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Association of C-reactive protein and muscle strength in the English Longitudinal Study of Ageing

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Abstract Sarcopenia has been associated with systemic inflammation and a range of other biological risk factors. The purpose of this study was to assess the systemic inflammation–muscle strength relationship in a large representative community-based cohort of older adults, and to determine the independence of this association from other biological and psychosocial risk factors. Participants were 1,926 men and 2,260 women (aged 65.3±9.0 years) from the English Longitudinal Study of Ageing, a study of community dwelling older adults. We assessed hand grip strength and lower body strength (time required to complete five chair stands). Biological measures included C-reactive protein (CRP), fibrinogen, cholesterol, haemoglobin, glycated haemoglobin, adiposity, and blood pressure. Approximately 33% of the sample demonstrated elevated concentrations (≥3 mg/L) of CRP. After adjustments for age, smoking, physical activity, education, inflammatory diseases, and all other biological factors, elevated CRP was associated with poorer hand grip strength and chair stand performance in women but only chair stand performance in men. Low haemoglobin levels were consistently associated with poorer performance on both tests in women and men. These results confirm an independent association between low grade systemic inflammation (as indexed by CRP) and muscle strength that appears to be more robust in women.

Keywords Inflammation · Muscle strength · Sarcopenia · Community sample

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Introduction

Age-related declines in muscle mass and strength, known as sarcopenia, is often an important antecedent of the onset of disability in older adulthood. Reduced muscle strength confers greater risk of mortality (Ruiz et al. 2008; Newman et al. 2006; Gale et al. 2007; Rantanen et al. 2000) and may also explain an accelerated decline of physical function in the elderly (Landers et al. 2001; Ferrucci et al. 2002). Various biological mechanisms have been examined in relation to loss of muscle strength. Several lines of evidence suggest inflammation might be associated with loss of muscle strength with ageing. Animal studies have shown that administration of interleukin (IL)-6 or tumour necrosis factor (TNF)-α increases skeletal muscle breakdown, decreases the rate of protein synthesis, and inhibits plasma concentrations of insulin-like growth factor that may impair muscle

anabolic processes (Charters and Grimble 1989; Garcia-Martinez et al. 1993; De Benedetti et al. 1997). In humans, cross sectional studies have shown associations between various inflammatory markers and objective markers of muscle strength, as assessed by hand grip and knee extensor measures (Taaffe et al. 2000; Visser et al. 2002). In older men and women, higher levels of IL-6 and C-reactive protein (CRP) were associated with a two- to three-fold greater risk of losing more than 40% of grip strength over 3 years follow up (Schaap et al. 2006), although there were no longitudinal associations between inflammatory markers and changes in grip strength among high functioning elderly participants from the MacArthur Study of Successful Ageing (Taaffe et al. 2000).

Identifying reliable biomarkers of muscle strength may have relevance for targeting individuals who might require interventions to prevent activity limitations. Since some of the previous work has been limited by small sample sizes (Taaffe et al. 2000; Schaap et al. 2006), further larger scale community-based population studies that are adequately powered are required to confirm associations between low grade inflammation and muscle strength. In addition, it is important to determine the independence of this association from other potentially relevant metabolic or behavioural processes. The aim of the present study was therefore to assess the systemic inflammation–muscle strength relationship in a large representative community-based cohort of older adults and to determine the independence of this association from other relevant biological and psychosocial risk factors.

Materials and methods

Design/setting and participants

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study that contains a nationally representative sample of the English population living in households (see UK Data Archive ELSA user guide and documentation; http://www.data-archive.ac.uk/findingData/snDescription.asp?sn=5050, accessed 21 August 2008). The original ELSA cohort consists of men and women born on or before 29 February 1952. The sample was drawn from households that have participated in Health Survey for England (HSE) in 1998, 1999, and 2001. HSE recruits participants using multistage stratified probability sampling with postcode sectors selected at the first stage, and household addresses selected at the second stage. For the present analyses, we report data from wave 2 (2004–2005), which consisted of biological and physical function measures taken by nurses. A total of 7,666 participants attended the wave 2 assessment, although 3,480 of them were excluded because of missing biological data (n=2,094) or incomplete data on physical function measures (n=1,386), leaving a final sample size of 4,186 individuals (46.0% men, aged 65.3±9.0 years). Missing biological data was mainly because participants did not consent to give blood or were ineligible (participants with clotting and bleeding disorders, or taking anti-coagulant medication). In comparison with the overall sample, the sub-group used in the present analyses were slightly younger, more highly educated, had a lower prevalence of morbidity, and better health behaviours including lower rates of smoking and greater physical activity. In order to account for missing data, all analyses were weighted for non-response. Participants gave full informed consent to participate in the study and ethical approval was obtained from the London Multi-centre Research Ethics Committee.

Measurements

Demographic and health-related questions included education (categorised as: higher education, A-level or equivalent, O-level or equivalent, none), smoking (current or non-smoker), the frequency of participation in vigorous, moderate, and light physical activities (more than once per week, once per week, one to three times per month, hardly ever), and presence of inflammatory conditions (including doctor-diagnosed angina, acute myocardial infarction, heart failure, stroke, hypertension, diabetes, or arthritis) and prescribed medication usage. Nurses collected anthropometric data (weight, height), recorded seated blood pressure (Omron HEM-907 blood pressure monitor), and collected blood samples. Blood samples were analysed for CRP, fibrinogen, cholesterol, haemoglobin, and glycated haemoglobin (HbA1c). The analysis of the blood data was carried out in the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis,

the internal quality control, and the external quality assessment for the laboratory that carried it out can be retrieved from the 2004 HSE technical report (Graig et al. 2006) since both HSE and ELSA employed the same laboratory, and the same guidelines and protocols for blood analysis.

Physical strength measures included hand grip and a timed chair stand test. Hand grip strength (kg) of the dominant hand was assessed using a hand held dynamometer, with the average of three measures used in the analyses. The chair stand test, a measure of lower body strength, assessed the time required to rise from a chair to a full standing position five times with arms folded across the chest. The test incorporated the use of respondent's own armless, straight backed chair.

Statistical analyses

In order to examine associations between muscle strength measures and CRP we employed general linear models. Given the skewed distribution of CRP we derived a categorical variable based on the established clinical cut off points (Pearson et al. 2003) representing low (<1 mg/L), medium (1 to <3 mg/L), high risk (≥3 mg/L). We calculated adjusted beta regression coefficients and 95% CIs for hand grip strength (kg) and chair stand time (seconds) with reference to the CRP categories. These analyses were performed separately among men and women. Several models were fitted that included a basic age-adjusted model, then additional adjustment for body mass index, physical activity, smoking, education, inflammatory conditions and medication (model 1), then a fully adjusted model that included all other biological measures (model 2). Biological measures were categorised into sex-specific thirds. Independent *t*-tests were conducted to examine sex differences in demographic and biological risk factors. All analyses were conducted using SPSS version 15.

Results

Table 1 displays the characteristics of the sample. Men were slightly younger, more educated, had a slightly lower prevalence of CVD and arthritis, were more likely to be smokers but were more physically active than women. Women displayed higher concentrations of fibrinogen and cholesterol, and lower HbA1c, haemoglobin, and blood pressure. Men performed better on both strength tests, as might be expected.

Approximately 33% of the sample demonstrated clinically elevated concentrations (≥3 mg/L) of CRP. Plasma concentrations of CRP were positively associated with systolic blood pressure (r=0.14, P<0.001), fibrinogen (r=0.59, P<0.001), body mass index (r=0.31, P<0.001), HbA1c (r=0.13, P<0.001), and smoking (r=0.10, P<0.001), and inversely with haemoglobin (r=−0.04, P=0.009), physical activity level (r=−0.17, P<0.001) and education (r=−0.16, P<0.001). Tables 2 and 3 display the associations of CRP and strength measures. Among women, higher CRP was independently associated with lower grip strength and a longer time to complete five chair raises, although in men these associations were observed only for chair raises. In addition, women in the highest fibrinogen third demonstrated lower grip strength (β=−0.78, 95% CI, −1.48, −0.09 kg) than those in the lowest third. Higher levels of haemoglobin consistently predicted better performance on both tests in men and women. For example, hand grip strength was greater in men (β=2.02, 95% CI, 0.37, 3.68 kg) and women (β=1.60, 95% CI, 0.93, 2.26 kg) in the highest compared with the lowest haemoglobin third. Lower grip strength (β=−1.16, 95% CI, −1.70, −0.72 kg) and a longer time to complete five chair raises (β=0.61, 95% CI, 0.26, 0.95 secs) was observed in women with inflammatory conditions (CVD or arthritis), although this association was not present in men.

Discussion

Results from the present study confirm an association between low grade inflammation, as indexed by circulating CRP levels, and lower muscle strength in a large representative community-based cohort of older adults that appears to be independent of several potentially related behavioural and metabolic process. The associations were particularly marked among women, which is consistent with previous findings (Visser et al. 2002). Previously, it has been suggested that higher levels of inflammation in the elderly may predispose to sarcopenia, thereby increasing the risk

Table 1 Characteristics of the sample. *CVD* Cardiovascular disease

Variable, mean ± SD	Men	Women	*P*-value
Age (years)	65.2±9.2	66.2±9.8	0.001
Education			
Higher education (%)	32.7	19.4	<0.001
No qualification (%)	30.1	42.3	<0.001
Current smokers (%)	12.5	11.2	0.034
Physically inactive (%)	13.1	18.6	0.001
Morbidity (%)			
CVD[a]	18.7	20.1	0.030
Arthritis	13.6	20.9	0.001
Taking medications (%)[b]	37.0	34.0	0.039
Body mass index (kg m^2)	27.8±4.2	27.7±5.0	0.684
C-reactive protein (mg/L)	3.40±5.68	3.76±6.28	0.058
Fibrinogen (g/L)	3.12±0.71	3.26±0.69	<0.001
Cholesterol (mmol/L)	5.64±1.16	6.20±1.16	<0.001
Haemoglobin (g/dL)	15.0±1.28	13.8±1.18	<0.001
HbA1c (%)	5.61±0.74	5.55±0.61	0.011
Systolic BP (mmHg)	135.4±17.5	134.4±19.8	0.080
Diastolic BP (mmHg)	75.9±11.4	74.8±10.7	0.001
Hand grip strength (kg)	39.11±9.15	23.02±6.05	<0.001
Time for 5 chair raises (secs)	11.3±4.0	12.0±4.6	<0.001

[a] Includes angina, acute myocardial infarction, heart failure, stroke, hypertension, diabetes

[b] Includes medications for blood pressure, diabetes, and cholesterol lowering

of activity limitation. Indeed, muscle mass partly explains the association between inflammatory cytokines and knee extensor strength (Visser et al. 2002). However, in a longitudinal study, CRP and IL-6 were associated with loss of grip strength but did not reliably predict loss of muscle mass (Schaap et al. 2006). Others have suggested that the association between inflammation and sarcopenia might operate through obesity (Cesari et al. 2005), although our results do not support this assertion.

In a previous analysis that incorporated data from the United States Health and Retirement Study with those of ELSA, the authors demonstrated protective effects of physical activity on impaired physical functioning (Lang et al. 2007). Although physical activity has known anti-inflammatory

Table 2 Regression of C-reactive protein (CRP) on hand grip strength (kg)

CRP category	Men (*n*=1,926)			Women (*n* =2,260)		
	Age adjusted β (95% CI)	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Age adjusted β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)
Low (<1 mg/L)	Reference	Reference	Reference	Reference	Reference	Reference
Middle (1–<3 mg/L)	−0.07 (−0.88, −0.75)	−0.58 (−1.39, 0.24)	−0.73 (−1.57, 0.10)	−0.76 (−1.30, −0.21)*	−0.75 (−1.30, −0.21)*	−0.76 (−1.31, −0.22)*
High (≥3 mg/L)	0.12 (−0.77, 1.01)	−0.44 (−1.35, 0.48)	−0.52 (−1.54, 0.51)	−1.03 (−1.58, −0.48)*	−1.01 (−1.61, −0.41)*	−0.83 (−1.46, −0.20)*

*P <0.05 in comparison with reference group

[a] Adjusted for age, education, smoking, physical activity, body mass index, inflammatory conditions (CVD, arthritis), medication usage

[b] Includes all adjustments from model 1 plus fibrinogen, blood pressure, haemoglobin, glycated haemoglobin, total cholesterol

Table 3 Regression of CRP on chair stand performance (time in seconds for five raises)

CRP category	Men (n=1,926)			Women (n=2,260)		
	Age adjusted β (95% CI)	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Age adjusted β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)
Low (<1 mg/L)	Reference	Reference	Reference	Reference	Reference	Reference
Middle (1–<3 mg/L)	0.21 (−0.16, 0.59)	0.02 (−0.36, 0.39)	0.08 (−0.31, 0.46)	0.68 (0.26, 1.10)*	0.31 (−0.11, 0.73)	0.33 (−0.10, 0.75)
High (≥3 mg/L)	0.93 (0.52, 1.35)*	0.53 (0.11, 0.95)*	0.54 (0.06, 1.01)*	1.54 (1.12, 1.97)*	0.68 (0.22, 1.15)*	0.60 (0.11, 1.09)*

*P <0.05 in comparison with reference group

[a] Adjusted for age, education, smoking, physical activity, body mass index, inflammatory conditions (CVD, arthritis), medication usage

[b] Includes all adjustments from model 1 plus fibrinogen, blood pressure, haemoglobin, glycated haemoglobin, total cholesterol

effects (Hamer 2007) and may also help maintain muscle function, the associations between inflammation and muscle strength were independent of physical activity levels in the present analysis. In a recent randomised controlled trial that employed aerobic and strength training in a group of elderly participants, significant reductions in various inflammatory markers (IL-6, IL-18, CRP) were observed for aerobic but not strength training (Kohut et al. 2006). In contrast, combined resistance and aerobic training that increased strength by 38% resulted in significant reductions in CRP (Stewart et al. 2007). Further exercise training studies will therefore be required to tease apart the independent effects of strength and aerobic capacity in relation to inflammation.

Our data also suggest a strong association between haemoglobin and muscle strength. These findings confirm previous results that showed anaemia and haemoglobin were associated with muscle strength and muscle density in elderly populations (Cesari et al. 2004; Penninx et al. 2004), and highlight a major clinical problem in older persons (Salive et al. 1992). We did not, however, find any reliable associations between HbA1c (a marker of glycaemic control) and muscle strength. Previous studies have demonstrated an association between type 2 diabetes and loss of muscle strength (Park et al. 2007; Andersen et al. 2004) and an improvement in insulin sensitivity following strength training (Brooks et al. 2006). However, given that Park et al. (2007) showed the association between diabetes and muscle strength was attenuated after adjustments for IL-6 and TNF-α, this suggests a potential role for inflammatory cytokines on muscular function in diabetes.

Our study has a number of strengths and limitations. The study is cross sectional, thus we cannot infer causality. Although we adjusted for several specific inflammatory diseases, it is possible that elevated CRP levels reflect sub-clinical disease processes that might be the cause of muscle strength loss. We were also unable to account for severity of disease. Nevertheless, participants retained in our analyses were generally healthier than the overall sample and we accounted for this potential bias in our analytic approach. The strengths of our study include the collection of objective measures of strength and the nationally representative nature of ELSA with its rigorous design. In summary, we found a robust association between a marker of low grade inflammation and muscle strength in a population of older adults. The development of clinical trials exploring the nature of the sarcopenia process is urgent (Cesari and Pahor 2008). In particular, further experimental work will be required to test the effects of interventions to enhance muscle strength on inflammatory risk markers and to examine if a reduction in inflammation can lead to reductions in or delayed onset of activity limitations.

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