Sarcopenia is associated with incident Alzheimer's dementia, mild cognitive impairment, and cognitive decline

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Abstract

Objective: We examined whether sarcopenia is associated with the occurrence of late-life cognitive impairment.

Methods: Nondemented older adults ($N = 1175$) underwent annual testing with 17 cognitive tests summarized as a global cognitive score. A composite sarcopenia score was constructed based on muscle mass measured with bioelectrical impedance and muscle function based on grip strength. Cox proportional hazard models were employed to examine associations of sarcopenia with incident Alzheimer's dementia (AD) and incident mild cognitive impairment (MCI). Linear mixed-effect models determined the association of sarcopenia with cognitive decline. All models controlled for age, sex, education, race, and height squared.

Results: Average follow-up was 5.6 years. More severe sarcopenia at baseline was associated with a higher risk of incident AD (hazard ratio [HR], 1.50 [95% confidence interval 1.20–1.86]; $p < 0.001$) and of MCI (1.21 [1.01–1.45]; 0.04) and a faster rate of cognitive decline (estimate = -0.013; $p = 0.01$). Analyses of the individual components of sarcopenia showed that muscle function was associated with incident AD, incident MCI, and cognitive decline with and without a term for lean muscle mass in the model. In contrast, lean muscle mass was not associated with incident cognitive impairment or cognitive decline when a term for muscle function was included in the model.

Conclusions: Poor muscle function, but not reduced lean muscle mass, drives the association of sarcopenia with late-life cognitive impairment. Further work is needed to identify features of muscle structure, which may increase the specificity of sarcopenia for identifying older adults at risk for late-life cognitive impairment.

KEYWORDS
Alzheimer's disease, cognitive decline, mild cognitive impairment, sarcopenia

INTRODUCTION

Sarcopenia is a common aging phenotype defined as loss of muscle structure and its function.[1-3] While cross-sectional studies suggest an association of sarcopenia with cognition, there is little data on the association of sarcopenia with incident cognitive impairments and cognitive decline. Motor function is a complex volitional behavior and its impairment precedes and predicts cognitive decline, incident mild cognitive impairment (MCI),

and Alzheimer's dementia (AD) in many older adults.[4-6] Considerable data suggest that shared neural substrate underlies motor and cognitive resources underlying volitional motor control, suggesting a common etiopathogenesis. For example, both motor and cognitive decline are related to many of the same AD and other related brain pathologies[7] as well as cortical proteins,[8] which drive late-life decline. Higher body mass index (BMI), which encompasses muscle mass, is related to faster cognitive decline and incident AD.[9,10] Changes in BMI in older adults is also related to the same ADRD brain pathologies underlying cognitive decline[11] and recent reports suggest that muscle proteins may reach the central nervous system (CNS) via systemic circulation to affect cognition.[12] These studies support the biological plausibility for prior observational studies linking both elements of sarcopenia, that is, muscle structure and function with late-life cognitive impairment.

Recently, emerging technologies, such as bio-impedance, have made it easier to obtain measures of muscle mass outside of the laboratory setting permitting a reassessment of the independent role of lean muscle mass metrics as part of the construct of sarcopenia in predicting adverse health outcomes such as mortality and disability.[1,3] We are unaware of prior studies which have examined whether lean muscle mass is independently associated with incident AD, incident MCI, and cognitive decline when controlling for muscle function.

In this study we combine measures of grip strength with measures of lean muscle mass to assess the association of sarcopenia with incident AD, MCI, and cognitive decline in a sample of approximately 1200 community-dwelling older adults participating in the Rush Memory and Aging Project (MAP).[13] In further analyses, we examined each of the components used to assess sarcopenia to test the hypothesis that lean muscle mass is independently associated with incident MCI and AD as well as the rate of cognitive decline when controlling for muscle function.

METHODS

Participants

All participants were from MAP, a longitudinal cohort study of chronic conditions of aging.[14] Participants were recruited from over 40 facilities from the metropolitan Chicago area, including subsidized senior housing facilities, retirement communities, and retirement homes, in addition to social service agencies and Church groups. Participants provided written consents and signed a repository consent to all their data to be repurposed. All

> ### Key Points
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> - Sarcopenia is related to incident Alzheimer's dementia (AD) and mild cognitive impairment and to cognitive decline.
> - Muscle function, and not muscle mass, drives the associations of sarcopenia with cognitive impairment.
> - Identification of granular metrics to improve the accuracy of sarcopenia in predicting cognitive impairment is merited.
>
> ### Why Does this Paper Matter?
>
> Older adults with sarcopenia are at higher risk of developing AD and other poor cognitive outcomes.

participants were assessed annually in their homes. All assessments were performed at the participant's residence to reduce burden and maintain high follow-up rates. A Rush University Medical Center's Institutional Review Board approved the study.

Analytic baseline for this study was defined as the first visit with a valid sarcopenia measure based on grip strength and muscle mass determined by bioelectrical impedance. Eligibility criteria for these analyses required absence of clinical dementia at baseline and at least one or more valid cognitive assessments so we could examine incident cognitive impairment and the rate of cognitive decline. MAP began in 1997 and bioimpedance testing was added in 2005. Thus, of 2116 participants who had completed MAP baseline when analysis was conducted, 1507 participants had completed a baseline assessment for the current analyses. We excluded 17 participants with missing race data, 92 who had dementia at baseline, and 223 without follow-up testing. The 1175 participants remaining for these analyses were on average younger, had more women, lower education, less sarcopenia, and better global cognition than those who were excluded from analyses, but did not differ in race or the prevalence of vascular risk factors and vascular diseases.

Assessment of cognition and cognitive status

Each participant underwent uniform annual clinical testing. The Mini-Mental State Examination[15] was administered and was used only for descriptive purposes but was

not included in the global cognition score. Seventeen cognitive tests administered at each annual evaluation were used to construct a summary global cognitive score and five cognitive abilities: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability, as described in prior publications.[14,16]

To compute the composite measures, raw scores on each test were first converted to z-scores using the baseline mean and standard deviation for the entire cohort. The z-scores for all 17 tests were then averaged together to obtain a global cognition score. A similar approach was used to calculate the scores for each of the five cognitive abilities.

Cognitive tests were scored by a computer, and reviewed by a neuropsychologist. Using all the available clinical and cognitive testing data a clinician diagnosed AD based on the recommendations of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[17] A diagnosis of MCI was rendered if the participant was judged cognitively impaired by the neuropsychologist, but did not meet dementia criteria by the clinician[18] (see Supporting Information for details on methods for MCI diagnosis). Each year the diagnosis was made blinded to data from prior assessments.

Assessment of sarcopenia and its components

We used the definition of sarcopenia suggested by recent published consensus panels that defined sarcopenia based on assessment of both muscle mass based on bioelectrical impedance and muscle function based on grip strength.[2]

Skeletal muscle mass index

Skeletal muscle mass was based on bioelectrical impedance analysis (BIA) (ohms) recorded with Body Comp Scale (BCS-1) series (Firmware version: 1.34; Valhalla Scientific, Inc.).[19,20] Janssen et al. derived a formula to convert BIA to estimated muscle mass from magnetic resonance imaging evaluation; the expression is 0.401 times the product of the square of the height in centimeters and the reciprocal of the bioimpedance in ohms, with adjustments for age, sex, and race.[19,21] Following the familiar conversion from total body mass to BMI, a skeletal muscle mass index (SMI) was computed by dividing the estimate of skeletal muscle mass (SMM) by weight squared. We computed this index for the Janssen formula for SMM as an intermediate step in deriving composite

and binary variables. While age, sex, race, and height squared were included in the formula used to derive skeletal muscle mass, muscle mass still varied with age, sex, race, and height squared. Therefore, we also controlled for these terms in the modeling outlined in the analytic plan in the following text.

Muscle function

Grip strength was measured with the Jamar hydraulic hand dynamometer (Lafayette Instruments). Two trials of isometric grip strength were obtained bilaterally and averaged to yield grip strength. Gait speed (m/s) was based on the self-paced time to walk 8 feet.[13]

Composite sarcopenia

Categorical and continuous measures are complementary and usually employed for different purposes. Binary assessments of sarcopenia developed to date have been utilized to estimate its prevalence, for the design of clinical trials and because of the ease of binary measures for decision-making in the clinical setting. Prior aging research has shown that continuous composite measures for motor function, cognition, parkinsonism, and physical frailty improve metric properties for capturing the heterogeneity of aging phenotypes and have an important role for longitudinal modeling of the trajectories of aging motor phenotypes.[7,22,23] Here we chose to use a continuous measure of sarcopenia because to circumvent some of the limitations of dichotomous measures, to capture the heterogeneity of different levels of muscle mass and function and represent with greater fidelity the nature of the sarcopenia range. The composite sarcopenia average is calculated as the mean sex-specific z-score, where z-scores for SMI and for grip strength are computed separately for men and for women and then multiplied by -1 so higher scores represent more sarcopenia. To ensure that our composite sarcopenia measure could be linked to prior studies which employed a categorical measure, we also calculated a previously published binary sarcopenia measure utilizing sex-specific binary classifications of low or not low muscle mass (male <8.87; female <6.42) and grip strength (male <30 kg; female <20 kg).[2]

Other covariates

Demographic covariates included age, sex, years of education, race, and measured height squared. Our models included terms to adjust for seven chronic health

conditions including the sum of three self-reported vascular risk factors, including hypertension, type 2 diabetes, and smoking, and four vascular diseases (heart attack, congestive heart failure, claudication, and stroke) as described in prior publications.[24] Briefly, hypertension was determined by self-reported medical diagnosis, current use of antihypertensive medication, or a measure of systolic/diastolic blood pressure of $\geq 160/90$ mm Hg. Diabetes was also either a self-reported medical diagnosis or indicated by the current use of diabetic medication. Smoking was self-reported and defined as ever/never smoked. Myocardial infarction was self-reported by the use of cardiac glycosides (e.g., digoxin, lanoxin, etc.) as medication. History of claudication was defined as self-reported pain in calves while walking. History of stroke was based on self-reported questions, cognitive testing, interviews with participants, and neurological examination (when available).

Statistical analyses

Pearson correlations were used to examine the associations of composite sarcopenia with age and education. Student's t tests were used to compare measures between men and women, race, and participants who did and did not develop AD. To test the association of composite sarcopenia with incident AD and incident MCI, we employed Cox proportional hazard models. All models were adjusted for age, sex, education, race, and height squared. We repeated these models adding terms to test for interactions of composite sarcopenia with each of the demographic measures. We used Cox proportional hazard models to examine the associations between the individual measures, used to construct composite sarcopenia (muscle mass and grip strength) with incident AD and incident MCI.

Linear mixed models[25] were employed to examine whether composite sarcopenia was associated with the annual rate of cognitive decline, the clinical hallmark of AD. The core model included terms for time (representing annual rate of change in global cognition score), baseline composite sarcopenia, and its interaction with time and terms for age, sex, education, race, and height squared and their interactions with time. In initial modeling of these data, baseline sarcopenia was not associated with terms for nonlinear cognitive decline (Time × Time) or its interaction with demographics so we did not include nonlinear terms in further analyses. As global cognition is constructed from five cognitive abilities, we used similar models to examine if the association of sarcopenia varied with the rate of decline of these different cognitive abilities. Models were examined

graphically and analytically, and assumptions were judged to be adequately met. Programming was done in SAS (SAS Institute, Inc.).

RESULTS

There were 1175 older adults included in these analyses. All adults included in these analyses were without dementia at baseline; 121 of 914 (13.2%) with no cognitive impairment (NCI) at baseline developed AD dementia and 122 of 261 (46.7%) with MCI at baseline developed AD dementia during the study. Participants who developed AD dementia were followed on average for 5.2 (SD = 3.2) years while those who did not develop AD dementia were followed for 5.8 (SD = 3.5) years. Participants who developed AD dementia were older, had lower education and more severe sarcopenia. The percentage of adults with vascular diseases was similar in both subgroups, but those developing AD dementia showed slightly less vascular risk factors. The average participant was 80.9 (SD = 7.1) years old and had 15.1 (2.9) years of education. The majority (77.2%) of the participants were females. Additional clinical characteristics for the analytic cohort are summarized in Table 1.

Metric properties of composite sarcopenia score

Composite sarcopenia score ranged from −2.60 to 2.80 (interquartile range = 1.03, median = −0.57) with a lower composite sarcopenia score indicating more severe sarcopenia. Composite sarcopenia was related to older age ($r = -0.46$, $p < 0.001$) and fewer years of education ($r = 0.12$; $p < 0.001$). Women showed more severe sarcopenia at baseline (women; mean = −0.62; SD = 0.78) compared to men (mean = −0.17; SD = 0.79), $t(1173) = -8.21$, $p < 0.001$. Finally, composite sarcopenia was strongly correlated with the previously published binary sarcopenia measure ($r = -0.78$, $p < 0.001$).

Composite sarcopenia and incident AD

During a mean of 5.6 years of follow-up, 243 (20.6%) individuals without dementia at baseline developed AD dementia. In a Cox proportional hazards model controlling for age, sex, education, race, and height squared, a higher baseline composite sarcopenia score was associated with a greater risk of incident AD (Table 2; Figure 1). In this model, each 1 SD above the composite

TABLE 1 Clinical characteristics of the cohort at baseline

Characteristic	All, N = 1175	Developed AD, N = 243	Did not develop AD, N = 932	Statistic[a]; p-value
Age (years)	80.9 (7.1)	84.6 (5.7)	80.0 (7.1)	−10.8; <0.001
Women (%)	77.2%	78.6	76.8	0.35; 0.56
Education (years)	15.1 (2.9)	14.7 (3.0)	15.1 (2.9)	2.3; 0.02
Race (% white)	95.1%	96.7	94.6	1.8; 0.18
Vascular risk factors, % of at least one risk factor:	77.7	72.5	79.0	8.7; 0.003
Hypertension	57.5	52.3	58.9	3.5; 0.06
Diabetes	13.3	11.1	13.8	1.2; 0.26
Smoking (ever)	41.7	35.4	43.4	5.0; 0.02
Vascular diseases, % of at least one vascular disease:	25.7	25.0	19.7	1.6; 0.21
Claudication	10	12.4	9.3	1.9; 0.16
Stroke	9.1	11.5	9.4	0.8; 0.36
Heart attack	9.5	11.1	9.1	0.9; 0.35
Congestive heart failure	4.9	3.1	5.6	2.4; 0.12
Composite sarcopenia (%)[b]	52.3%	70.0	47.6	38.5; <0.001

Abbreviation: AD, Alzheimer's dementia.
[a] t test for continuous variables and chi-square test for categorical variables.
[b] Percentage based on binary sarcopenia.[2]

TABLE 2 Composite sarcopenia and incident Alzheimer's dementia (AD) and incident mild cognitive impairment (MCI)

Terms	Model 1, HR (95% CI); p-value	Model 2, HR (95% CI); p-value	Model 3, HR (95% CI); p-value	Model 4, HR (95% CI); p-value
Incident AD				
Composite sarcopenia	1.50 (1.20–1.86); <0.001			
Grip strength		0.65 (0.55–0.78); <0.001		0.66 (0.55–0.78); <0.001
Muscle mass			0.92 (0.80–1.07); 0.31	0.96 (0.83–1.11); 0.59
Incident MCI				
Composite sarcopenia	1.21 (1.01–1.45); 0.04			
Grip strength		0.88 (0.75–1.02); 0.09		0.89 (0.76–1.03); 0.13
Muscle mass			0.91 (0.80–1.04); 0.16	0.92 (0.81–1.05); 0.24

Note: Each cell shows the hazard ratio (HR), 95% confidence interval (CI), and *p*-value for the term shown in the left column in a Cox proportional hazards models, which also included terms for age, sex, years of education, race, and height squared which are not shown. The upper panel examined the associations of the predictors in the left column, alone and together, with incident AD (Models 1–4) and the lower panel examined these same predictors alone and together with incident MCI (Models 5–8).

sarcopenia median score at baseline was associated with a 50% higher risk of incident AD. The association of sarcopenia with incident AD was not attenuated when we added terms for the number of vascular risk factors and vascular diseases (Table S1). This association of sarcopenia with incident AD was stronger for younger participants (age × sarcopenia, estimate = 0.05, SE = 0.02; $p = 0.01$), for males (sex × sarcopenia, estimate −0.53, SE = 0.26, $p = 0.04$) and among black participants (race × sarcopenia, estimate = −1.36, SE = 0.68; $p = 0.05$). The association of sarcopenia with incident AD did not vary with education, vascular risk factors, or diseases (results not shown). Consistent with the associations of composite sarcopenia with incident AD,
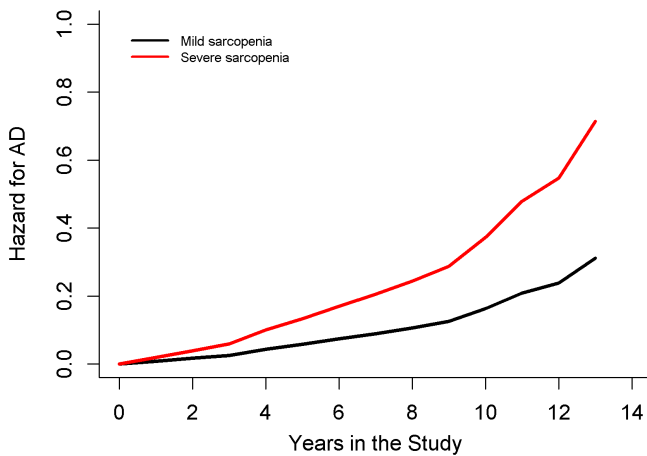
FIGURE 1 Sarcopenia is associated with incident Alzheimer's dementia (AD). Risk of incident AD is higher in a participant with severe sarcopenia at baseline (red line, high composite sarcopenia score, 90th percentile) as compared to an individual with mild sarcopenia (black line, low composite sarcopenia score, 10th percentile)

Figure S1 uses binary sarcopenia and shows higher incident AD in individuals with sarcopenia compared to those without sarcopenia.

Composite sarcopenia and incident MCI

There were 816 participants with NCI at baseline. During a mean of 4.9 years of follow-up, 316 (38.7%) cases of 816 developed incident MCI. In a Cox proportional hazards model controlling for age, sex, education, race, and height squared, a higher baseline composite sarcopenia score that is, more severe sarcopenia was associated with a higher risk of incident MCI (Table 2). In this model, each additional 1 SD above the baseline median composite sarcopenia score was associated with a 21% higher risk of incident MCI. The association of sarcopenia with incident MCI was not attenuated when we added terms for number of vascular risk factors and vascular diseases (Table S1) and did not vary with age, sex, education, race, vascular risk factors, or diseases (results not shown).

Components of composite sarcopenia and incident AD

Composite sarcopenia was constructed from measures of muscle mass and grip strength. We repeated the models described above replacing composite sarcopenia with terms for muscle mass and grip strength alone and together. Muscle mass was not associated with incident AD (Table 2, AD Model 3). Better grip strength was associated with a reduced risk of incident AD (Table 2, AD Model 2). The association of grip strength with incident AD was not attenuated when both grips strength and muscle mass were included in the same model (Table 2, AD Model 4). Grip strength alone, muscle mass alone, or the inclusion of both in the same model were not associated with incident MCI (Table 2, MCI models 2–4, respectively).

To examine whether the association of muscle function with incident AD and MCI was specific for grip strength or was observed with other muscle function phenotypes which have been examined by other investigators, we repeated the models described above replacing grip strength with gait speed. A faster gait speed was associated with a reduced risk of AD (Table S2, AD Model 1); Muscle mass did not attenuate the association of gait speed with incident AD (Table S2, AD Model 3) when both were included in the model. Faster gait speed was marginally associated with a reduced risk of incident MCI (Table S2) and reached statistical significance when adjusting for muscle mass (Table S2, MCI Model 3).

Composite sarcopenia and cognitive decline

As the clinical hallmark of AD is the progressive loss of cognitive function and to ensure that diagnostic misclassification of cognitive status did not affect our results, we employed linear mixed effect models to examine the association of composite sarcopenia with a continuous measure for cognitive function to assess its association with the annual rate of cognitive decline. A higher baseline composite sarcopenia score was associated with a faster rate of cognitive decline (Table 3, term of "Time × composite sarcopenia"). The association of sarcopenia with global cognitive decline did not vary with age, sex, education, or race. These associations were unchanged when including terms for vascular risk factors and vascular diseases.

Our measure of global cognition summarized five different cognitive abilities. We examined if the association of baseline composite sarcopenia varied with the rate of decline of the five cognitive abilities used to construct global cognition score. A higher baseline composite sarcopenia score was associated with faster decline in episodic memory and working memory, which seems to drive the findings with global cognition score (Table 3). In further analyses we replaced composite sarcopenia with its components. Grip strength (estimate = 0.01, SE = 0.004, p = 0.004) but not muscle mass (estimate = 0.004, SE = 0.004, p = 0.285) was associated with the rate of cognitive decline.

TABLE 3 Composite sarcopenia and declining cognitive abilities

Model	Cognitive ability outcome	Model term	Estimate (SE, *p*-value)
1	Global cognition	Time	−0.07 (0.008, <0.001)
		Time × composite sarcopenia score	−0.013 (0.005, 0.01)
2	Semantic memory	Time	−0.07 (0.009, <0.001)
		Time × composite sarcopenia score	−0.009 (0.005, 0.07)
3	Episodic memory	Time	−0.05 (0.005, <0.001)
		Time × composite sarcopenia score	−0.014 (0.006, 0.02)
4	Working memory	Time	−0.05 (0.008, <0.001)
		Time × composite sarcopenia score	−0.01 (0.005, 0.050)
5	Perceptual speed	Time	−0.11 (0.008, <0.001)
		Time × composite sarcopenia score	−0.004 (0.005, 0.37)
6	Visuospatial abilities	Time	−0.02 (0.007, 0.003)
		Time × composite sarcopenia score	−0.003 (0.005, 0.55)

Note: Each of models shows the results for the model terms of "Time," that is, the annual rate of change in global cognition and the interaction of baseline composite sarcopenia score with "Time" form a single linear mixed-effect model, which also included an additional 10 terms for age, sex, education, race, and height squared and their interaction with time.

DISCUSSION

This study of 1175 well-characterized community dwelling older adults without dementia provides evidence that baseline sarcopenia is associated with incident AD dementia, incident MCI and the rate of cognitive decline. Analyses of the components used to construct sarcopenia suggest that muscle function, as measured by grip strength or gait speed rather than muscle mass is the primary driver of these associations. These longitudinal findings suggest that sarcopenia in older age is related to a wider range of adverse health outcomes including not only mortality and disability, but also late-life cognitive impairment. Our results provide additional support for the growing recognition that muscle function rather than muscle mass is the primary driver of the reported associations of sarcopenia with varied adverse health outcomes in older adults.

Aging adults show changes in body composition and habitus with loss of lean muscle mass. Thus, early definitions of sarcopenia focused primarily on reduced muscle mass or bulk as the primary driver of the associations of sarcopenia with adverse health outcomes in old age.[26] There has been increasing questions about the role of muscle mass as part of the definition of sarcopenia.[2] The recently published consensus position by the Sarcopenia Definition and Outcomes Consortium concluded that muscle function, and not lean muscle mass, drives the association of sarcopenia with risk of mortality and incident disabilities.[1,3,27] The current study lends further support to this conclusion by providing evidence that the association of sarcopenia with incident cognitive impairment in older adults is also driven primarily by muscle function and not muscle mass.

These reports emphasize previous findings in our cohort, that metrics of grip strength and gait speed are robust, but nonspecific predictors of adverse health outcomes in old adults.[5,6,13] In other words, while grip strength and gait speed show significant associations with diverse adverse health outcomes in older adults, these metrics cannot identify individuals at risk for specific outcomes. Thus, by measuring grip strength and gait speed alone, it is not possible to identify an individual at risk for incident cognitive impairment rather than other adverse health outcomes such as disability or mortality. Our novel longitudinal findings have important clinical implications in that they broaden the spectrum of adverse health outcomes associated with sarcopenia to include incident AD, incident MCI, and cognitive decline. These findings also underscore the need to identify more granular metrics for both components of sarcopenia. Understanding the underlying varied biological mechanisms linking body composition measures and muscle function with distinct adverse health outcomes is crucial for development of more accurate risk stratification and targeted interventions. Recent studies in this cohort have employed wearable sensors to capture a wider range of gait and balance metrics which may complement conventional gait speed metrics. These studies suggest that collecting a wider range of muscle function metrics with wearable sensors may improve prediction models for specific adverse health outcomes such as incident AD and MCI.[28]

Our results that muscle mass does not predict late-life cognitive impairment, highlight that further work is needed to identify which features of muscle structure

can be added to muscle function to improve the specificity of sarcopenia for identifying adults at risk for late-life cognitive impairment. For example, further studies of muscle morphology, including muscle fiber types and size, and fiber groupings may add to predictions of incident cognitive impairment. Many vital morphologic features of muscle are influenced by CNS structures distributed in regions extending from the brain to spinal motor neurons.[29] While lean muscle mass may not be the salient feature of muscle structure driving cognitive impairment, few studies have systematically investigated muscle morphology in large numbers of well-characterized older adults and none have linked morphologic changes in muscle with degeneration of nerve, spinal cord, and brain in the same older individuals. While muscle can be obtained in living older adults, the influences of muscle and CNS degeneration can only be studied together in well-characterized older individuals at the time of death.

The basis for the associations of sarcopenia and cognitive impairment is unknown. Muscle secretes hormone-like proteins may reach cognitive brain regions via systemic circulation rather than via CNS connection to affect cognition.[30,31] Myokines, secreted by muscle, contribute to the regulation of hippocampal function[32]; moreover, myostatin, a potent myokine that modulates muscle atrophy, when blocked, leads to increase in muscle mass and grip strength and improved memory and learning in a transgenic model of AD.[12] These recent studies highlight the need for further studies to identify which markers of muscle structure highlight these muscle links with cognition, which if added to muscle function metrics, may improve the specificity of sarcopenia for identifying adults at risk for incident cognitive impairment.

This study has several limitations. The clinical data analyzed were derived from a select cohort who agreed to autopsy at death and may differ in important ways from older persons in the general population such as education, socio-economic status, and lifestyle. It will be important to replicate these findings in more diverse cohorts. The adults in this study were very old and our results may not reflect the associations that might be observed in mid-life or younger older adults. Mild cognitive impairment is intermediate between an individual with NCI and one with dementia. Our complementary analyses showing the associations of sarcopenia with cognitive decline, the principal manifestation of AD, lends confidence that the association of sarcopenia with incident MCI was not likely to have been affected by diagnostic misclassification. While the use of electrical bioimpedence measures has expanded, these measures may be more variable than traditional measures of muscle mass, that is, dual-energy X-ray absorptiometry

(DXA), particularly in very old adults,[33,34] underscoring the importance of replicating our findings with more traditional measures of muscle mass[35] and advancing the investigation of muscle morphology. Our results remained robust after adjusting for cardiovascular risk factors and diseases, but other factors such as cancer may have affected muscle mass and function. Confidence in the findings from this study is enhanced by several factors. Participants were examined annually for up to 13 years with structured validated clinical measures of muscle mass, muscle and cognitive function in a large number of males and females.

In summary, in a large cohort of initially nondemented community-dwelling older adults we found an association of sarcopenia with late-life cognitive impairment. Adults with more severe baseline sarcopenia had an increased risk of incident AD, incident MCI, and a faster rate of cognitive decline. Our findings also suggest that the muscle function component of sarcopenia is the main driver of these associations. Further research is needed to identify which features of muscle structure and additional muscle function metrics can improve the specificity of sarcopenia for use as a clinical biomarker to identify adults at risk for late-life cognitive impairment.

CONFLICT OF INTEREST
The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS
Michal S. Beeri: study design and write-up of the manuscript; Sue E. Leugrans: analyses and interpretation of data and manuscript review; Osvaldo Delbono: interpretation of results and manuscript review; David A. Bennett: study concept and design, acquisition of data, and manuscript review; Aron S. Buchman: study concept and design, acquisition of data, and manuscript review.

SPONSOR'S ROLE

Sponsors were not involved in designing, conducting, analyzing, or writing this study manuscript.

REFERENCES

1. Cesari M, Kuchel GA. Role of sarcopenia definition and diagnosis in clinical care: moving from risk assessment to mechanism-guided interventions. *J Am Geriatr Soc.* 2020;68(7):1406-1409.

2. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019;48(1):16-31.

3. Bhasin S, Travison TG, Manini TM, et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. *J Am Geriatr Soc.* 2020;68(7):1410-1418.

4. Ganmore I, Elkayam I, Ravona-Springer R, et al. Deterioration in motor function over time in older adults with type 2 diabetes is associated with accelerated cognitive decline. *Endocr Pract.* 2020;26 (10):1143-1152.

5. Yu L, Boyle PA, Leurgans SE, Wilson RS, Bennett DA, Buchman AS. Incident mobility disability, mild cognitive impairment, and mortality in community-dwelling older adults. *Neuroepidemiology.* 2019;53(1–2):55-62.

6. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Arch Neurol.* 2009;66(11):1339-1344.

7. Buchman AS, Wang T, Yu L, Leurgans SE, Schneider JA, Bennett DA. Brain pathologies are associated with both the rate and variability of declining motor function in older adults. *Acta Neuropathol.* 2020;140(4):587-589.

8. Buchman AS, Yu L, Petyuk VA, et al. Cognition may link cortical IGFBP5 levels with motor function in older adults. *PLoS One.* 2019;14(8):e0220968.

9. Hayes JP, Moody JN, Roca JG, Hayes SM, Alzheimer's Disease Neuroimaging Initiative. Body mass index is associated with smaller medial temporal lobe volume in those at risk for Alzheimer's disease. *Neuroimage Clin.* 2020;25:102156.

10. Singh-Manoux A, Dugravot A, Shipley M, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the White-hall II study. *Alzheimers Dement.* 2018;14(2):178-186.

11. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. *Neurology.* 2005;65(6):892-897.

12. Lin YS, Lin FY, Hsiao YH. Myostatin is associated with cognitive decline in an animal model of Alzheimer's disease. *Mol Neurobiol.* 2019;56(3):1984-1991.

13. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and Rush Memory and Aging Project. *J Alzheimers Dis.* 2018;64:S161-S189.

14. Bennett DA, Schneider JA, Buchman AS, Mendes de Leon C, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology.* 2005;25(4):163-175.

15. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA.* 1993;269(18):2386-2391.

16. Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc.* 2005;11(4):400-407.

17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. *Neurology.* 1984;34(7):939-944.

18. Wilson RS, Boyle PA, James BD, Leurgans SE, Buchman AS, Bennett DA. Negative social interactions and risk of mild cognitive impairment in old age. *Neuropsychology.* 2015;29(4): 561-570.

19. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol (1985).* 2000;89(2):465-471.

20. Janssen I, Heymsfield SB, Wang Z, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol.* 2000;89(1):81-88.

21. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50 (5):889-896.

22. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci.* 2014;69(12):1536-1544.

23. Buchman AS, Yu L, Wilson RS, et al. Progressive parkinsonism in older adults is related to the burden of mixed brain pathologies. *Neurology.* 2019;92(16):e1821-e1830.

24. Boyle PA, Wilson RS, Aggarwal NT, et al. Parkinsonian signs in subjects with mild cognitive impairment. *Neurology.* 2005;65 (12):1901-1906.

25. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* New York: Wiley Interscience; 2004.

26. Cederholm TE, Bauer JM, Boirie Y, Schneider SM, Sieber CC, Rolland Y. Toward a definition of sarcopenia. *Clin Geriatr Med.* 2011;27(3):341-353.

27. Cawthon PM, Manini T, Patel SM, et al. Putative cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. *J Am Geriatr Soc.* 2020;68(7): 1429-1437.

28. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology.* 2012;78(17): 1323-1329.

29. Manini TM, Hong SL, Clark BC. Aging and muscle: a neuron's perspective. *Curr Opin Clin Nutr Metab Care.* 2013; 16(1):21-26.

30. Zhang J, Zhang W. Can irisin be a linker between physical activity and brain function? *Biomol Concepts.* 2016;7(4):253-258.

31. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. *Front Neurol.* 2018;9:698.

32. Pedersen BK. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol.* 2019;15(7):383-392.

33. Letra L, Santana I, Seica R. Obesity as a risk factor for Alzheimer's disease: the role of adipocytokines. *Metab Brain Dis.* 2014;29(3):563-568.

34. Sam S, Haffner S, Davidson MH, et al. Relation of abdominal fat depots to systemic markers of inflammation in type 2 diabetes. *Diabetes Care.* 2009;32(5):932-937.

35. Moon Y, Choi YJ, Kim JO, Han SH. Muscle profile and cognition in patients with Alzheimer's disease dementia. *Neurol Sci.* 2018;39(11):1861-1866.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1. Association of composite sarcopenia with incident AD and MCI (fully adjusted model)

Table S2. Association of muscle function (via gait speed) and mass with incident AD and MCI

Figure S1. Sarcopenia diagnosis is associated with incident AD. Risk of incident AD is higher in participants with a diagnosis of sarcopenia at baseline compared to those without sarcopenia

Editor's Note

Many cross-sectional studies have shown that sarcopenia and mobility disability often occur in the same individuals also experiencing cognitive difficulties. This study uses the Rush Memory and Aging Project (MAP) to demonstrate that in 1175 older adults (mean age = 80.9; 77% women) sarcopenia was associated with a higher incidence of Alzheimer's dementia (AD) and mild cognitive impairment (MCI), as well as a greater rate of cognitive decline at an average follow-up of 5.6 years. Moreover, it was muscle function in the form of handgrip strength as opposed to muscle mass that predicted such cognitive decline.

These findings highlight the importance of overcoming barriers between silo- and organ-based approaches to the care of older adults, while also illustrating the importance of screening for declines in physical performance in individuals being evaluated for the risk of MCI and AD. Furthermore, they also begin to shed some additional insights into the manner in which declines in muscle and cognitive function may be related to each other, offering opportunities for intervention. To that end, growing evidence has demonstrated the potential importance of targeting risk factors shared by declines in both functional domains. For example, exercise, increased physical activity, the Mediterranean diet, and improved control of elevated systolic blood pressure are all associated with the prevention or the slowing of both categories of functional decline.

Moreover, in addition to these shared risk factors, optimal physical and cognitive performance are closely interlinked with each other. Not only does normal muscle structure and function depend on a normal innervation, but higher cortical function and efficient neural processing contribute to optimal muscle function and physical performance. Conversely, myokines secreted by muscle and increased with exercise release neurotrophic factors, which help maintain normal brain integrity, plasticity, and function.

As noted by the authors, muscle function but not muscle mass are predictive of AD, MCI, and cognitive declines. Therefore, the saying "use it or lose it" applies equally well to physical and cognitive performance, as well as their influence on each other. While "increased activity" is clearly beneficial, much work remains to be done before specific mediators of such benefit or therapeutic agents can be prescribed clinically. However, what remains clear is that research and care focused on improving function in older adults can no longer address some functional domains, while ignoring other categories of function.

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