Handgrip strength, inflammatory markers and mortality

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Abstract

Purpose: To investigate the extent to which inflammatory markers explain the association between handgrip strength and mortality.

Methods: Analyses of data from The English Longitudinal Study of Ageing. Handgrip strength and inflammatory marker data (C-reactive protein and Fibrinogen) were collected at baseline (2004/5) and inflammatory marker data at follow up (2012/13). Participant data were linked with death records. General linear models were used to explore associations between handgrip strength and inflammatory markers at follow up. Cox proportional hazards regression models were used to examine associations between grip strength and risk of death. Models were estimated with the covariates age, sex, wealth, physical activity, smoking, depressive symptoms, long standing illness, adiposity.

Results: The sample comprised 5,240 participants (mean age 65.9 (SD 9.4) yrs; 53.8% female). Over an average 9.7 ±1.4yrs follow up there were 650 deaths. Inverse associations were evident between handgrip strength and change in inflammatory markers in women only. There was an association between grip strength and lower risk of mortality in women (hazard ratio = 0.85; 95% CI, 0.74, 0.98) after adjusting for age and wealth. The association was attenuated after adjustment for clinical and behavioural risk factors (0.92; 0.79, 1.07), and further attenuated after adjusting for inflammatory markers (0.95; 0.82, 1.11).

Conclusion: Higher grip strength is associated with lower levels of inflammation at 8-year follow-up, and inflammatory markers partly explained the association between handgrip strength and mortality.

Keywords: Handgrip strength, mortality, inflammatory markers, ELSA

INTRODUCTION

Physical activity promotes cardiorespiratory fitness and the maintenance of lean muscle mass with ageing.[1] The health benefits of cardiorespiratory fitness are well established[2] although less is known about muscle strength.[3,4]

Handgrip strength is a valid measure of physical function/ performance that has been widely used in observational cohort studies and clinical settings.[5-8] Several studies have shown that handgrip strength is inversely associated with risk of mortality[9-11] although the mechanisms linking muscle strength and disease outcomes is poorly understood. One possible explanation is systemic inflammation. Systemic inflammation has been shown to be associated with a plethora of noncommunicable diseases (e.g. see, Ridker et al[12] and Sin et al[13]).

Three well studied inflammatory biomarkers include Interleukin 6 (IL-6), C-reactive protein (CRP), and Fibrinogen. Briefly, IL-6 is a pleiotropic cytokine that is secreted by T cells and macrophages to activate immune responses during infection or after trauma (tissue injury).[14] CRP is produced in the liver and it is an acute phase reactant thus levels will rise when inflammation is present.[15] Finally, Fibrinogen is a blood plasma protein that is made in the liver. It is also an acute phase reactant and levels rise when inflammation is present.[16] Unfavourable levels of these three inflammatory biomarkers have been found to be associated with several physical and mental health conditions.[17-19]

Inflammatory processes have also been linked with muscle atrophy (and thus weaker grip strength),[20] and muscle tissue expresses various transcriptional co-activators that may promote systemic anti-inflammatory effects.[21] We have previously shown cross-sectional associations between systematic inflammation and muscle strength,[22] consistent with others.[23] In another study, higher levels of IL-6 and CRP were associated with a two- to three-fold greater risk of losing more than 40% of grip strength over 3 years follow-up.[24] The current

literature therefore suggests that inflammation is associated with muscle strength although the direction of the association is not clear.

We hypothesized that inflammatory processes might in part explain the association between handgrip strength and mortality. The primary aim of the present study was to investigate the longitudinal association between handgrip strength and inflammatory markers, and examine the extent to which inflammatory markers explain the association between handgrip strength and mortality.

METHODS

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) is a cohort study of older adults previously described.[25] The sample was drawn from participants in the Health Survey for England (HSE), an annual cross-sectional survey that is designed to monitor the health of the general population. For wave 1, participants were recruited from the HSE in 1998, 1999 and 2001. Eligibility criteria included, membership of a participating household from HSE in which at least one person had agreed to follow-up, born before 1 March 1952 and living in a private household in England at the time of the first wave of fieldwork. Data on grip strength and inflammatory markers was first collected at wave 2 (2004/5), and was thus used as the baseline for the present analyses. Inflammatory marker data collection were repeated at wave 6 (2012/13) in survivors. Participants gave full informed consent to participate in the study. Ethical approval was obtained from the London Multi-center Research Ethics Committee, compliant with the Declaration of Helsinki.

Clinical assessments

Anthropometric data (weight, waist, hip), grip strength and blood samples were collected by trained nurses. Participants were excluded from providing blood if they reported clotting and bleeding disorders, or taking anti-coagulant medication, and excluded from hand grip tests if they had swelling or inflammation, severe pain, or a recent injury or surgery to the hand in the preceding 6 months. Handgrip strength (kg) of the dominant hand was assessed using the Smedley hand-held dynamometer (Stoelting Co, IL, USA), using the average of three measurements. Participants were required to hold the device at a right angle to their body and exert maximum force for a couple of seconds when instructed. Successive trials were alternated between dominant and non-dominant hands. Body weight was measured without shoes and in light clothing using Tanita electronic scales. Waist circumference was recorded twice midway between the iliac crest and lower rib and hip circumference around the widest portion of the buttocks using measuring tape. Central obesity was defined using waist to hip ratio (WHR) World Health Organization criteria (WHR≥0.85 in women and WHR≥0.90 in men). Blood samples were analyzed for high sensitivity C-reactive protein (CRP) and fibrinogen, described elsewhere.[26]

Mortality

The individual participant data were linked with death records from National Health Service registries for all consenting respondents (96.5% of the sample) up to February 2012.

Covariates

Trained interviewers asked questions on cigarette smoking (current, ex-smoker or non-smoker), frequency of vigorous, moderate- and low-intensity physical activity (> once a week, once a week, 1 – 3 times a month, and hardly ever/never), chronic illnesses (at least one vs. none), and depressive symptoms (using a score >3 on the 8-item Centre of

Epidemiological Studies Depression scale).[27] Wealth was self-reported, comprising of the total value of the participant's home (excluding mortgage), financial assets such as savings, business assets, and physical wealth such as artwork or jewelry, which has been shown to best capture the material resources available to older adults.[28] Wealth was grouped into quintiles relative to the ELSA sample.

Statistical analysis

Handgrip was standardised for body mass (as the two variables were moderately correlated, r>0.40) and treated as a continuous variable using the standardised score. Inflammatory markers were examined for normality and log transformed where appropriate. In all analysis we ran models separately for men and women as handgrip strength was greater in men. We used general linear models to explore longitudinal associations between handgrip strength and change in inflammatory markers. Models were adjusted for age, sex, levels of inflammatory marker at baseline, wealth, physical activity, smoking, depressive symptoms, long standing illness, WHR.

Cox proportional hazards regression models were employed to examine associations between grip strength and death. Years were the time scale for the follow-up calculated from age at death, and for participants with no record of an event, the data were censored at February 2012. Plots of the Nelson-Aalen cumulative hazard estimates were examined to assess the proportional hazards assumption. We estimated models that initially contained the covariates age, sex, wealth (model 1), with further adjustment for physical activity, smoking, depressive symptoms, long standing illness, WHR (model 2). These covariates were considered as confounders and selected a priori based on previous literature.[29-31] We then added inflammatory markers (log CRP, fibrinogen) as continuous variables to theoretically test for mediation. In these mediation analyses we primarily focused on the change in effect estimate

and confidence intervals as "statistical significance" is less relevant.[33] In sensitivity analyses we removed participants with activity limiting illnesses to examine if reverse causation was driving the results. All analyses were conducted using SPSS version 22 (SPSS, Chicago, IL).

RESULTS

At baseline 5,812 participants provided a blood sample and data on hand grip strength. After removing participants not consenting to mortality linkage (n=138) and those with missing covariates (n=434) the analytic sample for survival analyses comprised 5,240 participants (mean age 65.9 (SD 9.4) yrs; 53.8% female). In the longitudinal analyses that modelled change in inflammatory markers we further excluded participants that died through follow up (n=650) and those that did not provide blood samples at 8 years follow up (n=1,885), leaving an analytic sample of 2,705 participants (age 63.3±7.8 yrs; 55.2% female).

At baseline the mean handgrip strength of dominant hand was 38.4±9.7 kg (men) and 22.5±6.6 kg (women); normalised for body mass 0.47±0.12 (men) and 0.33±.10 (women). Participants in the highest hand grip strength tertiles were younger, more vigorously active, more affluent, reported less illness and depressive symptoms, and recorded lower prevalence of central obesity (Table 1).

In longitudinal analyses that examined baseline grip strength and change in inflammatory markers over 8 years follow up inverse associations were evident with both fibrinogen and CRP in women only (Table 2). This was the case in fully adjusted analyses and also among the pooled sample of men and women. In men, the inverse associations between grip strength and change in inflammatory markers were evident in age adjusted models but did not persist in models adjusted for all covariates.

Over an average 9.7 ±1.4yrs follow up there were 650 deaths. There was an association between baseline grip strength and lower risk of mortality in women (hazard ratio [per SD increase in grip strength] = 0.85; 95% CI, 0.74, 0.98) after adjusting for age and wealth; no associations were seen in men (0.94; 0.83, 1.06) (Table 3). The association was somewhat attenuated after adjustment for clinical and behavioural risk factors, and further attenuated after adjusting for inflammatory markers. In mutually adjusted models the covariates associated with mortality included longstanding illness, physical inactivity, smoking, and CRP (Table S1, SDC, association between clinical and behavioural covariates with mortality).

In sensitivity analyses we repeated the survival models after removal of participants who reported that their illness/disability limited their activity (n=1,409). The effect estimates remained largely unchanged albeit confidence intervals became wider as a result of reduced numbers (Table S2, SDC, the extent to which baseline clinical and biological factors explain associations between handgrip and mortality (excluding participants with activity limiting illnesses at baseline)).

DISCUSSION

In this population-based sample of older English adults, those with higher levels of grip strength were significantly more likely to have lower levels of systemic inflammatory markers, CRP and Fibrinogen, at follow-up. This association was seen in females, only. Grip strength was inversely associated with risk of mortality in females only. However, this association was attenuated to the null after adjustment for clinical and behavioural risk factors, and further attenuated after adjusting for inflammatory markers.

Our findings support previous research on the association between grip strength and inflammatory markers[34,35] and add to this body of work by showing that longitudinal

associations persist when controlling for a range of clinical and behavioural risk factors including measures of central adiposity.

One plausible explanation for the association between grip strength and inflammation is that muscle mass is a predictor of greater grip strength and those who partake in regular exercise tend to have greater muscle mass. Exercise using large muscle groups produces a short-term, inflammatory response, and both cross-sectional comparisons and longitudinal exercise training studies demonstrate a long-term "anti-inflammatory" effect.[36] Models in the present study controlled for levels of physical activity, though the types of activities (aerobics vs. resistance training) were not clearly separated. One other possible explanation is that high levels of circulating inflammatory markers and/or cytokines are associated with low muscle mass per se in older and obese people thus suggesting that muscle itself my play a role in regulating inflammatory markers.[37-39]

It is feasible that inflammatory markers could be exercising their effect through a combination of lifestyle and behavioural factors; indeed adding inflammatory markers directly to Model 1, (Table 3) in women closely mimicked (HR=0.91; 95% CI, 0.79 - 1.05) the effect of adding lifestyle / behavioural covariates. The association of grip strength with inflammation and mortality was more robust in females, which is consistent with other findings.[22,40]). Recent meta-analytic data showed grip strength was associated with reduced mortality in both genders, although the association was stronger in women.[41] Our sex specific findings are unremarkable as the aging process particularly affects women, such that women are more susceptible to sarcopenia than men.[42,43] In our own sample, the proportion of men having grip strength above the gender specific sarcopenia diagnosis cut-off is higher (90.5%>= 26kg) than that of women (84.8%>= 16kg).[44] Furthermore, male and female hormones modulate the immune system differently, thus resulting in differential age-related

pathologies.[45] Therefore, muscle strength might be particularly important for women in regulating chronic inflammation.[46]

Clear strengths of the present study include the large population-based sample of older English adults, the longitudinal design, the objective measure of both the exposure and the outcome, and repeated measure of inflammatory biomarkers. However, the data must be interpreted considering the following limitations. Data on skeletal muscle mass were not available in the present cohort and we relied on measurements of muscle strength alone. While lean mass and strength (muscle quality) may not decline at the same rate, loss of lean mass is strongly associated with strength decline in both men and women.[47] In our study, grip strength was standardized for body weight in the analyses. This approach allows us to account for muscle strength driven by body composition. There are ongoing discussions on how to standardize the procedure and utilization of grip strength measures in clinical and epidemiological studies, particularly in the ageing population.[48] Although a unified method is yet to be developed, our approach of body weight standardized grip strength has shown to be a superior technique in the aging population.[49,50] We were unable to account for underlying disease that were not detected through our measures; however, the results were largely unchanged after excluding participants with activity limiting illnesses suggesting reverse causation is an unlikely interpretation of our data. Participants retained in our analyses were generally healthier than the overall sample (driven by our exclusion criteria for blood and handgrip tests), thus our results are likely to reflect a conservative estimate of the true associations. Since the data are observational we cannot exclude the possibility of residual confounding. Nevertheless, recent evidence using Mendelian randomisation approaches suggested genetic correlations of grip strength with cardiometabolic traits and markers of frailty.[51] Our study provides evidence on plausible biological pathways linking strength and mortality thus further strengthening causal inferences.

Perspective

The present longitudinal analyses suggest that higher grip strength is associated with lower levels of inflammation at 8-year follow-up, and inflammatory markers partly explain the association between handgrip and mortality. Interventions designed to prevent a decline in physical functioning in females, especially, may improve inflammatory profiles and health. Such interventions may want to focus on functional task exercises as opposed to resistance exercises as functional task exercises have been shown to be more effective at improving functional task performance. Moreover, other literature suggests that functional task exercises may have an important role in helping maintain an independent lifestyle.[52]

Authors contribution Statement

Hamer is the guarantor; he conceptualized and designed the study, performed statistical analyses, and approved the final manuscript as submitted. Smith conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted; Yang conceptualized and designed the study, provided critical revision of the manuscript and approved the final manuscript as submitted.

Conflicts of Interest

The authors have no conflicts of interest. The results of the present study do not constitute endorsement by ACSM and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation

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409 **Table 1.** Baseline descriptive characteristics by sex specific handgrip tertiles.

Baseline variable	Sex specific handgrip tertile‡		
	Low	Middle	High
Age (yrs; mean, SD)	70.6 ± 10.3	65.8 ± 9.0	62.3 ± 7.8
Smoking (%)	14.2	14.4	18.6
Vigorous physical activity (%)	18.8	29.3	41.2
Highest wealth quintile (%)	17.4	24.2	28.5
Longstanding illness (%)	66.0	49.9	41.7
Depressive symptoms (%)	18.8	11.9	10.2
Central obesity (%)	68.0	56.9	23.7
C-reactive protein (mg/L)†	2.8 (4.3)	2.0 (3.0)	1.3 (2.2)
Fibrinogen (g/L)†	3.3 (0.9)	3.2 (0.9)	3.0 (0.8)

410 ‡ grip strength standardised for body weight values; lowest tertile (<0.42 men, <0.28 women),

411 middle (0.42 – 0.52 men, 0.28 – 0.37 women), highest (>0.52 men, >0.37 women).

412 † data are median (interquartile range)

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Table 2. Longitudinal association between grip strength and inflammatory markers over 8 years follow up: English Longitudinal Study Ageing

	Log C-reactive protein	
	Model 1	Model 2
Whole sample (n=2705)	-0.060 (-0.092, -0.028)	-0.049 (-0.083, -0.015)
Men (n=1211)	-0.046 (-0.087, -0.006)	-0.038 (-0.082, 0.006)
Women (n=1494)	-0.068 (-0.11, -0.030)	-0.055 (-0.095, -0.015)
	Fibrinogen	
	Model 1	Model 2
Whole sample (n=2624)	-0.053 (-0.077, -0.029)	-0.044 (-0.070, -0.019)
Men (n=1168)	-0.041 (-0.073, -0.009)	-0.026 (-0.060, 0.008)
Women (n=1456)	-0.053 (-0.081, -0.025)	-0.046 (-0.075, -0.016)

B (95% CI) coefficients per SD increase in grip strength standardised for body weight

Model 1 adjusted for age, sex and CRP or fibrinogen at baseline (sex adjustment excluded for sex specific models).

Model 2 adjusted for age, sex, CRP or fibrinogen at baseline, waist-hip-ratio, smoking, physical activity, depressive symptoms, chronic illness, wealth.

Table 3. The extent to which baseline clinical and biological factors explain associations between handgrip and mortality

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Whole sample (n=5240; 650 events)	0.87 (0.78, 0.97)	0.90 (0.80, 1.00)	0.93 (0.82, 1.04)
Men (n=2422; 355 events)	0.94 (0.83, 1.06)	0.93 (0.82, 1.06)	0.95 (0.84, 1.08)
Women (n=2818; 295 events)	0.85 (0.74, 0.98)	0.92 (0.79, 1.07)	0.95 (0.82, 1.11)

Hazard ratio, HR, (95% CI) for risk of mortality per SD increase in grip strength standardised for body weight.

Model 1: adjusted for age, sex, wealth (sex adjustment excluded for sex specific models);

Model 2: further adjusted for clinical and behavioural covariates; smoking, physical activity, chronic illness, central obesity, depressive symptoms

Model 3: further adjusted for C-reactive protein, fibrinogen