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Research Article

Appendicular Lean Mass, Grip Strength, and the Incidence of Dementia Among Older Adults in the Health ABC Study

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Abstract

Background: Identification of novel risk factors for dementia in older adults could facilitate development of methods to identify patients most at risk and improve their cognitive outcomes. We aimed to determine whether lower appendicular lean mass (ALM), assessed by dual-energy x-ray absorptiometry (DXA), and lower grip strength are associated with a greater likelihood of incident dementia among older adults in the Health Aging and Body Composition Study (Health ABC).

Methods: Health ABC data from 1997 to 2008 were analyzed (n = 2 704). Baseline ALM to body mass index (BMI) ratio (ALM_{BMI}) was assessed by DXA. Baseline grip strength was assessed by hand-held dynamometry. Incident dementia diagnosis was defined as either (i) dementia-related hospitalization plus a Modified Mini-Mental State Examination (3MS) score of ≤ 90; or (ii) record of prescription for anti-dementia medication; or (iii) decline of at least 1.5 *SD*s on the 3MS score compared to baseline. Cox proportional hazard models estimated associations of ALM_{BMI} and grip strength with incident dementia over follow-up with and without adjusting for covariates, stratified by sex.

Results: Among older men, each standard deviation decrement in ALM_{BMI} (adjusted hazard ratio [aHR]: 1.33; 95% confidence interval [CI]: 1.07, 1.65) or grip strength (aHR 1.22; 95% CI: 1.06, 1.41) was associated with increased likelihood of incident dementia.

Conclusions: Lower ALM_{BMI} and grip strength may be important risk factors for the development of dementia among older men. How these factors may belong to a causal pathway of dementia must be elucidated in future work.

Keywords: Body composition, Cognition, Muscle, Sex

Tools to identify older adults at greatest risk for developing dementia are limited (1). Given the increasing global population of older adults (2), improving methods to identify older adults at increased risk for dementia would have significant public health benefits. Identification of novel, potentially modifiable risk factors for dementia in older adults could help efforts to identify older adults at greatest risk for dementia and ultimately could also facilitate the development of new strategies to improve cognitive outcomes for these individuals.

Body composition changes with age (3), and differences in body composition may be associated with cognitive function in older adults (1,4,5). In particular, skeletal muscle mass and strength decline with age (6). Lean mass is commonly measured, such as by

bioimpedance or dual-energy x-ray absorptiometry (DXA), as a proxy for skeletal muscle mass in studies of body composition in older adults (7). The cross-sectional associations of lower lean mass or muscle strength with adverse cognitive outcomes in older adults are well established (4,8,9). However, longitudinal data are needed to better evaluate lower lean mass and grip strength as risk factors for the development of dementia. Such longitudinal data are highly limited. Recently, lower grip strength but not lower lean mass was associated with increased risk of incident mild cognitive impairment (MCI) and of Alzheimer's dementia (AD) among older adults (10). Total body lean mass was assessed by bioimpedance, which may have greater variability than lean mass assessed by DXA (7,11).

The aim of the present study was to determine whether lower appendicular lean mass, assessed by DXA rather than by bioimpedance, and lower grip strength are associated with an increased likelihood of incident dementia over follow-up among older men and women in the Health Aging and Body Composition Study.

Method

Participants

Participants for the current study were from the Health Aging and Body Composition Study (Health ABC). Health ABC was an observational cohort study examining changes in body composition and physical function among 3 075 older adults. Enrollment for Health ABC began in 1997, and White and Black men and women ages 70–79 years who reported no difficulty performing activities of daily living at baseline were eligible (12). The current study analyzed the first 11 years of data from Health ABC. Individuals with baseline cognitive impairment, defined as Modified Mini-Mental State (3MS) score <78 or taking anti-dementia medications (n = 246) (13,14), or who were missing baseline measures of appendicular lean mass and/or grip strength (n = 125) were excluded. The final sample for the current study included 2 704 older adults (men: n = 1 290; women: n = 1 414).

Measures

The primary predictors for the present study are appendicular lean mass to body mass index (BMI) ratio (ALM_{BMI}) and grip strength, measured at the time of enrollment (baseline) into the Health ABC study. ALM and grip strength are commonly used measures in evidence-based definitions of sarcopenia in older adults (7,15–17). ALM_{BMI} was chosen as the primary measure of lean mass for multiple reasons. First, ALM_{BMI} is used in the Foundation for the NIH (FNIH) Sarcopenia Project's primary definition for low lean mass among older adults (7,18). Second, this definition of low lean mass was developed using data that included Health ABC participants (19). Third, our group has experience using ALM_{BMI} to assess relationships between lean mass and adverse clinical outcomes among older adults in Health ABC (13,20), and using ALM_{BMI} to assess lean mass facilitates comparison with these prior studies. However, we acknowledge that other evidence-based definitions of low lean mass (eg, ALM and ALM/(height^2) exist, and we have included these measures in pre-planned sensitivity analyses below. ALM was measured by whole-body DXA (Hologic QDR 4500A; Hologic, Bedford, MA). ALM_{BMI} was calculated as ALM divided by BMI. ALM/(height^2) was also calculated. Low ALM_{BMI} was defined as <0.789 for men and <0.512 for women, low ALM as <19.75 kg for men and <15.02 kg for women (18), and low ALM/(height^2) as <7 kg/m^2 for men and <5.5 kg/m^2 for women (16). Grip strength (kg) in the dominant hand was measured by hand-held dynamometer (Jamar) in two separate trials, and the maximum baseline strength measurement was analyzed. Low grip strength was defined as <26 kg for men and <16 kg for women (21). Two participants, one man and one woman, were excluded from the grip strength analyses because their measured values of 80 and 82 kg were determined to be outliers.

The primary outcome for the present study is incident dementia, which is defined as in a prior study of Health ABC participants (22). As in the prior study, incident dementia was defined as either hospital records indicating a dementia-related hospitalization (participants were asked about recent hospitalization every 6 months in Health ABC, and hospital records were reviewed for primary or secondary admission diagnoses of dementia) and a 3MS score of ≤90 (3MS was assessed in Heath ABC years 1, 3, 5, 8, 10, and 11); or record of prescription for anti-dementia medication (galantamine, rivastigmine, memantine, donepezil, or tacrine) based on annual drug inventory; or decline of at least 1.5 *SD*s on the 3MS score compared to baseline (22).

Sociodemographic characteristics (age, race, and years of education), self-reported medical comorbidities (history of falls, diabetes, cancer, arthritis, pulmonary disease, cardiac disease, stroke, and depression), current smoking status, BMI, fat mass index (FMI), and physical activity (self-report of walking activity per week) were assessed following a standardized protocol at the time of enrollment in Health ABC (12,23,24).

Statistical Analysis

A Cox proportional hazard model was used to assess the associations of ALM_{BMI} and grip strength measures with incident dementia over follow-up. Separate models, stratified by sex, evaluated the association of ALM_{BMI}, low ALM_{BMI}, grip strength, or low grip strength with the incidence of dementia over follow-up with and without adjustment for covariates. All multivariable models were adjusted for the following potential confounders which are associated with both differences in muscle mass and strength (12,25) and with the risk of incident dementia among older adults (1): age, race, FMI, years of education, baseline 3MS score, study site, physical activity, smoking status, history of falls, diabetes, cancer, arthritis, pulmonary disease, cardiac disease, stroke, and depression. Kaplan–Meier curves examined the time to development of dementia by ALM_{BMI} or grip strength status among men and among women. We assessed for evidence of nonlinear trends in ALM_{BMI} and grip strength by plotting ALM_{BMI} or grip strength against the Martingale residuals (26). We evaluated the Schoenfeld residuals (27) to confirm that our models met the proportional hazards assumption.

The following preplanned sensitivity analyses were performed. First, the associations of ALM, low ALM, ALM/(height^2), and low ALM/(height^2) with incident dementia were each evaluated using Cox proportional hazard models similar to above. Second, to evaluate whether or not the associations of baseline ALM_{BMI} or grip strength with incident dementia were influenced by prevalent subclinical dementia, incident dementia cases occurring within 2 years of baseline were excluded and the analyses were repeated.

Results

Participant Baseline Characteristics and Incidence of Dementia Over Follow-up

Table 1 depicts participant baseline characteristics, stratified by sex. Forty-three percent of women and 32% of men were

Table 1. Participant Baseline Characteristics*

	Men n = 1 290	Women n = 1 414	Total n = 2 704
Age	73.8 ± 2.9	73.4 ± 2.8	73.6 ± 2.9
Black race, n (%)	413 (32)	615 (43)	1 028 (38)
Memphis HABC study site, n (%)	636 (49)	707 (50)	1 343 (50)
Pittsburgh HABC study site, n (%)	654 (51)	707 (50)	1 361 (50)
3MS score	91.6 ± 5.5	92.0 ± 5.6	91.8 ± 5.5
Smoking status, n (%)			
Never	386 (30)	805 (57)	1 191 (44)
Former	784 (61)	477 (34)	1 261 (47)
Current	120 (9)	132 (9)	252 (9)
Drinks per week			
0	534 (42)	794 (56)	1 328 (49)
<1	245 (19)	316 (22)	561 (21)
1–7	351 (27)	251 (18)	602 (22)
>7	155 (12)	51 (4)	206 (8)
Walking activity, kCAL/kg/wk	9.3 ± 20.5	6.5 ± 14.6	7.9 ± 17.7
BMI	27.1 ± 3.9	27.6 ± 5.3	27.3 ± 4.7
FMI	8.1 ± 2.3	11.4 ± 3.5	9.8 ± 3.4
Education, years	13.3 ± 3.4	12.6 ± 2.7	12.9 ± 3.1
Prevalent health conditions, n (%)			
Non-skin cancer	345 (27)	261 (18)	606 (22)
Lung disease	151 (12)	160 (11)	311 (12)
Heart disease	390 (30)	242 (17)	632 (23)
Stroke	85 (7)	106 (8)	191 (7)
Diabetes mellitus	211 (16)	184 (13)	395 (15)
Falls	235 (18)	345 (24)	580 (21)
Arthritis	634 (49)	867 (61)	1 501 (56)
Depression	94 (7)	173 (12)	267 (10)
ALM, kg	23.9 ± 3.5	16.5 ± 3.1	20.0 ± 4.9
Low ALM†	146 (11)	485 (34)	631 (23)
ALM_{BMI}	0.89 ± 0.11	0.61 ± 0.08	0.74 ± 0.17
Low ALM_{BMI}†, n (%)	242 (19)	163 (12)	405 (15)
ALM/(height^2)	7.9 ± 1.0	6.5 ± 1.1	7.2 ± 1.3
Low ALM (height^2)‡	217 (17)	81 (6)	298 (11)
Grip strength, kg	37.4 ± 8.4	22.6 ± 5.8	29.6±10.3
Low grip strength†, n (%)	78 (6)	126 (9)	204 (8)
Follow-up time, years; median (IQR)	8.9 (4.6, 10.3)	10.1 (5.4, 10.3)	9.2 (5.0, 10.3)

Notes: ALM = appendicular lean mass; ALM_{BMI} = ALM to BMI ratio; BMI = body mass index; FMI = fat mass index; 3MS = Modified Mini-Mental State Examination.
*Values reported as mean ± *SD* unless otherwise noted.
†Low ALM: men <19.75, women <15.02; low ALM_{BMI}: men <0.789, women <0.512; low grip strength men <26 kg, women <16 kg (18).
‡Low ALM/(height^2): men<7 kg/m^2, women <5.5 kg/m^2 (16).

Black. Among men, 27% and 30% had non-skin cancer and heart disease, respectively; compared to 18% and 17%, respectively, among women. The mean 3MS score was 91.6 ± 5.5 and 92.0 ± 5.6 among men and women, respectively. Nineteen percent of men and 12% of women had a low ALM_{BMI} (defined as <0.789 for men and <0.512 for women (19)), and 6% of men and 9% of women had a low grip strength (defined as <26 kg for men and <16 kg for women (21)).

Over follow-up among men, 928 (72%) were censored (of whom 436 died) and 362 (28%) developed dementia (of whom 27 had a dementia-related hospitalization, 40 were prescribed an anti-dementia medication, and 295 had a decline in 3MS score). Over follow-up among women, 1 004 (71%) were censored (of whom 348 died) and 410 (29%) developed dementia (of whom 22 had a dementia-related hospitalization, 37 were prescribed an anti-dementia medication, and 351 had a decline in 3MS score). The median number of years of follow-up was 9.2 (inter-quartile range: 5.0, 10.3).

Associations of Baseline ALM_{BMI} or Grip Strength with Incident Dementia

Measures of ALM_{BMI} were associated with development of incident dementia among older men but not among women (**Table 2**). Among older men, baseline lower ALM_{BMI} (as a continuous measure) and low ALM_{BMI} (as a categorical measure) were each associated with a greater hazard of incident dementia in adjusted models. For example, each standard deviation decrement in ALM_{BMI} was associated with a 33% greater likelihood of incident dementia (adjusted hazard ratio [aHR] 1.33; 95% confidence interval [CI]: 1.07, 1.65). In addition, baseline lower grip strength (as a continuous measure) was associated with development of dementia among older men, such that each standard deviation decrement in baseline grip strength among older men was associated with a 22% relative increase in the likelihood of incident dementia (aHR 1.22; 95% CI: 1.06, 1.41). Baseline low (as a categorical measure) grip strength had a borderline significant association with development of dementia (aHR 1.51; 95% CI: 0.99, 2.29), suggestive of a possible dose–response effect. Among

Table 2. Hazard Ratios and 95% Confidence Intervals for the Effect of Baseline Appendicular Lean Mass to BMI Ratio (ALM_{BMI}) or Grip Strength on Likelihood of Incident Dementia* Through Year 11 in the Health ABC Study, Stratified by Sex

	Men (n = 1 290)		Women (n = 1 414)		
	Unadjusted	Adjusted*	Unadjusted	Adjusted†	Sex Interaction p Value**
ALM_{BMI}‡	1.13 (0.96, 1.34)	**1.33 (1.07, 1.65)**	0.83 (0.68, 1.02)	1.22 (0.94, 1.60)	.12
Low ALM_{BMI}#	1.19 (0.93, 1.53)	**1.39 (1.04, 1.86)**	0.75 (0.54, 1.06)	1.02 (0.71, 1.46)	.03
Grip strength‡	**1.15 (1.01, 1.32)**	**1.22 (1.06, 1.41)**	0.91 (0.76, 1.08)	1.10 (0.91, 1.34)	.10
Low grip strength#	1.40 (0.94, 2.11)	1.51 (0.99, 2.29)	0.88 (0.62, 1.26)	1.04 (0.72, 1.52)	.07

Notes: Bold font denotes hazard ratio with $p < .05$. BMI = body mass index; FMI = fat mass index.

*Incident dementia is defined per ref. (22)

†Adjusted for age, race, FMI, baseline Modified Mini-Mental State Examination score, study site, physical activity (self-report of walking per week), smoking status, education in years, # of drinks per week, and history of comorbidities (falls, diabetes, cancer, arthritis, pulmonary disease, cardiac disease, stroke, and depression).

‡Hazard ratios are expressed **per standard deviation decrement** of the exposure measure.

#Low ALM: men <19.75, women <15.02; Low ALM_{BMI}: men <0.789, women <0.512; low grip strength men <26 kg, women <16 kg (18).

**p Value for the interaction of sex with ALM or grip strength measure.

women, none of the associations tested between ALM_{BMI} or grip strength measures and incident dementia reached statistical significance. Table 2 also depicts the p-values for the interaction of sex on the associations between lean mass or grip strength measures and the development of dementia. We observed a statistically significant interaction of sex with low ALM_{BMI} and both grip strength measures' associations with incident dementia (all p values <.1). **Figure 1A and B** depict the time to dementia for those with low versus not low ALM_{BMI} or grip strength, stratified by sex.

Sensitivity Analyses

Supplementary Table 1 depicts baseline participant characteristics stratified by either normal versus low ALM_{BMI} or normal versus low grip strength. ALM and ALM/(height^2) were each associated with incident dementia among older men similar to the observed associations ALM_{BMI} (**Supplementary Table 2**). When incident dementia cases occurring within 2 years of baseline were excluded and the analyses were repeated, the overall trends in associations of baseline ALM_{BMI} or grip strength with incident dementia among older men were similar (**Supplementary Table 3**).

Discussion

Among a cohort of older Black and White adults, lower ALM and lower grip strength were each associated with an increased likelihood of incident dementia among men, but not among women. Each standard deviation decrement in lean mass or grip strength was associated with approximately 20%–30% increased hazard of incident dementia even when adjusting for covariates, including age, race, physical activity, and comorbidities. In addition, the presence of low (as categorical measure) lean mass, defined using validated criteria (16,19), was also associated with a similarly increased hazard of incident dementia. These findings corroborate recent observations that lower grip strength may be associated with an increased likelihood of incident dementia among older adults (10); and they are among the first to our knowledge (i) to demonstrate an association between lower lean mass and the risk of incident dementia and (ii) to suggest that relationships of lean mass and/or grip strength with the development of dementia may differ by sex. Thus, lower lean mass and grip strength may be important, modifiable, risk factors for the development of dementia among older men; and future studies are needed to elucidate these potential relationships.

In contrast to prior studies, we observed significant sex differences in the relationships of ALM or grip strength with the development of dementia. A recent study found that lower grip strength was associated with an increased likelihood of incident MCI and of AD (10). In addition, they observed that lean mass, assessed by bioimpedance, was not associated with the development of either MCI or AD. None of these observed trends differed between older men and women. However, in the present study, both lower ALM, assessed by DXA, and lower grip strength were each associated with an increased hazard of incident dementia only among older men. The observed difference in the present study does not appear to be due to differences in the incidence of dementia between men and women. Twenty-eight percent of men and 29% of women in the current study developed dementia over follow-up. Moreover, survival bias and depletion of susceptible men to incident dementia does not appear to explain the observed sex difference as men were more likely than women to die prior to the end of follow-up (47% vs 35%). The observed sex difference may be due to various biological (eg, sex hormones or APOE-e4 genetics), social (eg, differential educational attainment), or behavioral (eg, occupation or health behaviors) differences between men and women (28–30). Despite accounting for many of these factors in the present analysis (eg, physical activity, comorbidities, years of education), differences by sex persisted. Future prospective studies, conducted across diverse patient populations are needed to further examine these hypotheses.

The present study observed that lower ALM, assessed by DXA, was associated with an increased hazard of incident dementia among older men. This relationship between lower lean mass and increased hazard of incident dementia among older men remained largely unchanged irrespective of whether lean mass was measured as ALM_{BMI} or as ALM/(height^2). This observation differs from prior data where lean mass, assessed by bioimpedance, was not associated with the likelihood of incident dementia among older men and women (10). The difference between prior data and the current results may reflect methodologic differences between DXA and bioimpedance in assessing body composition. Lean mass assessed by DXA is an approximation of skeletal muscle mass in that it includes not only muscle, but also water and all non-fat and not-bone mass (7). Despite this limitation, DXA-based measures of lean have various advantages, are commonly used in studies of body composition among older adults and are included in the European Working Group on Sarcopenia in Older People's definition of sarcopenia (16). Future studies on the incidence

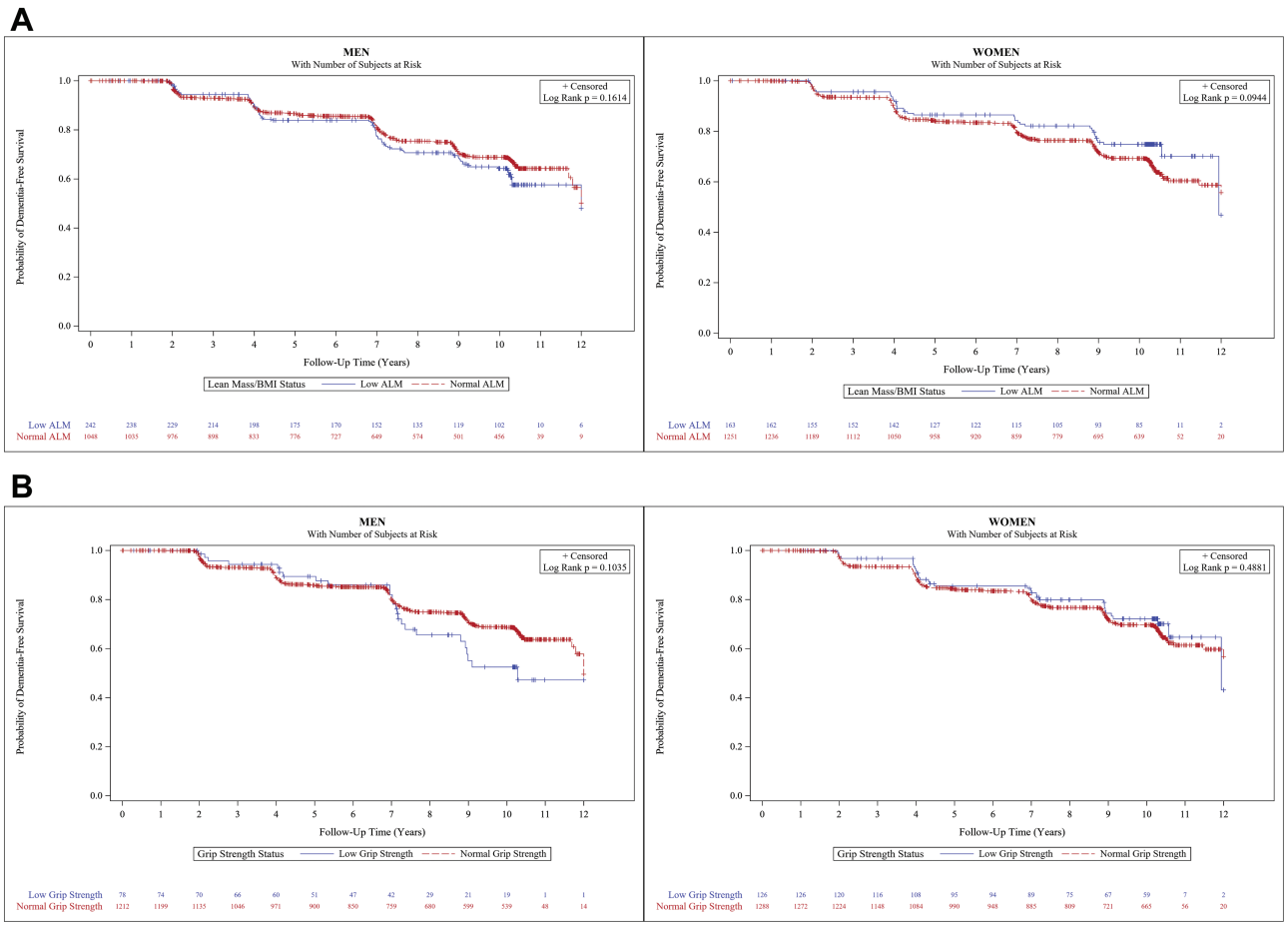

Figure 1. (**A**) Kaplan–Meier curves depicting the probability of dementia-free survival by baseline appendicular lean mass to BMI ratio (ALM_{BMI}) status among older adults in the Health ABC study, stratified by sex. (**B**) Kaplan–Meier curves depicting the probability of dementia-free survival by grip strength status among older adults in the Health ABC study, stratified by sex.

of dementia in older adults where lean mass is assessed by both DXA and bioimpedance, or by more precise measures of skeletal muscle size or mass such as magnetic resonance imaging or D_3-creatine dilution (31), would help to further elucidate these relationships.

Various mechanisms may underly this potential relationship of lean mass and grip strength with the development of dementia among older men. First, declines in skeletal muscle mass and strength (ie, sarcopenia) and declines in cognitive performance both commonly occur as part of aging, and it is possible that physical declines, such as declines in muscle mass and strength, may be clinically detectable earlier than cognitive declines. On the other hand, lower skeletal muscle mass and strength may indeed contribute to an increased risk of dementia due to shared underlying biological processes. For example, amount of physical activity is related to changes in cognitive function over time among older adults (32–35). The present analyses account for differences in self-reported walking activity per week, but not other types of physical activity or the distribution of daily activity (sleep, awake-inactive, awake-active). In addition, various cytokines that are released from skeletal muscle during exercise may be associated with changes in cognition in older adults (36,37), and these effects may help explain the present results. Next, chronic systemic inflammation occurs with aging, has been observed to be associated with the risk of incident dementia, and may also be related to declines in muscle mass and strength that occur with aging (38–40). This chronic inflammation of aging may contribute to the observed relationships of lower lean mass and grip strength with increased hazard of dementia. Finally, declines in cardiovascular health that develop with age may help explain the observed trends. Future studies, including population-based observational cohorts of older adults at risk for dementia and genetic and Mendelian randomization analyses, are needed to help address these various hypotheses. It may also be informative to include dementia and cognitive function outcomes in randomized trials that aim to improve grip strength and/or appendicular lean mass.

The current study has limitations. First, dementia was not ascertained by formal clinical assessment. Thus, whether or not the observed findings generalize to the incidence of clinically-diagnosed dementia is not known. Moreover, 28% of men and 29% of women developed the primary dementia outcome over follow-up in this study. In 2021, the prevalence of AD dementia among Americans ages 75–84 years and 85 years and older was estimated as 13.8% and 34.6%, respectively (28). The current analysis is not limited to AD dementia, but rather examines the incidence of all-cause dementia. While the observed incidence of dementia appears consistent with overall U.S. trends, future studies that use clinically diagnosed dementia outcomes are needed to corroborate these findings. Second, as in any observational study, the possibility or residual confounding cannot be excluded. Moreover, the size of the association was modest, which suggests that even mild to moderate unmeasured confounding could significantly affect the

results. Third, physical activity was assessed as self-reported walking activity, which may not capture all relevant aspects of physical activity. Fourth, the competing risk of death may result in underestimation of the potential relationships of appendicular lean mass or grip strength with the development of dementia (41). This effect would tend to bias our analyses toward the null hypothesis, and the actual associations may be greater than those observed. Fifth, while we adjust for medical comorbidities in all analyses, we are not able to adjust for history of recent acute illness as these data are not available. Sixth, data on type of dementia (eg, AD vs vascular) are not available. Lastly, Heath ABC includes only White and Black non-disabled older adults, and whether observed trends generalize to other populations is not known. The study also has several strengths. The study includes a relatively large cohort of older men and women in whom dementia status was assessed annually over many years of follow-up. Among this large cohort, appendicular lean mass and strength were assessed using well-established measures.

In conclusion, lower appendicular lean mass and lower grip strength at baseline were each associated with an increased likelihood of incident dementia over follow-up among older men, but not women. Thus, lower appendicular lean mass and grip strength may be important risk factors for the development of dementia among older men. Future studies, including diverse population-based prospective cohorts where skeletal muscle mass and strength are rigorously and thoroughly evaluated should further examine the potential contribution of lower appendicular lean mass and grip strength to the development of dementia in older adults.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Author Contributions

All authors were involved in study conception and design, drafting the article or revising it critically for important intellectual contact, and in data analysis and interpretation. All authors approved the final version to be published. Acquisition of data: J.S.A. and L.S.G.

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