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SEX DIFFERENCES IN THE ASSOCIATION BETWEEN MUSCLE QUALITY, INFLAMMATORY MARKERS, AND COGNITIVE DECLINE

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Abstract

Objective—Aspects of frailty such as sarcopenia and dementia are associated with a proinflammatory state; however, little research has examined the concurrence of these pathologies. This study examined sex-specific differences in the relationship between low muscle quality and impaired cognitive functioning, while considering the role of inflammatory markers.

Design—The nationally representative sample was drawn from a cross-sectional study.

Participants—Four hundred forty-five females and four hundred twenty-two males over age 60 from the National Health and Nutrition Examination Survey for 2001-2002 were included.

Measurements—Muscle quality was calculated as isokinetic strength per unit muscle mass. Skeletal muscle mass of the legs was measured using dual energy x-ray absorptiometry and isokinetic strength of the knee extensors was estimated using a Kin-Com dynamometer. Participants were assessed for cognitive functioning using the Wechsler Adult intelligence Scale, Third Edition (WAIS-III) Digit Symbol - Coding module. High sensitivity C-reactive protein (CRP) assays were performed on blood samples using a Behring Nephelometer to estimate levels of inflammation. Sex stratified ordinary least squares regression models were utilized to estimate the relationship between muscle quality and cognitive functioning, while examining CrP as a possible mechanism and controlling for potential confounds.

Results—In the first model a statistically significant positive relationship was found between cognitive functioning and muscle quality for both sex groups. In the second model, CRP was found to have a statistically significant negative association with cognitive functioning for females but not males. Furthermore, the inclusion of CRP in the second model significantly reduced the predictive power of muscle quality for females, as compared to model 1.

Conclusion—Measures of sarcopenia are associated with lower cognitive functioning in older adults, and for females, this association may be partly due to systemic inflammation. Further research is need to examine the relationship between these frailty-related pathologies, which have substantial health and economic implications.

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Keywords

Sarcopenia; cognitive impairment; frailty; inflammation

Introduction

The pervasiveness and risks associated with physical frailty increase with age, and strongly exacerbate early-onset morbidity and mortality. Although there is no clear consensus concerning the clinical definition of frailty, there is concurrence that decreases in muscle mass, muscle strength and cognition are associated with manifestations of frailty (1, 2).

Senescence has been consistently linked to significant anthropomorphic changes. The Greek term sarcopenia — meaning poverty of the flesh—has been operationalized to refer to decreases in muscle mass and strength which correlate with age (3). Recent evidence estimates that as many as 25% of adults over age 65 and 50% of adults over age 80 have sarcopenia, defined as “appendicular skeletal muscle mass two standard deviations below the mean of a young reference group” (4). Furthermore, mean age-related decreases in muscle strength for individuals in their seventh and eight decade, relative to younger cohorts, have been estimated to be between 20-40% (5-9). Further understanding of sarcopenia is essential, given that muscle mass and strength have implications for carrying out activities or employment, disability, physiological effects, declines in self-esteem, and falling (10-12). Recently, attention has shifted to include muscle quality as an important determinant of sarcopenia and frailty, which is believed by some to be a better predictor of adverse health outcomes (13, 14).

Research suggests that onset of sarcopenia is often accompanied or preceded by a pro-inflammatory state (15-17). Senescence contributes to a rise in levels of interleukin-6 (IL-6), which can occur without a specific stressor, trauma or infection. This increase may partly be due to changes in hormonal secretion related to aging which reduces their regulating effects on IL-6 and has consequences for musculoskeletal and metabolic function (18). The presence of Interleukin-6 stimulates the liver’s production and release of acute phase reaction products, such as C-reactive protein (CRP) (19, 20). In addition to sarcopenia, the increase in IL-6 levels also promotes other aspects of frailty-related pathology, including cognitive decline. Research has shown that systemic inflammation intensifies inflammatory responses within the central nervous system, contributing to cognitive decline (21-23).

A recent study by Nourhashémi et al. suggested that a link exists between sarcopenia-related declines and cognitive functioning (24); however, to the best of our knowledge no research has investigated the role of inflammation as a mediator. The purpose of this study is to examine the association between sarcopenia and cognitive decline and the mediating role of inflammation. In order to account for age-related reductions in both muscle mass and muscle strength we chose to use muscle quality to conceptualize sarcopenia. Furthermore, due to sex differences in frailty and levels of CRP (1, 3, 25), we chose to stratify sex and examine males and females separately. Based on previous research, we hypothesize that low muscle quality (sarcopenia) will be positively associated with cognitive decline, and that this association will be explained by the presence of high CRP levels.

Materials and Methods

Study Population

The study population included a sample of males and females aged 60 and older from the U.S. National Health and Nutrition Examination Survey (NHANES 2001-2002) which is a nationally representative, cross-sectional study conducted by the National Center for Health Statistics (NCHS) (26). Individuals over age 60, African Americans, Mexican Americans and low-income white Americans were over sampled. Data were collected from at-home interviews, and clinical and laboratory examinations, which took place at a Mobile Examination Center (MEC). Muscular strength, CRP levels, and anthropometric data measurements for height and body composition measured by dual x-ray adsorptiometry (DXA), were collected during the clinical and laboratory examination. The total sample size for NHANES 2001-2002 participants over age 60 was 1,872. Because not all participants in the interview took part in the examination, participants who were included represented 49.3% (N=867) of the original sample of people over age 60. An analysis comparing the missing participants to the sample population indicated statistically equivalent sociodemographic characteristics for both groups. Further details of recruitment, procedures and study design are available through the U.S. Department of Health and Human Services (27).

Socio-Demographic Characteristics

Age, race/ethnicity, and education were self-reported at the interview. These were used as control variables as they have been found to relate to frailty and cognitive decline (28). Age was measured as a continuous variable, in years and top-coded for participants with an age of 85 years or greater. Dummy variables were created to categorize race/ethnicity into four categories: non-Hispanic whites, non-Hispanic blacks, Hispanics, and other, with non-Hispanic whites used as a reference category. Education was assessed as years of school completed, using the midpoint of reported categories.

Muscle Quality

Skeletal muscle mass of the leg and isokinetic strength of the knee extensors were used to generate muscle quality measurements. Bioelectrical impedance measurements for regional bone, fat and lean-tissue content were collected by means of a whole body DXA scan. These measurements were then computed to estimate fat-free and bone-free mass in the legs by summing the lean-tissue masses (excluding bone mass) from the regions of the legs (in kilograms). A Kin Com MP dynamometer was used to assess knee extensor strength, with an outcome measurement of peak force (Newton) of the quadriceps at a single speed (60 degrees/second). Participants were allowed six trials, and the trial with the highest peak force was selected. Muscle quality (MQ) was defined as the muscle strength per kilograms of mass (29).

Inflammation

CRP in a non-specific indicator of general levels of inflammation. For NHANES 2001-2002, high sensitivity CRP assays were performed on blood samples using a Behring Nephelometer for quantitative CRP determination (29).

Cognitive Functioning

Cognitive Functioning was based on the score for the Wechsler Adult intelligence Scale, Third Edition (WAIS-III) Digit Symbol – Coding module administered during the household interview. Scores are based on the number of correctly drawn symbols, out of 133, within a 120 second period. The scale is considered to be a more precise indicator of dementia than the Mini-Mental Status Exam, and has been administered in the Health ABC study from the National institute on Aging (26).

Statistical Analysis

SAS statistical software package version 9.2 was used for all analyses. Analysis was separated by sex, in order to examine differences between males and females in regards to the relationship between cognitive functioning, muscle quality and CRP. An ordinary least squares regression was used to assess whether decreased muscle quality was associated with cognitive decline before and how this relationship is affected by controlling for CRP. During analysis, all models included possible confounding variables such as age, race/ethnicity, and education, and sample weights were utilized to account for complex sampling design.

Results

Sample Characteristics

Demographic, social and health characteristics of the sample are illustrated in Table 1. Participants ranged in age from 60 years to 85 years (top coded) and were 44.76% male and 55.24% female. Non-Hispanic whites made up 83.56% of the sample, non-Hispanic blacks made up 7.27% of the sample, Hispanics made up 5.73% of the sample and all other race/ethnicities made up 3.45% of the sample. The mean education for all subjects was 12.92 years. Measurements of MQ for males ranged from 6.81 Newton/kg to 40.78 Newton/kg, with a mean of 23.35 Newton/kg. For females, MQ measurements ranged from 3.49 Newton/kg to 39.51 Newton/kg, with a mean of 21.83 Newton/kg. The range in WAIS scores for men was 0.00 to 100.00, with a mean of 48.69 cm. For women, scores for the WAIS ranged from 3.00 to 96.00, with a mean of 50.81.

Cognition and Muscle Quality

Ordinary least squares regression models were used to determine whether muscle quality predicted cognitive functioning, and whether the relationship was mediated by a measure of inflammation (CRP) in both males and females while controlling for race/ethnicity, age and education.

As shown in Table 2 model 1, higher muscle quality is associated with higher cognitive scores for both men and women. The effect of a unit change in muscle quality is about the same for both men (.39) and women (.31). Age, education, being black, and being Hispanic

were statistically significant predictors of cognitive functioning ($p < .05$) for both males and females. In addition, other race/ethnicity was also a statistically significant predictor of cognitive functioning ($p < .05$) for females. Black females have cognitive scores 11.58 points lower, Hispanic females 9.35 points lower, and females of other race/ethnicities 11.03 points lower than non-Hispanic white females. Black males' cognitive score is 11.43 points lower, and Hispanic males is 6.78 points lower than that of white males. After the age of sixty, we can predict the mean score for cognitive functioning to decrease by 3.68 points in females and 3.17 points in males every five years. Finally, for every one year increase in education, cognitive functioning scores were 2.50 points higher for females and 2.44 points higher for males. Muscle quality, age, race/ethnicity, and education accounted for almost 36.06% of the variance in cognitive functioning for females and 43.69% of the variance in cognitive functioning for males.

In model 2, a higher CRP level was a statistically significant predictor of lower cognitive functioning among females ($\beta = -3.69$, $p=.006$) and marginally significant for males ($\beta = -1.39$, $p=.103$). The addition of CRP into the model had no effect on the other predictors of cognitive functioning score for males; however for females, the unstandardized coefficient for MQ was reduced 16.35%, but remained significant. As a result, we can infer that CRP levels capture some of the predictive capacity of muscle quality in predicting cognitive functioning for women.

Discussion

The current study has demonstrated a relationship between cognitive functioning and muscle quality, as well as sex-specific differences in how this relationship is mediated by the presence of inflammatory proteins. This study is in agreement with the work of Nourhashémi et al., who found that low muscle mass in women is associated with low cognitive functioning (24). The finding that decreased performance on the WASI-III is directly related to decreased muscle quality is of importance because it infers that components of frailty may occur synergistically, exacerbating the negative outcomes of the condition. Aging, being female, race/ethnicity, and low socioeconomic status have been shown to be associated with frailty (30-33). However, until now, few studies have attempted to examine the physiological mechanisms by which criteria for frailty such as sarcopenia and cognitive impairment influence one another, or to examine sex differences. Identification of such factors enables researchers to develop a framework in order to better understand frailty and its implications on the lives of older adults.

Aging has been shown to correlate with increases in incidences of frailty, such as cognitive decline and sarcopenia, as well as systemic inflammation, even in the absence of infection, stress, or trauma (18, 21). Our results showed that elevated levels of CRP played a part in the relationship between cognitive functioning and muscle quality in females but not in males. One hypothesis for why age is associated with increases in IL-6, and therefore CRP, is the reduction in sex steroid hormones. Therefore, among other things, future research should examine how menopause and andropause influence the relationship between cognitive decline and sarcopenia.

There are limitations in this study that should be acknowledged. First, the inclusion of only participants with a DXA scan, WAIS-III test and serum measurement participation, may have reduced the possibility of individuals with severe physical disability or dementia from being included in the study. Consequently, this may alter the impact of the variables being examined. Nevertheless, based on demographic characteristics, the sample appeared heterogeneous. Finally, the cross-sectional design eliminates our ability to infer causality, or track changes over time.

Despite these limitations, the present study is strengthened by the use of reliable techniques for measuring body composition, inclusion of a large representative random sample, disregard of arbitrary cutoffs, and acknowledgement of sex differences. Furthermore, it provides unique insight into the sex-specific relationships between aspects of body composition, cognition and inflammation. Given the implications of frailty on public health, these associations merit further investigation of sex differences as well as the possible role of aging-related hormonal reductions.

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Table 1

Weighted Sample Characteristics for Subjects Aged 60 and Older

Characteristics	Males	Females
Ethnicity, n (%)		
Non-Hispanic White	85.31	82.14
Non-Hispanic Black	6.45	7.93
Hispanic	5.06	6.27
Other	3.19	3.66
Education (years), mean (SD)	13.13 (3.5)	12.76 (3.0)
CRP (mg/dL) , mean (SD)	0.39 (0.7)	0.47 (0.6)
MQ (Newton/kg), mean (SD)	23.35 (5.7)	21.83 (5.9)
Cognitive Functioning, mean (SD)	48.69 (17.03)	50.81 (17.86)

Table 2

Regression Coefficients for Variables Predicting Cognitive Functioning

Model	β(S.E.)	1 t	β(S.E.)	2 t
Males				
MQ	0.39 (0.13)**	3.03	0.40 (0.13)**	3.04
Black	−11.43 (2.71)**	−4.21	−11.36 (2.71)**	−4.19
Hispanic	−6.78 (2.95)*	−2.30	−7.19 (2.96)*	−2.43
Other	1.36 (3.86)	0.35	0.90 (3.87)	0.23
Age	−0.63 (0.10)**	−6.44	−0.64 (0.10)**	−6.51
Education	2.44 (0.20)**	12.35	2.42 (0.20)**	12.22
CRP			−1.39 (0.85)	−1.63
R squared	0.437		0.44	
Females				
MQ	0.31 (0.12)**	2.59	0.26 (0.12)*	2.16
Black	−11.58 (2.66)**	−4.36	−11.27 (2.64)**	−4.27
Hispanic	−9.35 (2.87)**	−3.26	−9.50 (2.85)**	−3.34
Other	−11.03 (3.73)**	−2.96	−11.09 (3.70)**	−3.00
Age	−0.74 (0.10)**2	−7.53	−0.77 (0.10)**	−7.88
Education 2.50 (0.25)**		9.88	2.45 (0.25)**	9.71
CRP			−3.69 (1.33)**	−2.78
R Squared	0.361		0.372	

*Significant Difference (P < .05);

**Significant Difference (P < .01)