significant skeletal muscle loss can be a major risk factor for various adverse health outcomes, such as falls, immobility, frailty and functional decline[4]. A previous study revealed that low skeletal muscle mass was a predictor of all-cause mortality, especially in older individuals and/or those with chronic diseases, and it was more appropriate than body mass index (BMI) for classifying mortality risk because BMI might be affected by age, sex, race and other variables. The association between higher BMI and a greater risk of mortality might not be evident in older adults or individuals with chronic diseases. For example, older people may have a high BMI but low skeletal muscle mass because they tend to have increased fat mass but lose fat-free mass and skeletal muscle mass[1,4–8]. In addition, skeletal muscle mass supports daily physical function, and low physical function was found to be associated with a higher risk of all-cause mortality and cardiovascular mortality in older adults with type 2 diabetes[9]. Appendicular skeletal muscle accounts for >75% of total body skeletal muscle, which is the primary portion of skeletal muscle involved in ambulation and physical activities[10]. It refers specifically to the muscle mass in the limbs (arms and legs), which is closely linked

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to functional outcomes such as strength, mobility and physical performance[11]. Sarcopenia (the loss of muscle mass and function) and frailty are primarily characterized by a decrease in appendicular muscle mass, which has a more significant effect on physical disability than changes in overall skeletal muscle mass[12].

To date, the association between skeletal muscle mass and all-cause mortality has been well studied in the adult population but not in a large sample with long-term follow-up[1,2,4,10]. It is essential to characterize the long-term outcomes of low skeletal muscle mass in adults to develop targeted and effective interventions. However, there is a lack of studies focusing on the relationship of appendicular muscle mass and morality in a large sample. This study aimed to examine the associations of appendicular skeletal muscle mass with all-cause mortality on the basis of a nationally representative large sample of the adult population in the United States.

Methods

Study design and population

The data files analyzed in this study were retrieved from the National Health and Nutrition Examination Survey (NHANES), which is released by the Centers for Disease Control and Prevention (CDC). The NHANES is a continuous program of studies to assess the status of health and nutrition for children and adults in the United States. The contents and corresponding methods of the NHANES are introduced in detail on the CDC website (https://www.cdc.gov/nchs/nhanes/index.htm). Five cycles of data (1999–2006, 2011–2018) from the NHANES with ages ranging from 20 to 85 years for the participants and corresponding mortality data from the National Death Index (NDI) dataset were analyzed.

The protocol for NHANES was approved by the National Center for Health Statistics Research Ethics Review Board (Protocol #98 – 12, Protocol #2005-06, Protocol #2011-17, Protocol #2018-01). Informed consent was signed by the recruited participants before they were invited to complete the interview questionnaires and laboratory tests at a mobile examination center. All analyses in this study were performed in accordance with the NHANES guidelines and regulations.

A total of 55,081 participants with ages ranging from 20 to 85 years were included in the NHANES (1999–2006, 2011–2018) datasets. Participants without mortality/follow-up information ($n = 2805$) and without other covariates ($n = 6057$) were excluded. Furthermore, participants who had invalid data or incomplete appendicular dual-energy X-ray absorptiometry (DXA) information ($n = 24,281$) were excluded. Finally, a cohort of 21,938 participants with complete outcomes and covariates were examined in this study (Fig. 1).

Outcome

The mortality information of the participants in the NHANES was obtained from the National Death Index (NDI) dataset (https://www.cdc.gov/nchs/data-linkage/).

mortality-public.htm) until December 31, 2018, and merged with the NHANES data files via a unique identifier. Causes of death were ascertained from death certificates. The follow-up time was calculated in months from the date of the interview/examination to the date of death or the end of 2018. The major outcome in this study was mortality from all causes, and the secondary outcome was mortality from heart disease or cancer, which were the two major causes of death in the records. Death from heart disease was defined as the cause of death, including codes I00–09, I11, I13, and I20–51, via the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Death from cancer was defined as the cause of death, including code C00–97.

Exposure variable

Whole-body dual-energy X-ray absorptiometry (DXA) was used to measure body composition. The appendicular skeletal muscle mass index (SMI) was determined by the skeletal muscle mass in the arms and legs (in kg) divided by the square of the height (in meters)[2][13,14]. Sex-specific quintiles were then used to categorize the SMIs. The quintile cutoffs of SMI for males are 7.60, 8.28, 8.88, 9.66 kg/m^2 respectively, while for females are 5.71, 6.29, 6.90 and 7.81 kg/m^2 respectively.

Covariates

The demographic covariates extracted from the NHANES included age, sex, race, marital status, education level, income-to-poverty ratio (IPR), and body mass index (BMI). Other functional covariates included history of myocardial infarction (MI), history of diabetes, history of stroke, and history of cancer (only for associations with all-cause mortality). We characterized "history of MI" with self-reported heart attack. A history of diabetes was defined as having self-reported diabetes or glycosylated hemoglobin, Type A1C (HbA1c) 6.5% or greater, fasting plasma glucose (FPG) 126 mg/dL or greater, or 2-hour plasma glucose (2hPG) 200 mg/dL or greater; a history of stroke was defined as a self-reported physician diagnosis of stroke, and a "history of cancer" with self-reported cancer or malignant neoplasms.

Statistical analysis

As weights were created to explain the complex survey design (including oversampling, survey nonresponse, and poststratification), we followed the analytic guidelines and survey methods from the NHANES and used appropriate sampling weights and corresponding survey analysis procedures to analyze the data in this study.

The demographic covariates of the sample in this study were compared between the first and last quintiles of the SMI among the adult participants via the Rao–Scott χ^2 test. The log-rank test was used to test the proportional hazard assumption, and Kaplan–Meier estimates and Log rank tests were used to compare all-cause mortality survival curves for the different quintiles of SMI. The Cox proportional hazards regression model was used to assess the HRs and 95% CIs of the associations between all-cause mortality and the SMI. Two models were performed: Model 1 was adjusted for age and sex (male or female), and Model 2 was adjusted for age, sex (male

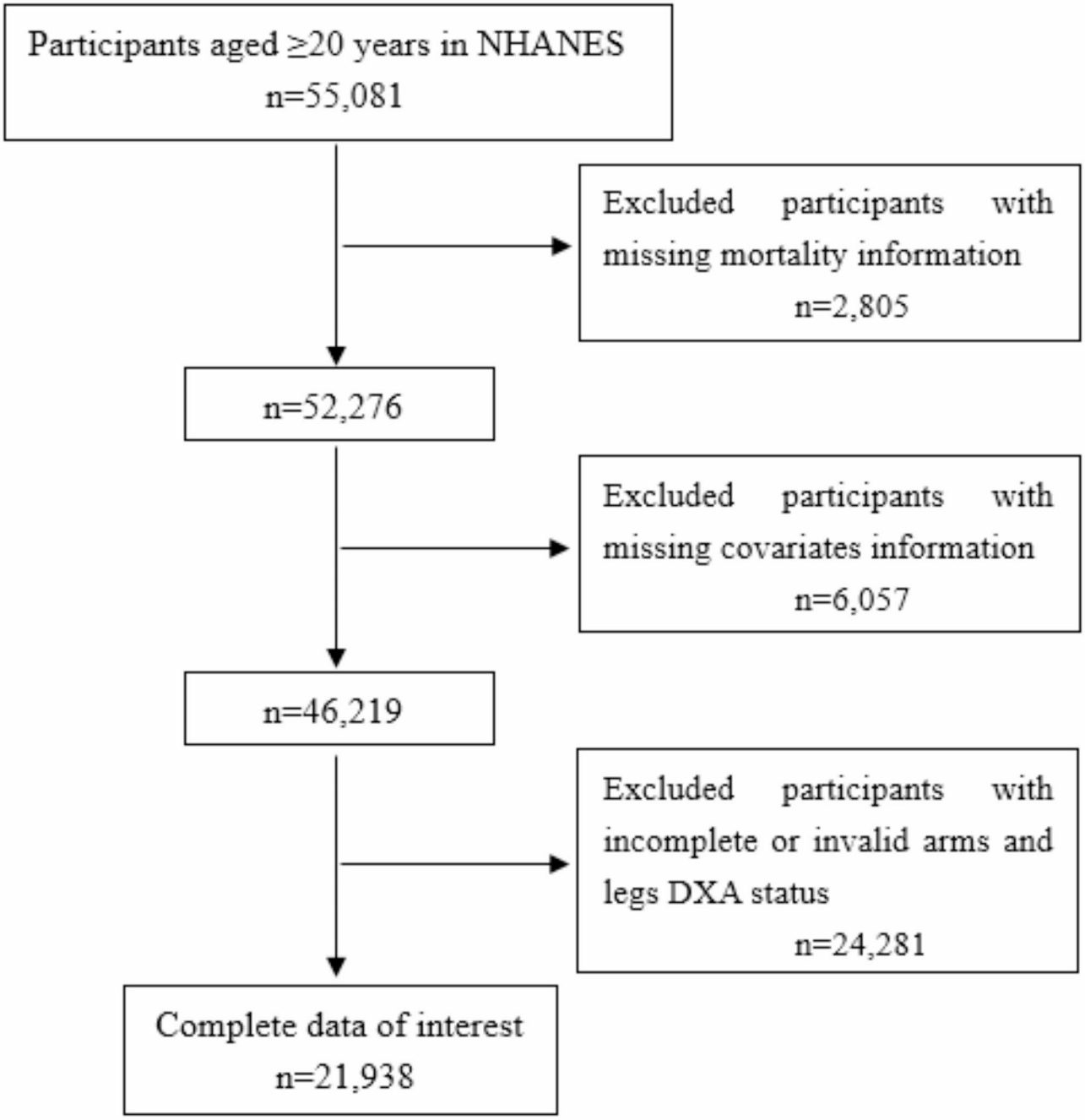

Fig. 1. Flow chart of the participants included from NHANES 1999–2006, 2011–2018.

or female), race/ethnicity (non-Hispanic white, other), marital status (married/cohabiting, other), educational level (less than college, college or above), the family income-to-poverty ratio (<2.5, >=2.5), BMI, and history of chronic diseases (yes or no). The trends were estimated by treating the quintiles as a continuous variable. The above two models were applied in the males and females subgroups specifically. The association between SMI and all-cause mortality was then examined by multivariate adjusted Cox restricted cubic spline regression models. Competing risk analysis was performed on the associations between cause-specific mortality (mortality due to heart disease or cancer) and the SMI.

To evaluate the potential modification by subgroups, the survey-weighted Wald F statistic was used to test for an interaction between the SMI and the subgroup variables. Additionally, several sensitivity analyses were conducted to test the robustness of our findings. First, the participants who died during the first year of follow-up were excluded. Second, participants with a history of diabetes, myocardial infarction (MI), stroke or cancer were excluded.

All analyses in this study were conducted via SAS (version 9.4, 2013; SAS Institute Inc. Cary, NC). All tests were conducted as two-tailed tests, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study participants

During a 10.9-year follow-up [interquartile range (IQR): 5.2–16.6]. A total of 1632 males and 1253 females in the cohort died (2885 in total, 1070 in the first quintile of SMI, and 346 in the fifth quintile), including 739 deaths from heart disease and 687 from cancer. The mean age of the total population was 41.1 years, and 49.6% were male (11,025 males and 10,913 females). The weighted median (interquartile range) SMIs for males and females were 8.6 (7.8, 9.4) kg/m^2 and 6.6 (5.9, 7.5) kg/m^{2,} respectively. The baseline characteristics of the target cohort and comparisons of the characteristics between the deceased and alive patients, as long as between the first and last quintiles of SMIs are displayed in Table 1. The deceased participants tend to be older, with lower education level, lower family income than the alive participants; more males and more participants deceased than females and participants with chronic disease were more likely to be deceased. Participants with highest SMI were 4.7 years younger than the participants with the lowest SMI on average. Non-Hispanic Black people, participants with higher BMI and/or history of diabetes and hypertension tend to have higher SMI than the others.

Associations between the SMI and mortality

SMI was significantly associated with all-cause mortality (Table 2). In the Cox proportional hazard regression analysis, the multivariable-adjusted HRs of all-cause mortality from the lowest and highest quintiles of SMI were 1 (reference), 0.81 (95% CI, 0.72–0.92), 0.63 (95% CI, 0.52–0.76), 0.52 (95% CI, 0.43–0.63), and 0.65 (95% CI, 0.52–0.81) ($P<0.001$ for trend) after adjusting for age, race, marital status, education, the family income-to-poverty ratio, BMI, history of diabetes, MI, stroke and cancer, respectively. A 20-percentile increase in the SMI was associated with a 14% lower risk of all-cause mortality (HR, 0.86; 95% CI, 0.81–0.91). The multivariable-adjusted hazard ratio (HR) per 20th-percentile increase in SMI was 0.87 (95% CI, 0.78–0.96) ($P=0.009$ for trend) for mortality from cancer and 0.81 (95% CI, 0.74–0.88) ($P<0.001$ for trend) for other types of mortality, whereas the association between SMI and heart disease mortality was not significant (eTable 1 in the Supplement).

Characteristic, *n* (%)	Total (21,938)	Alive (19,053)	Deceased[b] (2885)	*P* value[c]	SMI Quintile1 (4499)	SMI Quintile5 (4679)	*P* value
Age (years, mean ± SD[a])	42.3 ± 0.2	40.3 ± 0.2	62.4 ± 0.4	< 0.001	44.7 ± 0.3	40.0 ± 0.3	< 0.001
Sex				0.99			0.990
Male	11,025 (49.6)	9393 (49.3)	1632 (52.6)		2405 (49.6)	2223 (49.6)	
Female	10,913 (50.4)	9660 (50.7)	1253 (47.4)		2094 (50.4)	2456 (50.4)	
Race/Ethnicity				< 0.001			< 0.001
Hispanic	5605 (14.6)	5039 (15.3)	566 (7.6)		1045 (11.6)	998 (14.8)	
Non-Hispanic Black	4397 (10.5)	3835 (10.4)	562 (10.9)		362 (4.1)	1877 (23.0)	
Non-Hispanic White	9629 (68.1)	7948 (67.1)	1681 (77.8)		2327 (73.2)	1516 (57.3)	
Others	2307 (6.8)	2231 (7.2)	76 (3.6)		765 (11.1)	288 (4.9)	
Marital status				0.03			0.030
Married/Cohabiting	13,502 (64.4)	11,877 (59.0)	1625 (59.2)		2693 (61.0)	2740 (63.5)	
Other	8436 (35.6)	7176 (35.1)	1260 (40.8)		1806 (39.0)	1939 (36.5)	
Education				0.02			0.020
Less than college	10,284 (39.3)	8381 (37.1)	1903 (60.3)		2192 (41.7)	2065 (39.3)	
College or above	11,654 (60.7)	10,672 (62.9)	982 (39.7)		2299 (58.3)	2614 (60.7)	
Income to poverty ratio (IPR)[d]				< 0.001			< 0.001
< 2.5	11,649 (42.1)	9852 (40.9)	1797 (54.5)		2513 (45.6)	2613 (46.3)	
≥ 2.5	10,289 (57.9)	9201 (59.1)	1088 (45.5)		1986 (54.4)	2066 (53.7)	
BMI (kg/m^2)				< 0.001			< 0.001
< 30	14,713 (68.1)	12,689 (68.0)	2024 (68.4)	< 0.001	4464 (99.4)	596 (12.5)	< 0.001
> 30	7225 (31.9)	6364 (32.0)	861 (31.6)		35 (0.6)	4083 (87.5)	
Chronic disease				< 0.001			< 0.001
Yes	2550 (8.4)	1812 (6.9)	738 (22.4)		1459 (27.4)	1813 (35.7)	
No	19,388 (91.6)	17,241 (93.1)	2147 (77.6)		3040 (72.6)	2866 (64.3)	
History of diabetes	2550 (8.4)	1812 (6.9)	738 (22.4)	< 0.001	421 (6.1)	789 (13.8)	< 0.001
History of hypertension	4873 (19.6)	3399 (16.6)	1474 (48.5)	< 0.001	922 (17.1)	1268 (24.7)	< 0.001
History of MI	579 (2.1)	262 (1.2)	317 (10.8)	< 0.001	179 (2.8)	94 (1.6)	< 0.001
History of stroke	493 (1.6)	253 (1.0)	240 ((7.4)	< 0.001	135 (2.0)	88 (1.4)	0.140
History of cancer	1303 (6.2)	796 (5.0)	507 (17.8)	< 0.001	404 (8.9)	198 (4.5)	< 0.001

Table 1. Basic characteristics stratified by all-cause mortality status in the U.S. Adult population, NHANES 1999–2006, 2011–2018. [a]SD, standard deviation; n, number of subjects; %, weighted proportion. [b]Each survey participant who is linkage eligible for mortality follow-up is defined as deceased, and the rest are alive. [c]Chi-square test was used to compare proportions between the population of the first and last quintiles. [d]A ratio of family income to poverty threshold.

Characteristic	Quintiles for SMI					*P* for trend	Per 20-percent increase
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Appendicular SMI							
Median SMI (IQR)	5.69 (5.33–7.13)	6.28 (6.00-7.95)	6.89 (6.59–8.57)	7.81 (7.29–9.23)	9.80 (8.57–10.43)	NA	NA
Deaths, No.	1070	633	456	380	346	NA	NA
Unadjusted HR (95% CI, P value)	1 [Reference]	0.62 (0.54–0.71, $P<0.001$)	0.48 (0.42–0.56, $P<0.001$)	0.39 (0.33–0.46, $P<0.001$)	0.45 (0.38–0.52, $P<0.001$)	<0.001	0.79 (0.76–0.82)
Age- and sex- adjusted HR (95% CI)	1 [Reference]	0.81 (0.72–0.92, $P=0.001$)	0.73 (0.63–0.84, $P<0.001$)	0.66 (0.57–0.76, $P<0.001$)	1.02 (0.88–1.19, $P=0.786$)	0.010	0.95 (0.92–0.99)
Multivariable- adjusted HR (95% CI)*	1 [Reference]	0.81 (0.70–0.94, $P=0.004$)	0.63 (0.52–0.76, $P<0.001$)	0.52 (0.43–0.63, $P<0.001$)	0.65 (0.52–0.81, $P<0.001$)	<0.001	0.86 (0.81–0.91)
Male:							
Unadjusted HR (95% CI, P value)	1 [Reference]	0.54 (0.45–0.63, $P<0.001$)	0.43 (0.35–0.52 $P<0.001$)	0.29 (0.23–0.37, $P<0.001$)	0.37 (0.29–0.47, $P<0.001$)	<0.001	0.74 (0.70–0.78)
Age- adjusted HR (95% CI)	1 [Reference]	0.69 (0.59–0.80, $P<0.001$)	0.66 (0.53–0.81, $P=0.001$)	0.51 (0.40–0.65, $P<0.001$)	0.84 (0.67–1.05, $P=0.132$)	<0.001	0.90 (0.85–0.95)
Multivariable-adjusted HR (95% CI)	1 [Reference]	0.72 (0.61–0.84, $P<0.001$)	0.59 (0.47–0.74, $P<0.001$)	0.44 (0.34–0.56, $P<0.001$)	0.54 (0.41–0.72, $P<0.001$)	<0.001	0.82 (0.77,0.88)
Female:							
Unadjusted HR (95% CI, P value)	1 [Reference]	0.74 (0.59–0.93, $P=0.009$)	0.55 (0.46–0.67, $P<0.001$)	0.53 (0.42–0.66, $P<0.001$)	0.56 (0.45–0.68, $P<0.001$)	<0.001	0.84 (0.80–0.89)
Age- adjusted HR (95% CI)	1 [Reference]	0.98 (0.78–1.21, $P=0.825$)	0.80 (0.66–0.98, $P=0.029$)	0.84 (0.68–1.04, $P=0.116$)	1.24 (0.97–1.58, $P=0.081$)	0.880	1.00 (0.95–1.07)
Multivariable-adjusted HR (95% CI)	1 [Reference]	0.95 (0.73–1.24, $P=0.718$)	0.68 (0.51–0.91, $P=0.009$)	0.66 (0.48–0.92, $P=0.013$)	0.85 (0.58–1.24, $P=0.402$)	0.076	0.92 (0.84–1.01)

Table 2. Associations between the SMI and all-cause mortality. *HR* hazard ratio, *IQR* interquartile range, *NA* not applicable. *Adjusted for age, sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other), marital status (married/cohabiting, never married and widowed/divorced/separated), educational level (above high school, high school or equivalent and under high school), family income to poverty ratio (≤1.3, 1.3–3, ≥3), BMI, history of diabetes (yes or no), history of MI (yes or no), history of stroke (yes or no) and history of cancer (yes or no).

The results in Table 2 also indicated that for males, the multivariable-adjusted hazard ratios (HRs) of all-cause mortality from the lowest to the highest quintiles of SMI were 1 (reference), 0.72 (95% CI, 0.61–0.84), 0.59 (95% CI, 0.47–0.74), 0.44 (95% CI, 0.34–0.56), and 0.54 (95% CI, 0.41–0.72), with a significant trend ($P<0.001$). A 20-percentile increase in SMI was associated with an 18% reduction in the risk of all-cause mortality (HR = 0.82; 95% CI, 0.77–0.88). The association between different SMI quintiles and all-cause mortality was significant. In contrast, for females, the HRs of all-cause mortality from the lowest to the highest quintiles of SMI were 1 (reference), 0.95 (95% CI, 0.73–1.24), 0.68 (95% CI, 0.51–0.91), 0.66(95% CI, 0.48–0.92), and 0.85 (95% CI, 0.58–1.24), with no significant trend ($P=0.076$). The HRs for quintile 2 and 5 were not significant comparing to quintile 1.

In the restricted cubic spline regression models with full adjustment for confounders, the relationships between SMI and all-cause mortality for the overall population (Fig. 2A), for males (Fig. 2B) and for females (Fig. 2C) were all non-linear. There is an L-shaped relationship between SMI and all-cause mortality for males. The hazard ratio decreases rapidly as SMI increases, reaching a minimum around 10 kg/m². And it plateaus beyond that, suggesting no significant additional risk with higher SMI values. The graph for females illustrates the relationship between SMI and hazard ratio, revealing a U-shaped curve. The mortality risk decreases as SMI increases, reaching its lowest point round 7–8 kg/m². The wider confidence interval area reflects greater uncertainty for higher SMI.

The Kaplan–Meier survival curves according to different SMI quintiles for all-cause mortality are shown in Fig. 3 (Log rank $P<0.001$). The participants in the first quintile of SMI had a relatively greater risk than the other participants did, which means that these participants tended to die at an earlier age than the other participants did.

Subgroup and sensitivity analyses

In the subgroup analysis shown in Fig. 4, the results remained persistent in most subgroups.

A significant interaction effect on all-cause mortality was detected between the SMI and BMI ($P=0.001$ for interaction); the HR per 20th-percentile increase was 0.80 (95% CI, 0.75-0.84) among participants with a BMI < 30 vs. 0.96 (95% CI, 0.87–1.06) among participants with a BMI > = 30. In the sensitivity analyses, the results did not change substantially when participants whose deaths occurred within 12 months of follow-up were excluded (eTable 2 in the Supplement) or when participants with diabetes, hypertension, cancer, stroke or MI at baseline were excluded (eTable 2 in the Supplement).

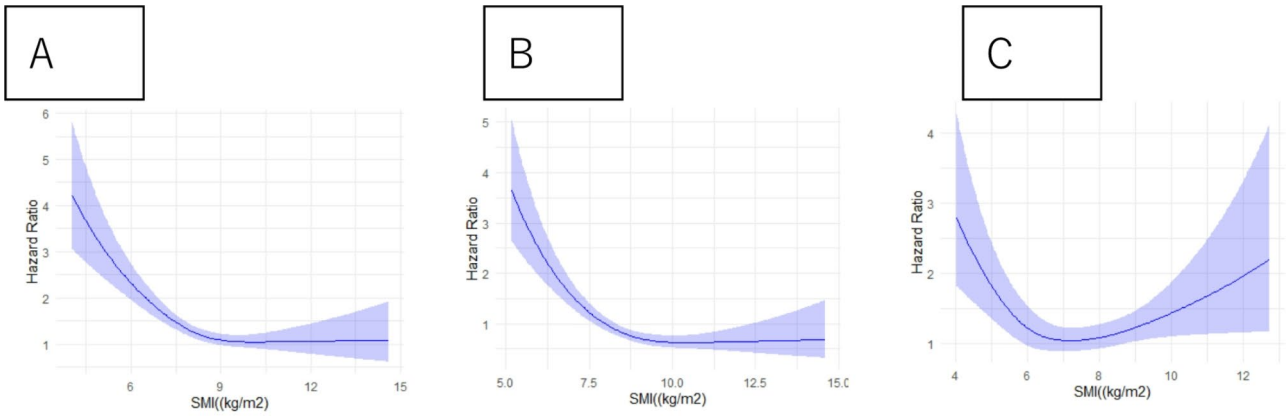

Fig. 2. Spline analyses of all-cause mortality by SMI in the overall cohort (**A**) and males (**B**) and females (**C**) (spline analyses were adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other), marital status (married/cohabiting, never married and widowed/divorced/separated), educational level (above high school, high school or equivalent and under high school), family income to poverty ratio (≤ 1.3, 1.3–3, ≥ 3), BMI, history of diabetes (yes or no), history of MI (yes or no), history of stroke (yes or no) and history of cancer (yes or no).

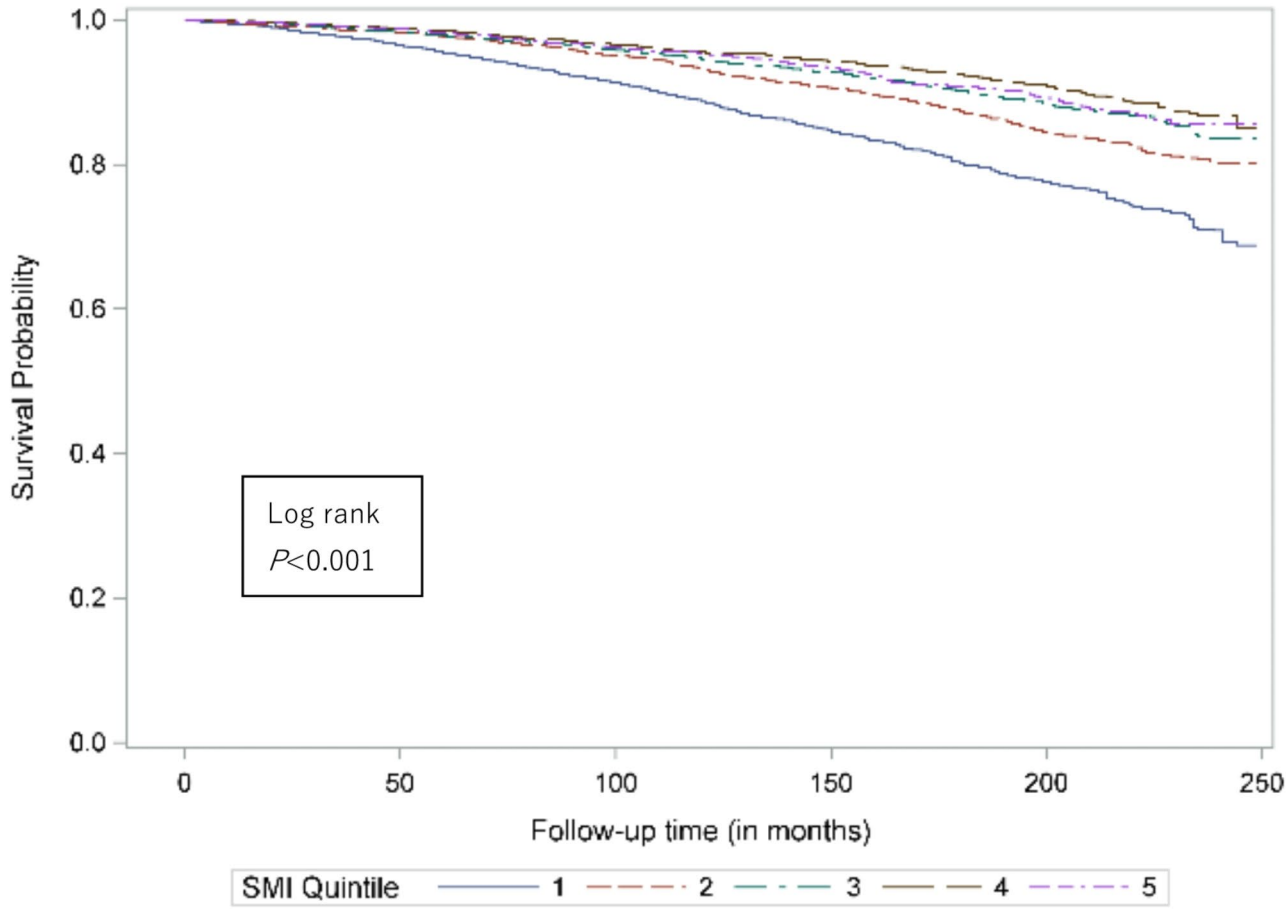

Fig. 3. K–M survival curves for the participants according to different SMI quintiles. 1, 2, 3, 4 and 5 represent the first, second, third, fourth and fifth SMI quintiles, respectively, from low to high.

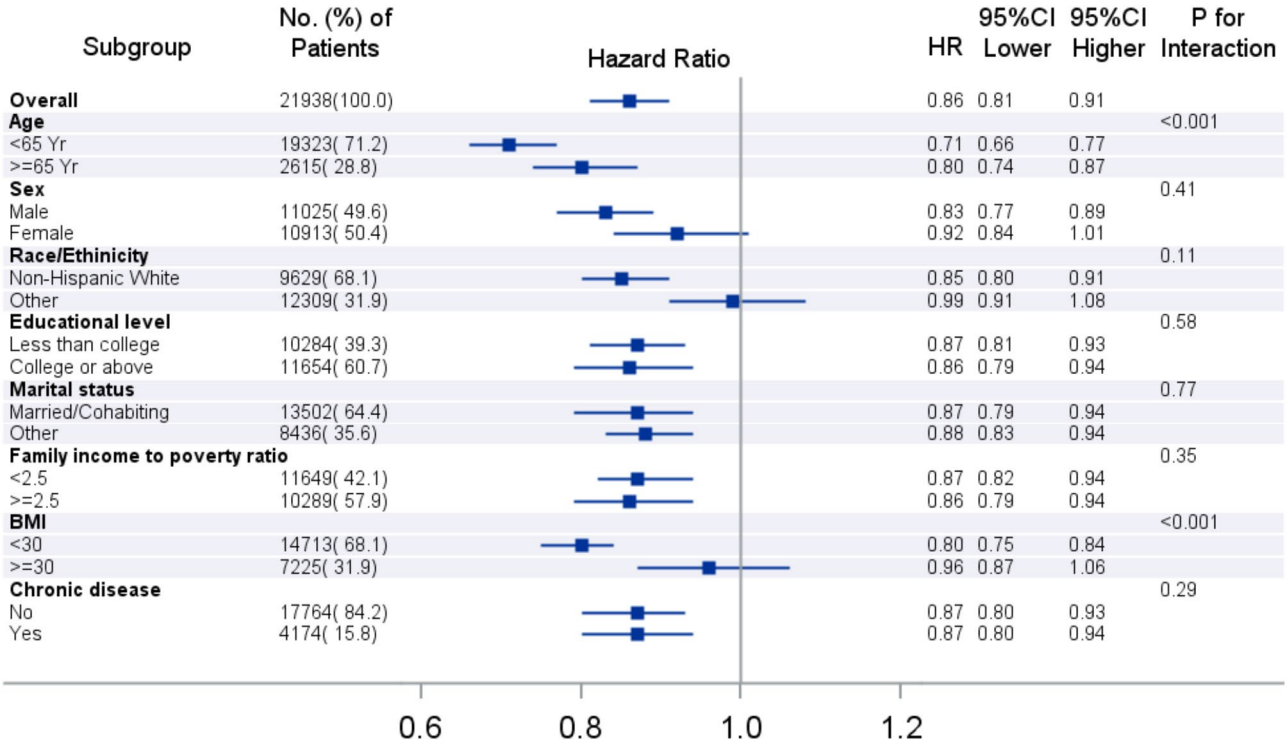

Fig. 4. Hazard ratios (HRs) of all-cause mortality per 20th percentile increase in the SMI by subgroup.

Discussion

The results from our study revealed that in the population studied, adults with higher SMIs tended to be younger and non-Hispanic Black, and participants with lower SMIs were significantly associated with a higher risk of all-cause mortality and cancer mortality.

This study examined the associations between appendicular skeletal muscle index (SMI) and all-cause mortality among a large cohort of U.S. adults over a follow-up period of approximately 10.9 years. Non-Hispanic Black individuals, as well as those with higher BMI and/or a history of diabetes and hypertension, generally had higher SMI compared to other groups. The findings demonstrated that higher appendicular SMI was associated with a lower risk of death, independent of various sociodemographic, clinical, and lifestyle factors, especially for males. The results emphasize the clinical relevance of muscle mass, particularly appendicular skeletal muscle, as a significant predictor of longevity, suggesting that maintaining or improving appendicular muscle mass could be crucial for reducing the risk of mortality.

Some studies have recently reported that low skeletal muscle mass is associated with increased mortality risk in end-stage kidney disease patients on hemodialysis, in critically ill surgical patients, in ever smokers and in Asians with cirrhosis[15–18]. As a nationally representative survey, our study provided evidence that high skeletal muscle volume could generally be associated with a lower mortality risk in adults, independent of sex, race, educational level, marital status, the family income-to-poverty ratio, obesity status and the presence of chronic diseases. Skeletal muscle is responsible for approximately 80% of glucose clearance, and loss of skeletal muscle mass due to aging or underlying diseases can exacerbate abnormalities in glucose metabolism[19]. Additionally, a low SMI could be related to weakness, disability and morbidity[3]. These factors may all be risk factors for mortality. Skeletal muscle is a major organ involved in insulin-induced glucose metabolism, and decreased muscle mass and strength are associated with the development of metabolic syndrome and insulin resistance[19,20]. Sarcopenia is characterized by the loss of skeletal muscle mass and strength, and low skeletal muscle mass is an important indicator of sarcopenia. Sarcopenia is known to contribute to increased frailty, weakness, dependence, morbidity and mortality[19]. Xu et al. reported that sarcopenia is associated with mortality independent of the population and sarcopenia definition[21], and other current studies have shown that sarcopenia adversely affects not only the elderly population but also young adults[22,23], especially those with obesity[24]. Our results revealed that the association between the SMI and mortality also exists for adults younger than 65 years. In recent years, the definition of sarcopenia has gradually evolved from focusing solely on skeletal muscle mass to incorporating a more comprehensive assessment that includes muscle function and strength. Some studies have proposed using muscle strength (e.g., handgrip strength) and physical performance (e.g., gait speed) as key diagnostic criteria rather than relying solely on imaging-based measurements of muscle mass[25]. Therefore, future research should further explore how these functional indicators can be integrated with traditional measurement of skeletal muscle mass in predicting all-cause mortality, cancer mortality, and other health outcomes.

In our study, the association between SMI and all-cause mortality was not as statistically significant as males, which suggests that SMI may not have the same protective effect for females as it does for males, or that other

factors not accounted for in the analysis may be influencing the relationship between SMI and mortality in females. Several factors could explain the gender differences observed in these results. Physiological differences between males and females, such as differences in muscle mass, hormonal influences, and metabolic rates[10,15], might contribute to a stronger association between SMI and mortality in males. Additionally, other potential confounders, such as comorbid conditions or lifestyle factors, could vary between genders and affect these associations differently. Further studies, including gender-specific analyses, may help to clarify the underlying mechanisms behind these findings and whether interventions targeting muscle mass could be equally beneficial across both genders.

In addition to all-cause mortality, a higher SMI was noted to be a protective factor for cancer mortality in our study. This finding is in line with some studies showing that low skeletal muscle mass is associated with mortality in cancer patients[26–28] and that muscle-strengthening activities may reduce cancer mortality[29,30] These results highlighted the crucial role of maintaining skeletal muscle mass in cancer prevention and management. Moreover, interventions targeting muscle strengthening, could be integrated into comprehensive care strategies to improve outcomes and quality of life in cancer patients. Further research is warranted to explore the underlying mechanisms and to establish guidelines for muscle-preserving interventions in this population. Therefore, it is critical for young and old adults, especially those with underlying diseases or cancer, to monitor their body composition regularly and pay attention to a sufficient protein supply and regular exercise to prevent skeletal muscle loss to preserve their health condition or prolong life.

The strengths of this study include the following. The large sample of NHANES patients with long follow-up periods could represent the general U.S. population, and the data were collected via a rigorous study protocol, which allowed us to analyze the hazard ratios of different quintiles of SMI to mortality with high precision. The limitations of this study should be noted. First, in this study, muscle functions such as handgrip strength and gait speed were not considered or analyzed, which should be another good evaluation of muscle quality for adults, in addition to SMI, which will be considered in future research. Second, the history of MI, stroke, and cancer were all from self-reported records, which might not be the actual situation of the participants. Finally, there was only one cross-sectional investigation and death outcome in this cohort, without other follow-ups; thus, the causal associations between SMI and all-cause, cause-specific mortality could not be established.

Conclusion

In conclusion, high appendicular skeletal muscle mass was associated with decreased all-cause mortality and cancer mortality. Interventions aimed at maintaining appropriate appendicular skeletal muscle mass may help prevent premature death.

Data availability

The datasets supporting the conclusions of this article are available at https://wwwn.cdc.gov/nchs/nhanes.

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Author contributions

Y.C.: Conceptualization, methodology and writing—original draft; G.H., T.L., D.H., S.L., Y.L. and T.Z.: Writing—review and editing; J.L.: supervision, conceptualization and methodology. All the authors have read and agreed to the published version of the manuscript.

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Ethics declarations

Competing interests

The authors declare no competing interests.

Ethics approval

and informed consent were obtained from all the subjects involved in the study.

Additional information

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