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Examining the Association Between Quadriceps Strength and Cognitive Performance in the Elderly

Wei-Liang Chen, MD, Tao-Chun Peng, MD, Yu-Shan Sun, MD, Hui-Fang Yang, MD, Fang-Yih Liaw, MD, Li-Wei Wu, MD, Yaw-Wen Chang, MD, and Tung-Wei Kao, MD, MSc

Abstract: Emerging evidences showed impaired muscle strength was prevalent in older adults with mild cognition impairment or dementia. However, little was known about the role of quadriceps strength in the cognition decline among older population. The objective of our study was to investigate the relation between quadriceps strength and cognitive performance. Using data from the National Health and Nutrition Examination Survey (1999–2002), a total of 1799 participants aged ≥60 years were enrolled in the study. Every subject completed a household interview, digit symbol substitution test (DSST), physical performances, and a questionnaire regarding personal health. Estimation of relationship between quadriceps strength and cognition was using multiple linear regression and quartile-based analysis with an extended-model approach for covariates adjustment. In a model adjusted for demographics, chronic diseases, health behaviors, and levels of folate and vitamin B12, the level of quadriceps strength was significantly associated with the scores of DSST. The β coefficient interpreted as change of DSST scores for each Newton increment in quadriceps strength comparing participants in the highest quartile of quadriceps strength to those in the lowest quartile was 5.003 (95% confidence interval, 2.725–7.281, $P < 0.001$). The trends of incremental DSST score across increasing quartiles of quadriceps strength were statistically significant (all P for trend <0.001). Higher quadriceps strength was associated with better cognitive performance.

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Abbreviations: AD = Alzheimer disease, BMI = body mass index, CRP = C-reactive protein, DSST = digit symbol substitution test, NCHS = National Center for Health Statistics, NHANES = National Health and Nutrition Examination Survey, WBC = white blood cell.

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From the Division of Family Medicine (W-LC, T-CP, Y-SS, H-FY, F-YL, L-WW, Y-WC, T-WK); Department of Family and Community Medicine, Division of Geriatric Medicine, Tri-Service General Hospital; and School of Medicine, National Defense Medical Center (W-LC, F-YL, L-WW, Y-WC, T-WK); Graduate Institute of Medical Sciences, National Defense Medical Center (W-LC, F-YL); and Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan (T-WK).
Correspondence: Tung-Wei Kao, Department of Family and Community Medicine, Division of Geriatric Medicine, Tri-Service General Hospital, National Defense Medical Center, Number 325, Section 2, Chang-gong Rd, Nei-Hu District, 114 Taipei, Taiwan (e-mail: ktw61916@yahoo.com.tw)
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INTRODUCTION

Muscle strength, one of the primary components of aging process, was generally defined as the ability to generate force at a given velocity of movement. Muscle wasting, commonly referred to as sarcopenia, was associated with detrimental outcome in the elderly, such as physical fitness, mobility decline, disability, and mortality.[1,2] Muscle strength was regarded as a better predictor of mobility decline and disability than muscle mass.[3,4] Emerging evidences suggested that handgrip strength was associated with accelerated decline in global cognitive performance and higher risk of Alzheimer disease (AD) and mild cognitive impairment in longitudinal studies.[5,6] In a longitudinal analysis of 934 adults aged ≥65 years enrolled in Chianti study, knee extension strength measured at one time point is predictive of mobility decline.[7]

Decline of cognitive function or loss of intellectual performance in the elderly population is imposing huge societal economic burdens in the next couple of decades. Approximately 10% of persons older than 65 years and almost 50% of those older than 85 years have dementia.[8] A variety of independent risk factors of dementia were clarified, including ApoE status,[9] walking speed,[10] exercise,[11] disability,[12] and fraility.[13] In a longitudinal study of aging to examine the association of muscle strength with incident dementia in >900 well-characterized persons initially free of dementia, grip strength was associated with risk of AD even after adjusting pertinent variables.[14] Despite its convenience and importance, muscle strength of lower and upper extremities was rarely used and evaluated in the geriatric assessment. Epidemiologic studies assessing the interaction between quadriceps strength and cognitive status in the old population were also lacking.

Based on the above-mentioned rationale, our aim in this study is to determine whether the quadriceps strength was associated with the cognitive performance in a national representative sample of elderly population aged 60 to 85 years.

METHODS

Study Populations

The National Health and Nutrition Examination Survey (NHANES) was a complex, multistage, and population-based survey designed to collect information on the health and nutrition status to obtain a representative sample of the noninstitutionalized civilian United States population. The data of NHANES were collected in the form of a detailed home interview and a health examination conducted in a mobile examination center. The study population consisted of adults aged 20 years and older. Beginning in 1999, NHANES became a continuous annual survey rather than the periodic survey that it had been in the past.[15] Detailed survey operations manuals, consent documents, and brochures of NHANES 1999–2002 are available on the NHANES website.[16] This dataset on the

NHANES website is accessible for download and analysis without any permission. The NHANES study received National Center for Health Statistics (NCHS) Institutional Review Board approval, and informed consent was acquired from participants prior to starting the study.

We collected 2 NHANES datasets (1999–2000 and 2001–2002), which included demographic, examination, laboratory, and questionnaire data. All participants aged <60 years of age were excluded from our analysis. Among these populations, elderly adults with incomplete data for the cognitive function, quadriceps strength measurement, household interview, or laboratory and clinical examinations were also excluded. In addition, examinees who had a history of myocardial infarction within the past 6 weeks, chest or abdominal surgery within the past 3 weeks, knee surgery or knee replacement surgery, severe back pain, difficulty in bending or straightening right knee, and brain aneurysm or stroke were excluded from the muscle strength examination.[17]

Measurement of Cognitive Performance

The Digit Symbol Substitution Test (DSST), a component of the Wechsler Adult Intelligence Test to examine the visuospatial and motor speed of processing, represented a sensitive measure of frontal lobe executive functions in which eligible individuals transcribe symbols matched to numbers using a legend. Within the 133 of maximum scores, the score represented the number of correct items completed in 2 minutes.

Measurement of Knee Extensor Strength

Muscle strength was assessed by measuring the isokinetic strength of the knee extensors (quadriceps). A Kinetic Communicator isokinetic dynamometer (manufactured by Chattanooga Group, Inc, Chattanooga, TN) was used to evaluate knee extensor strength. Maximal voluntary isometric knee extension strength was measured in Newton according to the NHANES examination protocol.[17] Strength of the knee extensor muscles was tested by measuring peak torque of the quadriceps at one angular velocity speed (60 degree/s). Six muscle strength measurements were obtained. Three warm-up/learning measurements and 3 test measurements were recorded for the muscle strength component. After 6 muscle strength trials were preformed, only the highest peak forced was reported in the data file. Certified health technicians conduct the examinations. All health technicians receive intensive training on the NHANES examination protocols.[17,18]

Covariates

The pertinent demographic information was obtained by self-report, including age, sex, race, educational levels, and smoking status. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The presence of diabetes mellitus was defined either by a self-report of the physician's diagnosis, or the presence of a fasting glucose level of $\geq$126 mg/dL, or the presence of a random glucose level of $\geq$200 mg/dL, or the use of diabetic medications. Systolic and diastolic blood pressures were measured in the right arm unless specific conditions prohibited the use of the right arm using a mercury sphygmomanometer by a NHANES physician. The definition of hypertension was used either by a self-reported doctor's diagnosis, or averaged blood pressure of $\geq$140/90 mmHg, or the use of antihypertensive medications. For comorbidities, heart diseases were defined as if participants had experienced or been told to have myocardial infarction, congestive heart failure, or angina. Alcohol intake was determined by the question, "In any 1 year, have you had $\geq$12 drinks of any type of alcohol beverage?" and was dichotomized. The methods used to derive complete blood count parameters such as white blood cell count and hemoglobin are based on the Beckman Coulter method of counting and sizing, in combination with an automatic diluting and mixing device for sample processing and a single-beam photometer for hemoglobinometry. C-reactive protein (CRP) was analyzed using a highly sensitive assay technique and was quantified by utilizing latex-enhanced nephelometry with a Behring Nephelometer Analyzer System (Deerfield, IL). Detailed specimen collection and processing instructions are discussed in the NHANES Laboratory Procedures Manual and are available on the NHANES website.[16]

Statistical Analyses

Some of the covariates were regarded as continuous variables, including age, vitamin B12, serum folate, and DSST scores. Some covariates were treated as categorical variables, such as sex and race. We used quartile-based analysis by dividing quadriceps strength into quartiles with the subjects in the lowest one as the reference group. The cutoff levels for quadriceps strength quartiles were as follows: Q1 <190.00 Newtons, 190.00 = Q2 <244.20 Newtons, 244.20 = Q3 <309.30 Newtons, and Q4 $\geq$309.30 Newtons. Linear regression analysis was investigated between the measurement of quadriceps strength and neuropsychological performance. An extended-model approach was used for covariates adjustment: Model 1 = age, sex, and race/ethnicity; Model 2 = Model 1 + educational level, BMI, current smoker, and alcohol consumption; Model 3 = Model 2 + history of hypertension, diabetes mellitus, and heart disease. Model 4 = Model 3+ CRP, serum folate, and vitamin B12. All analyses were conducted using Statistics Package for Social Science version 18.0 software (SPSS, Inc, Chicago, IL).

RESULTS

Characteristics of the Study Population

In the NHANES dataset from 1999 to 2002, a total of 1799 participants were included in the study. The characteristics of the participants categorized by quartiles of quadriceps strength were summarized in Table 1. The mean age was 70.43 ± 7.46 years and 49.9% of the participants were men. Participants with higher quartiles of quadriceps strength had a higher DSST scores, lower serum folate, lower alcohol consumption, and lower CRP than those with lowest quartiles of quadriceps strength.

Association Between Quadriceps Strength Level and Cognitive Performance

In the linear regression models (Table 2), the level of quadriceps strength was significantly associated with the scores of DSST. The adjusted β coefficient of DSST scores with adjustment of age, sex, and race was 0.026 (95% confidence interval (CI), 0.016–0.037, $P < 0.001$). After the adjustment of additional covariates, the positive association remained (β coefficient = 0.018, 95% CI, 0.009–0.028, $P < 0.001$). The results of quadriceps strength quartiles-based multiple linear regression analysis were shown in Table 3. From model 1 to model 4, the positive correlations between quadriceps strength and cognitive performance were observed. Subjects in the

TABLE 1. Characteristics of Study Participants

Variables	Quartiles of Quadriceps Strength, Newtons					
	Q1 (<190.00) (N = 451)	Q2 (190.00–<244.20) (N = 450)	Q3 (244.20–<309.30) (N = 450)	Q4 (≥309.30) (N = 448)	Total (N = 1799)	*P*
Continuous variables*						
Age, y	74.06 (7.79)	71.37 (7.42)	69.11 (6.66)	67.15 (6.02)	70.43 (7.46)	<0.001
DSST score	40.19 (17.61)	42.53 (18.09)	45.38 (19.58)	48.25 (17.51)	44.08 (18.45)	<0.001
BMI, kg/m^2	28.20 (5.26)	27.75 (4.88)	28.51 (4.94)	29.03 (4.41)	27.89 (4.98)	<0.001
Serum folate, ng/mL	20.44 (14.44)	19.02 (11.40)	17.94 (9.37)	17.01 (9.81)	18.61 (11.49)	<0.001
WBC 1000 cells/μL	7.06 (1.87)	7.03 (2.11)	6.96 (1.95)	6.78 (1.83)	6.96 (1.94)	0.126
Vitamin B12, pg/mL	783.73 (4820.49)	677.69 (2492.15)	557.24 (598.51)	513.27 (291.73)	633.23 (2736.39)	0.443
CRP, mg/dL	0.56 (0.93)	0.49 (0.79)	0.47 (0.61)	0.42 (0.70)	0.49 (0.77)	0.038
Categorical variables†						
Male	120 (26.6)	153 (34.0)	246 (54.7)	380 (84.8)	899 (49.9)	<0.001
Mexican American	77 (17.1)	87 (19.3)	86 (19.1)	91 (20.3)	341 (19.0)	0.653
Non-Hispanic white	296 (65.6)	267 (59.3)	273 (60.7)	268 (59.8)	1104 (61.4)	0.188
Non-Hispanic Black	46 (10.2)	61 (13.6)	68 (15.1)	67 (15.0)	242 (13.5)	0.110
Other Hispanic	21 (4.7)	22 (4.9)	17 (3.8)	11 (2.5)	71 (3.9)	0.229
Education >high school	160 (35.6)	157 (34.9)	171 (38.0)	200 (44.7)	688 (38.3)	0.007
Hypertension	308 (68.3)	316 (70.2)	304 (67.6)	267 (59.6)	1195 (66.4)	0.004
Diabetes mellitus	84 (18.6)	81 (18.0)	76 (16.9)	84 (18.8)	325 (18.1)	0.883
Heart disease	80 (17.7)	74 (16.4)	68 (15.1)	73 (16.3)	295 (16.4)	0.768
Alcohol consumption >12 drinks/year	207 (45.9)	205 (45.6)	149 (33.1)	116 (25.9)	677 (37.6)	<0.001
Current smoker	56 (12.4)	47(10.4)	50 (11.1)	57 (12.7)	210 (11.7)	0.678

BMI = body mass index, CRP = C-reactive protein, DSST = digit symbol substitution test, WBC = white blood cell.
*Values were expressed as mean (standard deviation).
†Values in the categorical variables were expressed as number (%).

higher quartiles of quadriceps strength tended to have higher DSST scores. There was a significant relationship between the increased quartiles of quadriceps strength and better cognitive function (*P* value for trend <0.001).

DISCUSSION

On the basis of a noninstitutionalized, geographically dispersed, and ethnically diverse national population-based sample, the most important finding of our study was that individuals with higher quartile of quadriceps strength had significantly better cognitive function compared with those with lowest quartile of quadriceps strength regardless of controlling for demographic factors and comorbidities. To the best of our knowledge, this was the first study of older adults to investigate the association between quadriceps strength and cognition.

Age-related reduction of muscle mass and strength were a major public health concern in older persons because of its important role in the causal pathway leading to functional limitations, increased risk of falls, mobility decline, disability, and mortality.[19,20] Increasing evidences suggested that muscle strength was a better predictor of mobility decline and disability than muscle mass.[3,21] In terms of upper extremity strength, handgrip strength was associated with accelerated decline in global cognitive performance,[6,22] higher risk of AD and mild cognitive impairment in longitudinal studies.[14,23] For the changes in the maximal isometric contractions of arm and leg with age, the decline in the isometric force of leg was more rapidly than that in the arm after 45 years of age regardless of sex. In cross-sectional study of 2481 participants aged ≥65 years, poorer cognitive performance had inverse association with greater disability mediated by habitual gait speed.[24] Notably, previous study provided strong evidence that significant independent association between lower extremity strength, and mobility performance, the time to walk 400 m at a steady pace.[25] It was tempting to speculate that lower extremity strength may be a significant predictor of declined cognitive performance. The speculation was in line with our study, although no previous studies have asked this question in detail. Our studies found the

TABLE 2. Association Between DSST Scores and the Level of Quadriceps Strength

Models*	β (95% CI)†	*P*
Model 1	0.026 (0.016–0.037)	<0.001
Model 2	0.020 (0.011–0.030)	<0.001
Model 3	0.019 (0.010–0.028)	<0.001
Model 4	0.018 (0.009–0.028)	<0.001

BMI = body mass index, CI = confidence interval, DSST = digit symbol substitution test.
*Adjusted covariates: Model 1 = age, sex, race/ethnicity. Model 2 = Model 1 + (educational level, BMI, current smoker, alcohol consumption). Model 3 = Model 2 + (history of hypertension, diabetes mellitus, heart disease). Model 4 = Model 3 + (C-reactive protein, serum folate, vitamin B12).
†β Coefficients were interpreted as change of DSST scores for each Newton increase in quadriceps strength.

TABLE 3. Association Between DSST Scores and Quadriceps Strength Quartiles

Models*	Quadriceps Strength Quartiles	β† (95% CI)	P	P for trend
Model 1	Q2 vs Q1	1.614 (−0.568–3.795)	0.147	<0.001
	Q3 vs Q1	3.985 (1.705–6.265)	0.001	
	Q4 vs Q1	7.144 (4.613–9.675)	<0.001	
Model 2	Q2 vs Q1	1.612 (−0.334–3.559)	0.104	<0.001
	Q3 vs Q1	3.500 (1.451–5.549)	0.001	
	Q4 vs Q1	5.404 (3.114–7.694)	<0.001	
Model 3	Q2 vs Q1	1.522 (−0.416–3.461)	0.124	<0.001
	Q3 vs Q1	3.275 (1.230–5.321)	0.002	
	Q4 vs Q1	5.119 (2.837–7.402)	<0.001	
Model 4	Q2 vs Q1	1.434 (−0.497–3.365)	0.146	<0.001
	Q3 vs Q1	3.193 (1.154–5.232)	0.002	
	Q4 vs Q1	5.003 (2.725–7.281)	<0.001	

BMI = body mass index, CI = confidence interval, DSST = digit symbol substitution test.
* Adjusted covariates: Model 1 = age, sex, race/ethnicity. Model 2 = Model 1 + (educational level, BMI, current smoker, alcohol consumption). Model 3 = Model 2 + (history of hypertension, diabetes mellitus, heart disease). Model 4 = Model 3 + (C-reactive protein, serum folate, vitamin B12).
† β Coefficients can be interpreted as differences in DSST scores comparing subjects in the upper three quadriceps strength quartiles to those in the lowest quartiles.

performance of quadriceps muscle strength was substantially correlated with cognitive function.

Despite the importance of muscle strength in preventing disability and cognitive decline, the biological mechanisms responsible for these phenomena were poorly understood. The plausible pathophysiological mechanisms underlying this positive association between muscle strength and cognition were multifactorial, including microvascular derangement, inflammation, social interaction, and derangement of homocysteine metabolism. First, decreased muscle strength directly reflected the systemic vascular dysfunction. The macrovascular or microvascular insults contributed to not only changes in muscular strength but also declines in executive-demanding cognitive tasks elicited by cerebral microvascular disease. Next, dysregulation of the inflammatory response had been found to play an important role in the association between muscle strength and cognition, such as increases in tumor necrosis factor-α, interleukin-6, interleukin-1α, or interleukin-1β. Increased inflammation or subclinical inflammation may bring about catabolism and contribute to muscle mass and strength decline. In addition, it was shown that poor strength was associated with reporting more difficulties in physical activities of daily living.[26] A growing body of evidence suggested that decreased lower limb function was associated with limitations or loss in activities of daily living following by social isolation and altered patterns of neural activation. Lesser social resources, as defined by social networks and social engagement, were associated with increased cognitive decline in old age.[27,28] Finally, participants in the highest quartile of homocysteine had lower peak quadriceps strength and slower gait speed compared with those in the lowest quartile in a cross-sectional studies.[29] Quadriceps strength presumably mediated the association between homocysteine and gait speed and late-life disability in the elderly population. In a prospective cohort study of 499 highly functioning men and women aged 70 to 79 years enrolled in the MacArthur Studies of Successful Aging, elevated plasma homocysteine levels were predictive of decline in balance, gait, lower body strength and coordination, and manual dexterity.[30] High levels of circulating homocysteine are associated with an increased risk of mild cognitive impairment, which is regarded as risk factor for the development of dementias, including AD.[31] The alteration in the homocysteine homeostasis may contribute to decreased muscle strength and impaired neuromuscular function and ensuing adverse metabolic insults harbored a predisposing milieu for subsequent cognitive decline and functional dependence.

In our study, strong evidence was demonstrated positively associating quadriceps muscle strength with cognitive performance. This led us to consider that possible detrimental relationship between the peripheral neuromuscular system and dementing processes. Frontotemporal dementia, classified as a cortical dementia, often occurs in association with motor neuron disease and amyotrophic lateral sclerosis.[32] Adeline et al[33] described genetic associations between dementia and neuromuscular disease, such as inclusion body myositis with Paget disease and frontotemporal dementia. Some myopathic process and neuromuscular diseases were associated with dementia, suggesting a shared pathology. To the best of our knowledge, there were no simple measures to predict the association between the neuromuscular disorders and dementing processes in recent years. Although the measurement of serum levels of muscle enzymes and peripheral electrodiagnostic testings were a critical part of the evaluation of neuromuscular dysfunction in clinical practice, these testings for early detection of mild cognitive impairment or dementia in the patients with neuromuscular disorders were not established.

There were several limitations to the present study. First, the study was a cross-sectional observational analysis of an existing database that limited causal inferences. The interaction between the quadriceps strength and change in the cognitive function over time was not analyzed because quadriceps strength and the other clinical variables were measured only once at enrollment rather than recording long-term repeated observations. Investigating the causality between the lower extremity strength and cognitive function warranted a cohort study. Next, although our analyses controlled for the potential confounders; however, other variables, such as vascular function, neurological function, or inflammatory status, were not fully addressed. Last, the self-reporting of medical comorbidities and health-related behaviors were implicated with inherent errors, leading to underestimation or overestimation of true interaction.

CONCLUSION

Our study exhibited evidences that higher quadriceps strength was related with better cognitive performance in the elderly population. Decreased muscle strength not only was an important determinant of falling and progression to disability but also related to the impaired cognitive performance. It was important from a health promotion perspective to recognize the role of decreased quadriceps strength during the progression of cognitive impairment. Measuring and comparing muscle strength of lower limbs throughout the late-life may be helpful to recognize cognitive impairment among the elderly population.

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