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Lower extremity strength, systemic inflammation and all-cause mortality: Application to the "fat but fit" paradigm using cross-sectional and longitudinal designs

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HIGHLIGHTS

- No study has examined the "fat-but-fit" paradigm when considering muscular strength.
- There was no difference in CRP between normal weight and unfit vs. overweight and fit participants.
- Overweight fit adults had a lower hazard rate compared to unfit normal weight adults.
- Adequate fitness (determined by strength) may attenuate inflammation and prevent premature mortality among overweight adults.

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ABSTRACT

Background: No study has applied the "fat-but-fit" paradigm with respect to muscular strength as an index of fitness, despite muscular strength being independently associated with functional ability and mortality.
Purpose: To examine the relationship between lower extremity muscular strength, C-reactive protein (CRP), and all-cause mortality among normal weight, overweight and obese individuals.
Methods: Data from the 1999–2002 NHANES were used (N = 2740 adults; ≥50 years). CRP values were obtained from a blood sample. Lower body isokinetic knee extensor strength (IKES) was assessed using a Kin Kom MP isokinetic dynamometer. Participant data was linked to death certificate data from the National Death Index to ascertain all-cause mortality status. Participants were classified, based on body mass index (BMI) and strength as: normal weight and unfit (<75th IKES percentile); overweight and unfit; obese and unfit: normal weight and fit (≥75th IKES percentile); overweight and fit; and obese and fit.
Results: Independent of physical activity and other confounders, compared to those who were normal weight and unfit, unfit overweight ($\beta = .14$, $p = 0.009$), unfit obese ($\beta = .33$, $p < 0.001$), and obese and fit ($\beta = .17$, $p = 0.008$) participants, had higher CRP levels. However, there was no difference in CRP levels between normal weight and unfit participants and overweight and fit participants ($\beta = 0.04$, $p = 0.35$). Compared to normal weight unfit adults, overweight fit (HR = 0.28; 95% CI: 0.11–0.70; $p = 0.008$) adults had a lower hazard rate for all-cause mortality.
Conclusions: These finding suggest that increased lower body strength, independent of physical activity, may reduce premature all-cause mortality and attenuate systemic inflammation among overweight adults.

1. Introduction

Obesity is associated with premature mortality [1]. However, regular exercise and physical activity (PA) appear to have protective effects in reducing the risk of premature mortality, even among obese individuals. For example, high levels of cardiorespiratory fitness, a consequence of regular engagement in exercise, have been found to protect against much, if not most, of the increased premature mortality associated with being overweight and obese [2]. In addition, obese active (meeting PA guidelines) individuals have more favorable biomarker profiles (e.g., less systemic inflammation) compared to their sedentary counterparts [3]. This suggests that PA status may be just as, or perhaps more important than, weight status. This paradigm has been termed the "fat but fit" paradigm. To our knowledge, no studies have addressed the "fat but fit" paradigm while considering an individual's muscular strength as opposed to their PA or cardiorespiratory fitness levels.

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Recently, strength training has received attention as an important component for health and fitness [4,5]. Recommendations from the United States Departments of Health and Human Services have recommended strength training at least two times a week to improve muscular strength [6,7]. Additionally, recent studies have shown that increased muscular strength is associated with decreases in all-cause mortality [4,8,9], inflammatory markers such as C-reactive protein (CRP) [5,10], total cholesterol [11], systolic blood pressure (SBP) [12], and an increase in insulin sensitivity [13].

Our main outcome of interest in this paper was CRP, as CRP is an established biomarker of overall health. For example, CRP has been identified as an independent risk factor for cardiovascular disease (CVD) and can predict CVD disease without the presence of other risk factors (e.g., hyperlipidemia) [13]. In addition, CRP has demonstrated an ability to enhance risk prediction of metabolic syndrome [14], diabetes [14], ischemic stroke [15], and transient ischemic attack (independent of other CVD risk factors) [15], is a strong indicator of all-cause mortality in patients with COPD [16], and could be a possible mechanism linking depression with CVD risk [17]. Although research has demonstrated lower levels of CRP among individuals with greater muscular strength [10], no study to our knowledge has investigated the relationship between muscular strength and CRP across different body mass index (BMI) levels. Furthermore, the majority of studies have used grip strength when examining the relationship between muscular strength and health outcomes; however, there has been conflicting evidence regarding the functional importance of this measurement [18]. Specifically, it has been suggested that grip strength may not serve as a surrogate for balance or dynamic assessment of lower body strength [18].

Therefore, the purpose of this study was to examine the relationship between muscular strength and CRP levels in normal, overweight and obese individuals. Specifically, we are interested in examining the "fat but fit" paradigm while considering an individual's lower body muscular strength as the surrogate for "fit", as, unlike grip strength, lower extremity muscular strength is consistently associated with mobility, function and balance [18,19], all of which are important indicators of independent living and quality of life. Further, lower extremity strength is also an important indicator of health, independent of PA participation [9,19]. Lastly, in addition to examining the "fat-but-fit" paradigm with respect to CRP, here, we examine this paradigm with all-cause mortality as an outcome of interest.

2. Design and participants

Data from the 1999–2002 NHANES were used (http://www.cdc.gov/nchs/nhanes.htm). The NHANES is an ongoing survey conducted by the Centers for Disease Control and Prevention that uses a representative sample of non-institutionalized United States civilians selected by a complex, multistage, stratified, clustered probability design. The multistage design consists of 4 stages, including the identification of counties, segments (city blocks), random selection of households within the segments, and random selection of individuals within the households.

Study procedures were approved by the NCHS ethics board. 2740 consented adults (≥50 years) provided data on the study variables described below. Data from participants in these cycles (1999–2002) were linked to death certificate data from the National Death Index; additional sources of mortality identification were obtained from the Social Security Administration and the Centers for Medicare and Medicaid. Person-months of follow-up were calculated from the date of exam until date of death or censoring on December 31, 2006, whichever came first.

2.1. CRP

Blood samples were obtained to assess high sensitivity CRP, using latex-enhanced nephelometry. Both strength and CRP measurements were taken during the participant's visit to the Mobile Examination Center. CRP measurements were taken prior to the strength assessments. The coefficients of variation (CV) ranged from 3.1% to 9.9%, with procedural and quality control details provided elsewhere [20]. To convert CRP from mg/dL to mg/L, multiply by 10. Also, given that in the clinical setting CRP is often expressed as nmol/L, to convert CRP from mg/dL to nmol/L, multiply by 9.524.

2.2. Peak muscle strength

A Kin Kom MP isokinetic dynamometer (Chattanooga Group, Inc.) was used to assess isokinetic knee extensor strength (IKES). As evidence of convergent validity, IKES has been associated with all-cause mortality [8]. Participants performed 3 warm-up trials followed by 3 maximal voluntary isokinetic muscle actions at a speed of 60°/s on the right leg. All values were gravity corrected for limb and lever arm weight. The highest peak torque was selected for analysis.

2.3. BMI

BMI was calculated from measured weight and height (kg/m^2). Normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥30 kg/m^2.

2.4. Classification of strength and weight status

Participants were classified as fit or unfit based on their peak muscle strength measurements. Fit was defined as ≥75th percentile (≥450 N) of IKES, otherwise unfit. The 75th percentile was used based on previous studies demonstrating the highest quartile of muscular strength inversely associating with all-cause mortality [9]. The following 6 mutually exclusive groups were created:

- normal weight and unfit
- overweight and unfit
- obese and unfit
- normal weight and fit
- overweight and fit
- obese and fit.

"Normal weight and unfit" was used as the referent group, in line with previous studies examining to the "fat but fit" paradigm with regard to physical activity [3]. The unfit group was used as a reference group, as "unfit" represents the majority of the population. In addition, this allows comparison across studies, helping to further develop strength as an important component to the "fat but fit" paradigm.

2.5. Covariates

The following covariates were included based on previous research demonstrating their association with CRP and muscular strength [3, 21]: age; gender; race-ethnicity; engagement in moderate to vigorous PA in the past 30 days [21]; mean arterial pressure; physician diagnosed diabetes, arthritis, coronary artery disease, and stroke; total cholesterol; self-reported smoking status; use of special equipment (e.g., cane) to assist in ambulation; and statin medication use. Details on the measurement of these parameters can be found elsewhere [20,22].

2.6. Analysis

Statistical analyses were computed in Stata (v. 12) and accounted for the complex NHANES survey design (analyzed in 2015). Linear regression was used to examine the association between strength–weight status (normal weight and unfit served as the referent group) and IKES (outcome variable). Three models were computed: unadjusted,