

Association of Muscle Strength With the Risk of Alzheimer Disease and the Rate of Cognitive Decline in Community-Dwelling Older Persons

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Background: Loss of muscle strength is common and is associated with various adverse health outcomes in old age, but few studies have examined the association of muscle strength with the risk of Alzheimer disease (AD) or mild cognitive impairment (MCI).

Objective: To test the hypothesis that muscle strength is associated with incident AD and MCI.

Design: Prospective observational cohort study.

Setting: Retirement communities across the Chicago, Illinois, metropolitan area.

Participants: More than 900 community-based older persons without dementia at the baseline evaluation and in whom strength was measured in 9 muscle groups in arms and legs, and in the axial muscles and summarized into a composite measure of muscle strength.

Main Outcome Measures: Incident AD and MCI and the rate of change in global cognitive function.

Results: During a mean follow-up of 3.6 years, 138 persons developed AD. In a proportional hazards model adjusted for age, sex, and education status, each 1-U increase in muscle strength at baseline was associated with about a 43% decrease in the risk of AD (hazard ratio, 0.57; 95% confidence interval, 0.41-0.79). The association of muscle strength with AD persisted after adjustment for several covariates, including body mass index, physical activity, pulmonary function, vascular risk factors, vascular diseases, and apolipoprotein E4 status. In a mixed-effects model adjusted for age, sex, education status, and baseline level of global cognition, increased muscle strength was associated with a slower rate of decline in global cognitive function ($P < .001$). Muscle strength was associated with a decreased risk of MCI, the precursor to AD (hazard ratio, 0.67; 95% confidence interval, 0.54-0.84).

Conclusion: These findings suggest a link between muscle strength, AD, and cognitive decline in older persons.

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ALTHOUGH ALZHEIMER DISEASE (AD) is characterized clinically by a progressive deterioration in memory and other cognitive abilities, it is associated with various noncognitive features, including affective manifestations (eg, depressive symptoms) and impaired motor function (eg, gait impairment).¹⁻⁵ Recent data suggest that these noncognitive features may be early signs of AD, as they often predict the onset of clinical AD.⁶⁻¹⁰ Although grip strength is related to the risk of AD, few studies¹¹⁻¹³ have examined grip strength, and the more general association of muscle strength (measured in multiple body regions) with incident AD remains unknown. Furthermore, body mass index (BMI) and physical activity are related to the risk of AD,¹⁴⁻¹⁷ yet it is unclear whether the association of muscle strength with AD

is independent of these important confounding variables.

We used data from the Rush Memory and Aging Project,¹⁸ a longitudinal study of aging, to examine the association of muscle strength with incident AD in more than 900 well-characterized persons initially free of dementia. Participants underwent structured evaluations of muscle strength, including strength testing of 9 muscle groups in the extremities and axial muscle strength based on maximum inspiratory pressure and maximum expiratory pressure and on detailed annual cognitive evaluations. Furthermore, because progressive cognitive decline is the hallmark of AD, we examined the relation between muscle strength and cognitive decline. Finally, we examined the association of muscle strength with the risk of incident mild cognitive impairment (MCI), the earliest manifestation of AD.¹⁹

PARTICIPANTS

Participants are from the Rush Memory and Aging Project,¹⁸ all of whom agreed to annual clinical evaluations and organ donation. The study was approved by the Institutional Review Board of Rush University Medical Center, Chicago, Illinois.

Eligibility for these analyses required muscle strength testing, the absence of a clinical diagnosis of dementia at baseline, and at least 1 follow-up evaluation. At the time of these analyses, 1121 participants had completed baseline testing; 76 with dementia were excluded. Of 1045 remaining, 75 had not yet completed or had died before their first follow-up evaluation. This resulted in a final group of 970 participants (241 men and 729 women [92.0% white]) who completed at least 1 follow-up evaluation (mean [SD] follow-up, 3.6 [1.5] years [range, 1-6 years]). Their mean (SD) age was 80.3 (7.5) years (age range, 54-100 years), education status was 14.5 (3.0) years (range, 3-28 years), and Mini-Mental State Examination score was 28.0 (2.1) (range, 18-30).²⁰ Of these participants, 88.5% had 2 or more evaluations, 75.0% had 3 or more, and 55.6% had 4 or more.

CLINICAL DIAGNOSES

Details of the clinical evaluation have been described.¹⁸ Briefly, each participant underwent a uniform structured baseline evaluation, including medical history and neurologic and neuropsychological examinations. Annual follow-up evaluations were identical to the baseline evaluation. Cognitive function was assessed annually via 21 tests,^{19,21} and the data were reviewed by an experienced neuropsychologist, who made a judgment regarding the presence of cognitive impairment. Participants were evaluated in person by a clinician who diagnosed dementia according to the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,²² which require a history of cognitive decline and evidence of impairment in 2 or more domains of cognition. Classification of AD, the primary outcome in this study, requires that memory is one of the domains affected.²² Participants were classified as having MCI if they had cognitive impairment but did not meet criteria for dementia, as previously described.¹⁹

ASSESSMENT OF MUSCLE STRENGTH

A composite measure of muscle strength derived from testing in 11 muscle groups (including arms, legs, and 2 axial muscles) was used in this study, as previously described.^{23,24} Appendicular muscle strength was measured using a handheld dynamometer (model 01163, Lafayette Manual Muscle Test System; Lafayette Instrument Co USA, Lafayette, Indiana) in the upper extremities (abduction, flexion, and extension in both arms) and in the lower extremities (hip flexion, knee extension, plantar flexion, and ankle dorsiflexion in both legs). Grip and pinch strength were measured bilaterally using the hydraulic hand and pinch dynamometer (Jamar; Lafayette Instrument Co USA). Axial strength was measured using a handheld device containing a pressure-sensitive transducer to assess maximal pressures generated during inspiration (maximum inspiratory pressure) and expiration (maximum expiratory pressure).^{23,25-27} Bilateral measures were averaged, and the scores from each muscle group were converted to *z* scores using sex-specific means (SDs) from the baseline evaluations. Finally, *z* scores of all muscles were averaged to yield a global measure of muscle strength.

Cognitive function was assessed at each evaluation via 21 tests.^{18,19} The Mini-Mental State Examination scores were used to describe the cohort, and Complex Ideational Material was used for diagnostic classification.^{18,19} Scores on the following 19 tests were used to create a composite measure of global cognition: immediate and delayed recall of story A from Logical Memory, immediate and delayed recall of the East Boston Story, Word List Memory, Word List Recall, Word List Recognition, a 15-item Boston Naming Test, Verbal Fluency, a 15-item reading test, Digit Span Forward, Digit Span Backward, Digit Ordering, Symbol Digit Modalities Test, Number Comparison, 2 indexes from the Stroop Test, a 15-item Judgment of Line Orientation, and a 16-item Standard Progressive Matrices. To compute the composite, the raw scores on each of the individual tests were converted to *z* scores using the baseline mean (SD) of the entire cohort, and the *z* scores of all 19 tests were averaged. Further psychometric information on this composite is given in previous publications.^{18,19}

ASSESSMENT OF COVARIATES

Age, sex, race/ethnicity, and education status were recorded at baseline. Weight and height were measured and recorded at each visit, and BMI was calculated as weight in kilograms divided by height in meters squared.⁹ Vascular diseases included stroke, claudication, and myocardial infarction, and vascular risk factors included smoking, hypertension, and diabetes mellitus; the numbers of diseases and risk factors present at baseline were used in analyses.¹⁹ Pulmonary function was tested using a handheld spirometer that measured vital capacity, forced expiratory volume, and peak expiratory flow.^{23,27} Physical activity was evaluated using questions from the 1985 Health Interview Survey.^{18,23}

STATISTICAL ANALYSIS

Pearson product moment correlations were used to examine bivariate associations, and *t* tests were used to compare men vs women and participants who did vs those who did not develop AD. A proportional hazards model²⁸ with time to AD as the outcome was used to examine the association of muscle strength with the risk of incident AD; this model controlled for age, sex, and education status. We also examined the influence of important covariates, conducted a series of sensitivity analyses, and, finally, examined the association of strength with the risk of MCI.

Mixed-effects models²⁹ were used to examine the association of muscle strength with cognitive decline. Therefore, we estimated the mean change in the group (conditional on covariates) as in standard fixed-effects repeated-measures models, and the mixed-effects model included random coefficients that provided estimates of individual differences from the group. Each participant was assumed to follow the average path of the group except for random effects that caused the baseline level of cognition to be lower or higher and the rate of change in cognition to be faster or slower. The variance-covariance matrix for the random coefficients was not assumed to be of a restricted form, and we assumed that residual error was normally distributed and independent of the random effects. A major strength of this approach is the ability to model all data available for each participant regardless of length of follow-up, number and spacing of evaluations, or missing data at some evaluations.

The mixed-effects model controlled for age, sex, and education status and included terms for time, time squared, muscle

Table. Baseline Characteristics of Participants Who Developed vs Those Who Did Not Develop Alzheimer Disease (AD)^a

Characteristic	Mean (SD)		P Value ^b
	Developed AD (n = 138)	Did Not Develop AD (n = 832)	
Age, y	84.5 (6.0)	79.8 (7.3)	<.001
Education, y	14.5 (3.0)	14.6 (7.2)	.90
Muscle strength, lb ^c			
Arm abduction	3.5 (2.4)	4.0 (2.2)	.02
Elbow flexion	11.6 (4.7)	12.9 (5.4)	.004
Elbow extension	9.6 (3.5)	10.8 (3.9)	.001
Grip	43.2 (17.6)	49.3 (18.0)	<.001
Pinch	9.9 (5.1)	10.9 (5.0)	.03
Hip flexion	9.8 (4.1)	10.6 (4.7)	.03
Knee extension	9.9 (3.8)	10.8 (4.1)	.02
Ankle plantar flexion	14.6 (4.5)	15.2 (5.2)	.13
Ankle dorsiflexion	10.4 (4.0)	11.7 (5.0)	.001
Pulmonary function, cm H ₂ O			
Maximum expiratory pressure	60.8 (25.2)	68.1 (24.5)	.002
Maximum inspiratory pressure	33.8 (18.4)	41.7 (20.8)	<.001
Body mass index ^d	26.3 (4.1)	27.5 (5.5)	.004
Physical activity, h/wk	3.1 (3.8)	3.1 (3.6)	.80
Vascular risk factors, No. of conditions present	1.1 (1.0)	1.2 (1.0)	.70
Vascular diseases, No. of conditions present	0.4 (0.6)	0.3 (0.6)	.40
Mini-Mental State Examination score	26.3 (2.8)	28.3 (1.8)	<.001
Global cognition score	-0.41 (0.49)	0.22 (0.48)	<.001

^aMen represented 19.5% (among participants who developed AD) and 80.5% (among participants who did not develop AD) of the cohort ($P = .03$).

^bStatistical significance is based on t test or χ^2 test, as appropriate.

^cTo convert pounds to kilograms, multiply by 1.6.

^dCalculated as weight in kilograms divided by height in meters squared.

strength, and the interaction of muscle strength with time. We also tested for nonlinearity in the association of the strength measure with cognition, but because this was not significant, the term for time squared \times muscle strength was not retained in the final models. All models were validated graphically and analytically, and programming was performed using commercially available statistical software (SAS, version 8; SAS Institute Inc, Cary, North Carolina).³⁰

RESULTS

METRIC PROPERTIES OF THE COMPOSITE MEASURE OF MUSCLE STRENGTH

Muscle strength ranged from -1.600 to 3.300 U (mean [SD], 0.006 [0.660] U), with higher scores reflecting greater strength. Muscle strength was negatively associated with age ($r = -0.35$, $P < .001$) and was positively associated with global cognition ($r = 0.20$, $P < .001$).

MUSCLE STRENGTH AND THE RISK OF AD

Over a mean of 3.6 follow-up years, 138 participants (14.2% of 970) developed AD. Participants who developed AD were older, had lower cognitive function, and showed decreased strength in several muscles compared with participants who did not (**Table**). In the core proportional hazards model adjusted for age, sex, and education status, muscle strength was associated with the risk of developing AD, such that each 1-U increase in muscle strength (based on 11 muscle groups) at baseline was associated with about a 43% decrease in the risk of AD (haz-

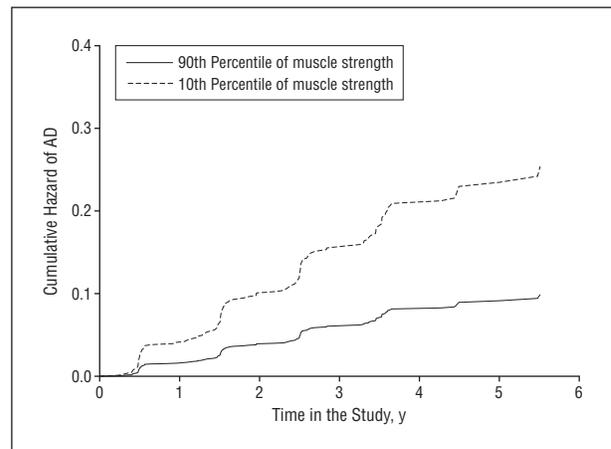


Figure 1. Cumulative hazard of Alzheimer disease (AD) for participants with low muscle strength vs those with high muscle strength.

ard ratio [HR], 0.57; 95% confidence interval [CI], 0.41-0.79). **Figure 1** shows that a participant having a high level of muscle strength (90th percentile [score, 0.850]) had about a 61% decreased risk of developing AD compared with a participant having a low level of muscle strength (10th percentile [score, -0.810]).

Next, because prior studies^{12,13} have shown that grip strength is related to the risk of AD and it is possible that our finding was driven by grip strength, we constructed a proportional hazards model to simultaneously examine the relative predictive association of the components of strength (ie, grip strength and all other measures of upper extremity strength, lower extremity

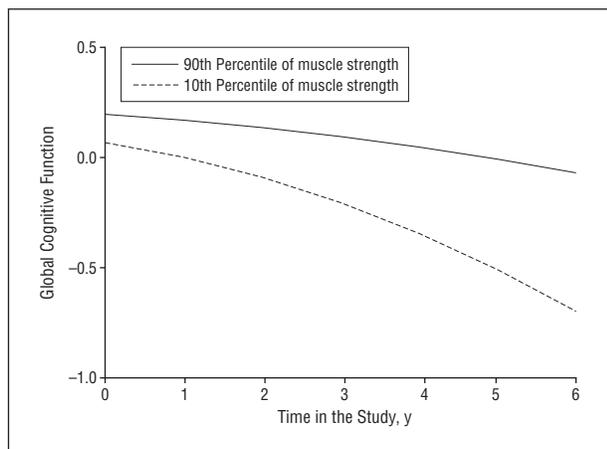


Figure 2. Decline in global cognitive function for participants with low muscle strength vs those with high muscle strength.

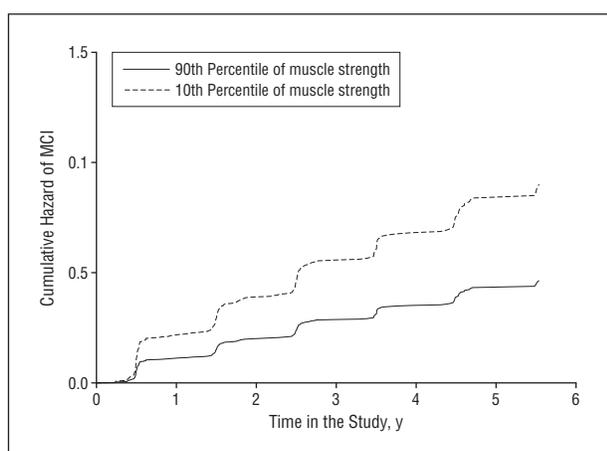


Figure 3. Cumulative hazard of mild cognitive impairment (MCI) for participants with low muscle strength vs those with high muscle strength.

strength, and axial muscle strength) with the risk of AD. In this model, grip strength was associated with the risk of AD (HR, 0.61; 95% CI, 0.47-0.80). However, axial muscle strength was associated with the risk of AD even after accounting for the effect of grip strength (HR, 0.68; 95% CI, 0.53-0.87). By contrast, lower extremity strength and upper extremity strength were not individually associated with the risk of AD.

Furthermore, because there are several covariates that may account for the association of muscle strength with AD, we repeated the core model after adding terms for the following covariates separately and together: physical activity, pulmonary function, vascular risk factors, vascular diseases, BMI, BMI squared (because low and high BMI are associated with AD), and the presence of the apolipoprotein E4 allele. The addition of these covariates individually (data not shown) or together in a single model did not substantially affect the association between muscle strength and the risk of AD (HR, 0.59; 95% CI, 0.41-0.84).

SENSITIVITY ANALYSES

We conducted a series of sensitivity analyses to address the possibility that the findings were driven by the in-

clusion of participants with very early and undiagnosed AD or participants with the lowest function at baseline. We repeated the core analysis after sequentially excluding participants who developed AD in the first year of follow-up ($n=32$) and then in the first or second year of follow-up ($n=74$); in these analyses, the association of muscle strength with AD was not substantially changed (HR, 0.59; 95% CI, 0.40-0.86; and 0.61; 0.37-1.03; respectively). Next, we repeated the core analysis after excluding participants in the bottom 15% in terms of cognition at baseline, and the association of muscle strength with AD persisted (HR, 0.48; 95% CI, 0.30-0.77). Finally, we repeated the core analysis after excluding participants in the bottom 15% in terms of muscle strength at baseline, and the association of muscle strength with AD persisted (HR, 0.57; 95% CI, 0.35-0.90).

MUSCLE STRENGTH AND CHANGE IN GLOBAL COGNITIVE FUNCTION

Because AD develops slowly over many years and its hallmark is change in cognitive function, we examined the association of muscle strength with cognitive decline. At baseline, scores on the composite measure of global cognition (based on 19 tests) ranged from -1.80 to 1.40 (mean [SD], 0.12 [0.54]), with higher scores indicating better performance. We constructed a mixed-effects model that controlled for age, sex, and education status and included terms for time, time squared, muscle strength, and the interaction of muscle strength with time to examine the association of strength with cognitive decline. Scores on the composite measure of global cognition showed linear and nonlinear decline ($P < .05$ for both). Furthermore, each 1-U increase in muscle strength at baseline was associated with about a 0.040-U decrease in the rate of decline in global cognition ($P < .001$). **Figure 2** shows that the rate of cognitive decline for a participant with a high level of muscle strength (90th percentile [score, 0.850 U]) was considerably slower than that of a participant with a low level of muscle strength (10th percentile [score, -0.810 U]). The addition of covariates did not substantially affect the association between muscle strength and the rate of cognitive decline (data not shown).

MUSCLE STRENGTH AND THE RISK OF MCI

Finally, because it is widely recognized that most persons who develop AD transition through an early stage of impairment referred to as MCI, we excluded participants with any evidence of cognitive impairment at baseline and constructed a proportional hazards model examining the association of muscle strength with incident MCI. Over a mean of 3.6 follow-up years, 275 participants (39.6% of 694) developed MCI. In the proportional hazards model adjusted for age, sex, and education status, muscle strength was associated with a decreased risk of developing MCI (HR, 0.67; 95% CI, 0.54-0.84). **Figure 3** shows that a participant with a high level of muscle strength (90th percentile [score, 0.850 U]) had about a 48% decreased risk of developing MCI compared with a participant with a low level of muscle strength

(10th percentile [score, -0.810 U]). Furthermore, muscle strength was associated with a decreased risk of persistent MCI (MCI followed by MCI, dementia, or death at a subsequent evaluation [HR, 0.55; 95% CI, 0.38-0.79]).

COMMENT

In more than 900 well-characterized community-based older persons without dementia, we found that greater muscle strength was associated with a decreased risk of developing AD. This finding persisted in sensitivity analyses in which we excluded participants who developed AD in the early follow-up years and participants with the lowest function at baseline and in models that controlled for BMI, physical activity, pulmonary function, vascular risk factors, vascular diseases, and the presence of the apolipoprotein E4 allele. Furthermore, muscle strength was associated with the rate of cognitive decline, such that participants with greater strength at baseline exhibited a considerably slower rate of decline. Finally, in an analysis that excluded participants with dementia or MCI at baseline, muscle strength was associated with the risk of developing MCI, the earliest manifestation of cognitive impairment. Overall, these data show that greater muscle strength is associated with a decreased risk of developing AD and MCI and suggest that a common pathogenesis may underlie loss of muscle strength and cognition in aging.

Although the clinical hallmark of AD is declining cognition, motor signs that frequently accompany AD often precede and predict the clinical diagnosis of AD.^{1-12,31-34} Loss of muscle strength and mass also are common in aging, and frailty and BMI changes are associated with the risk of AD.^{6-12,34} While measures of frailty and BMI can be obtained inexpensively, they do not inform about the role of muscle mass vs muscle strength in the risk of AD, and recent data suggest that muscle strength is associated with cognition independent of muscle mass.¹⁴ To date, data on muscle strength and AD are limited. One study¹¹ reported that grip strength was predictive of cognitive decline in older Mexican Americans, but this study likely included persons with mild dementia at baseline. In a cohort of Catholic clergy, it was found that grip strength was associated with incident AD.¹⁷ Although these findings are important and motivated the present study, grip strength may not fully capture the association of muscle strength (measured more comprehensively) with the risk of AD. We quantified muscle strength in all 4 extremities and in the axial muscles among a large cohort of older persons and found that greater muscle strength was associated with a reduced risk of AD. Furthermore, in analyses of the components of muscle strength, axial muscle strength was associated with the risk of AD even after accounting for grip strength, suggesting that comprehensive assessments of strength may be useful for identifying persons at risk for cognitive impairment. Finally, muscle strength was associated with a substantially decreased risk of MCI, suggesting a temporal relation whereby impaired muscle strength precedes the development of cognitive impairment in ag-

ing. Assessment of muscle strength may have usefulness for identifying persons at risk for the earliest manifestation of cognitive impairment and who may benefit most from intervention.

The basis of the association of muscle strength with AD is unknown. Although decreased muscle strength may represent a true risk factor for AD, it is more likely that loss of muscle strength is the result of an underlying disease process that also leads to cognitive decline and clinical AD. For example, muscle has an important role in energy production and regulation; the mitochondrial theory of aging proposes that damaged mitochondria accumulate over time and that these and related energy disruptions are in part responsible for loss of muscle strength and other signs of aging.³⁵ The discovery of mitochondrial diseases in aged organisms provides some support for this hypothesis; however, questions remain about its relevance to human aging. While muscle is situated outside the blood-brain barrier (making it vulnerable to systemic diseases), muscle function is controlled by spinal motor neurons, which reflect supraspinal motor control systems.^{36,37} Decreased strength may result from disorders of the central nervous system (eg, stroke) that may also unmask subclinical AD.³⁸ In this study, the association between muscle strength and AD was unchanged after controlling for vascular risk factors and vascular diseases, suggesting that other factors are important. One such factor is AD pathologic features, which accumulate slowly over time (before the onset of clinical dementia) and may contribute to decreased muscle strength and cognition. Pathologic features of AD frequently occur in regions that subservise motor function.³⁹⁻⁴² Furthermore, the link between executive cognition and movement may suggest that pathologic features of AD in cognitive regions may contribute to motor decline.⁴³ An association between pathologic features of AD in the cognitive regions and grip strength was previously reported.⁴⁴ Future studies are needed to clarify the neurobiological basis of the association of muscle strength with the risk of AD and the rate of cognitive decline.

Limitations of this study include the selected nature of the cohort, which included participants willing to provide organ donation. Replication of these results in a population-based study is important. Furthermore, although our results suggest that decreased muscle strength precedes the development of cognitive impairment, observational studies cannot directly address the issue of causality. We also cannot rule out the possibility of residual confounding or that a latent variable underlies the association of muscle strength with cognition. However, the study has several strengths, including the use of a large cohort of well-characterized older persons and composite measures of muscle strength and cognition, the uniform classification of AD and MCI, and the ability to examine several potential confounders of the association between muscle strength and AD.

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