

# Muscle Strength and Physical Performance Are Associated With Risk of Postfracture Mortality But Not Subsequent Fracture in Men

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## ABSTRACT

Muscle strength and physical performance are associated with incident fractures and mortality. However, their role in the risk of subsequent fracture and postfracture mortality is not clear. We assessed the association between muscle strength (grip strength) and performance (gait speed and chair stands time) and the risk of subsequent fracture and mortality in 830 men with low-trauma index fracture, who participated in the Osteoporotic Fractures in Men (MrOS) USA Study and had their index measurements assessed within 5 years prior to the index fracture. The annual decline in muscle strength and performance following index fracture, estimated using linear mixed-effects regression, was also examined in relation to mortality. The associations were assessed using Cox proportional hazards models adjusted for age, femoral neck bone mineral density (FN BMD), prior fractures, falls, body mass index (BMI), index fracture site, lifestyle factors, and comorbidities. Over a median follow-up of 3.7 (interquartile range [IQR], 1.3–8.1) years from index fracture to subsequent fracture, 201 (24%) men had a subsequent fracture and over 5.1 (IQR, 1.8–9.6) years to death, and 536 (65%) men died. Index measurements were not associated with subsequent fracture (hazard ratios [HRs] ranging from 0.97 to 1.07). However, they were associated with postfracture mortality. HR (95% confidence interval [CI]) per 1 standard deviation (1-SD) decrement in grip strength: HR 1.12 (95% CI, 1.01–1.25) and gait speed: HR 1.14 (95% CI, 1.02–1.27), and 1-SD increment in chair stands time: HR 1.08 (95% CI, 0.97–1.21). Greater annual declines in these measurements were associated with higher mortality risk, independent of the index values and other covariates. HR (95% CI) per 1-SD annual decrement in change in grip strength: HR 1.15 (95% CI, 1.01–1.33) and in gait speed: HR 1.38 (95% CI, 1.13–1.68), and 1-SD annual increment in chair stands time: HR 1.28 (95% CI, 1.07–1.54). Men who were unable to complete one or multiple tests had greater risk of postfracture mortality (24%–109%) compared to those performed all tests. It remains to be seen whether improvement in these modifiable factors can reduce postfracture mortality. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

**KEY WORDS:** MUSCLE STRENGTH; PHYSICAL PERFORMANCE; POST-FRACTURE MORTALITY; SUBSEQUENT FRACTURE; AGING; SARCOPENIA; GENERAL POPULATION STUDIES; FRACTURE PREVENTION; FRACTURE RISK ASSESSMENT SCREENING

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## Introduction

Osteoporosis is currently underdiagnosed and undertreated in men,<sup>(1,2)</sup> potentially due to poor understanding of who is at risk of developing adverse postfracture outcomes. Fractures are associated with substantial disability,<sup>(3)</sup> subsequent fracture,<sup>(4,5)</sup> and, most importantly, premature mortality.<sup>(6-10)</sup>

The risk of subsequent fracture is elevated following all clinical fractures,<sup>(4)</sup> particularly in the first 1 to 2 years following the first fracture.<sup>(11,12)</sup> Risk factors that have been identified as predictors of subsequent fractures include older age, lower femoral neck (FN) bone mineral density (BMD), smoking, and lower physical activity.<sup>(4)</sup> Poor muscle strength and physical performance are also associated with increased risk of first fracture.<sup>(13-18)</sup> However, the association between these measures and the risk of subsequent fracture in men has not been explored.

The risk of mortality after fracture is higher in men than women.<sup>(8,19,20)</sup> The mechanism of increased mortality risks after fracture is not completely clear. Risk factors that have been identified as predictors of postfracture mortality include older age, male sex, lower BMD,<sup>(9,21)</sup> bone loss,<sup>(22)</sup> smoking,<sup>(9,21)</sup> comorbidities,<sup>(23,24)</sup> lower physical activity,<sup>(9,21)</sup> and subsequent fractures.<sup>(9)</sup>

Although extensively studied in the general population,<sup>(25-29)</sup> the associations between poor muscle strength and physical performance and mortality have rarely been investigated in people with incident osteoporotic fractures.<sup>(30,31)</sup> People who sustained a fracture have higher risk of mortality than the general population.<sup>(8-10)</sup> Therefore, it is important to investigate the association between muscle strength and performance and mortality to understand the higher mortality risk associated with fracture.

In addition to the baseline values, the rate of decline in muscle strength and performance over time has been previously shown to be associated with all-cause mortality in the general population.<sup>(18,32-35)</sup> A recent study reported 9% and 19% increased risk of death per 1 standard deviation (1-SD) greater rate of decline in grip strength and gait speed, respectively.<sup>(32)</sup> Conversely, a few studies reported no association.<sup>(36-38)</sup> However, the impact of this decline on mortality risk in those who already sustained a fracture is not clear.<sup>(30)</sup>

Therefore, using a cohort of older community-dwelling men in the Osteoporotic Fractures in Men (MrOS) Study who had an incident fracture, we aimed to assess the association between (i) muscle strength and performance and the risk of subsequent fracture, and (ii) muscle strength and performance as well as their future decline and the risk of mortality after fracture. Because muscle strength and physical performance are modifiable,<sup>(39,40)</sup> identifying those at higher risk of poor postfracture outcomes may facilitate the design of interventions (such as targeted rehabilitation strategies) aimed at improving the health of older adults.

## Subjects and Methods

### Participants and settings

The MrOS study<sup>(41)</sup> is a prospective, longitudinal, observational study of 5994 community-dwelling men living in six communities in the United States (Birmingham, AL, USA; Minneapolis, MN, USA; Monongahela Valley near Pittsburgh, PA, USA; Palo Alto, CA, USA; Portland, OR, USA; and San Diego, CA, USA). To be eligible to participate in this study, men had to be able to walk without assistance, must not have had bilateral hip replacements, and must have provided written informed consent. Study design and recruitment strategies have been described.<sup>(42,43)</sup> The study commenced

between 2000 and 2002 and included men aged 65 years or older. The sample for the current analysis involved 830 participants who had suffered at least one low-trauma fracture between enrolment in 2000–2002 and 2019. Four clinical visits were conducted (2000–2002, 2005–2006, 2007–2009, and 2014–2016) where measurements of muscle strength (assessed by grip strength test) and physical performance (assessed by gait speed and chair stands tests) were taken.

MrOS was approved by the institutional review boards at all clinical centers and the San Francisco Coordinating Center (University of California, San Francisco, and California Pacific Medical Center Research Institute).

### Participant selection

The current analysis involved participants who had at least one incident fracture and had their grip strength, gait speed, and chair stands measurements taken within 5 years prior to their index fracture. Men with missing measurements due to participant refusal, incorrect protocol administration, or inability to perform the test due to physical and health reasons were excluded. The remaining men ( $n = 830$ ) who had at least one test measurement available constituted the primary analytical cohort. Each test-specific analysis was completed with all participants who had measurements available for that specific test (Fig. 1). Men who were unable to perform the tests, and separately those whose muscle strength and performance were measured >5 years prior to the index fracture, were later included in the sensitivity analyses.

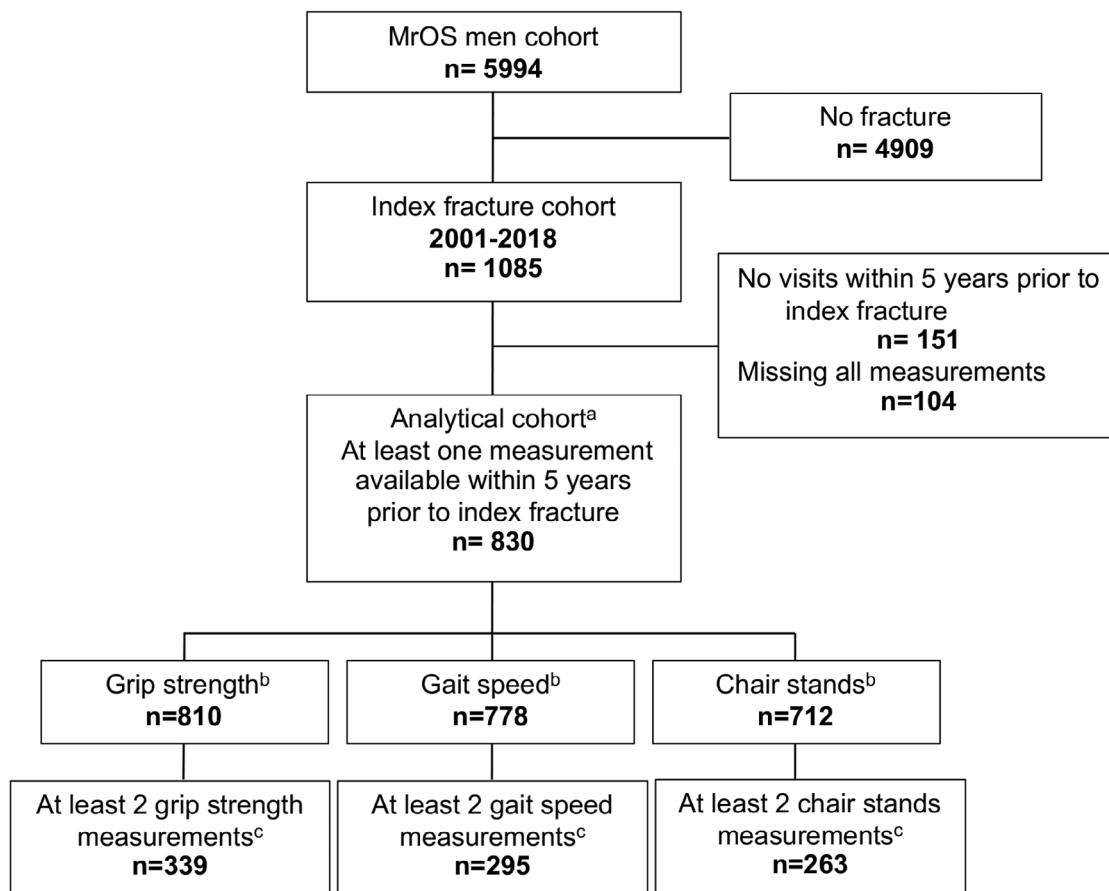
### Ascertainment of fractures and death

Every 4 months, participants were contacted by mail or phone to ask about recent fractures and to ascertain vital status.<sup>(42)</sup> All reported fractures were confirmed by review of radiology reports. Only minimal (falling from standing height or less) to moderate trauma fractures (falling from more than standing height or collisions during normal activities) fractures were included in this analysis. High trauma fractures (such as motor vehicle accidents), pathological fractures, fractures near prostheses, and fractures of the skull, fingers, and toes were excluded. This definition applied to both incident and subsequent fractures. The subsequent fracture represented the second low-trauma fracture occurring at a separate event at least 1 month following the index fracture. Three fractures reported within 30 days ( $n = 3$ ) after the index fracture were excluded because they were likely to have occurred in the same event as the index fracture. Fractures were classified as hip, clinical vertebral, proximal (above elbow and knee, ie, clavicle, rib, humerus, elbow, pelvis, upper leg), and distal (below elbow and knee, ie, forearm, lower leg, knee, ankle, hand, or foot) fractures. If multiple fractures occurred in one event, fracture site was assigned based on the more severe fracture.

Deaths were confirmed by death certificates. All deaths following the index fractures through 2019 were included.

### Assessment of covariates and muscle strength and physical performance

At all study visits, participants completed clinical examinations and completed a self-administered questionnaire<sup>(42)</sup> to collect information about age (years), smoking status (current, no), alcohol use (<3, ≥3 standard drinks/day), living alone (yes/no), fall history in the previous 12 months (yes/no), history of low trauma fractures since the age of 50 years (yes/no), parental history of hip



**Fig. 1.** Flowchart of men included in the analysis. <sup>a</sup>The analytical cohort included participants with at least one measurement available within 5 years prior to index fracture. <sup>b</sup>The test-specific cohorts excluded participants with missing data (grip strength  $n = 20$ , gait speed  $n = 52$ , and chair stands  $n = 118$ ). These were used to analyze the association between index muscle strength and performance measurements and the risk of subsequent fracture and mortality after fracture. <sup>c</sup>The rate of change cohorts excluded participants with only one measurement available (grip strength  $n = 471$ , gait speed  $n = 483$ , and chair stands  $n = 449$ ). These were used to analyze the association between the rate of change in muscle strength and performance and the risk of mortality after fracture.

fracture (yes/no), and previous glucocorticoid use (yes/no). Physical activity level was assessed from the Physical Activity Scale for the Elderly (PASE).<sup>(44)</sup> Self-reported health rating was categorized as excellent/good versus fair/poor/very poor. The history of medical conditions including non-skin cancer, stroke, myocardial infarction (MI), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes, hypertension, hypothyroidism, kidney disease, and rheumatoid arthritis was recorded. BMD was measured using dual-energy X-ray absorptiometry (DXA) machines (Hologic, Inc., Bedford, MA, USA) at the femoral neck.<sup>(42)</sup> Covariate data were obtained at the same time point as the muscle strength/physical performance assessment.

Grip strength (in kg) was measured using JAMAR dynamometers (Sammons Preston Rolyan, Bolingbrook, IL, USA).<sup>(45)</sup> The maximum measurement from two trials of both hands was used in this analysis. Gait speed (m/seconds) was assessed by a 6-m walk course at usual pace. Chair stands test was assessed by measuring the time in seconds required to rise from a chair five times from a full sitting position on an armless chair without using their arms. The coefficients of variation were reported in a previous MrOS report as 0.5%, 2.4%, and 4.9% for grip strength, gait speed, and chair stands tests, respectively.<sup>(46)</sup>

## Statistical analysis

To utilize all available data, separate test-specific datasets were constructed. Measurements of muscle strength and performance and covariates were retrieved from the last visit prior to the index fracture and considered as the index measurement. Men with missing data on muscle strength and performance at a visit within 5 years of the index fracture were excluded. We imputed missing data for covariates using the Last Observation Carried Forward method (missing BMD [ $n = 11$ ; 1.3%] and missing health rating [ $n = 1$ ; 0.1%]).

Subsequent fracture and mortality rates were calculated as numbers of subsequent fractures or deaths per 1000 person-years of follow-up under an assumption of Poisson distribution.

## The association between index measurements and the risk of subsequent fracture and mortality

We analyzed the association between the index measurements and subsequent fracture and mortality separately using Cox proportional hazard models. For the subsequent fracture analysis, follow-up time was calculated as the time interval between the

index fracture date until the subsequent fracture date, termination of participation, death, or end of study (August 6, 2019), whichever came first. For the mortality outcome analysis, follow-up time was calculated as the time from the index fracture date until the date of death, termination of participation, or end of study, whichever came first (Fig. S1).<sup>(47)</sup> To assess the impact of the competing risk of mortality in the analyses of subsequent fracture, further analyses were conducted using Fine-Gray sub-distribution hazards models that accounts for death as a competing risk.

For each test, both age-adjusted and multivariable-adjusted models were constructed. Predefined covariates considered for inclusion in the multivariable-adjusted models included potential confounders known to be risk factors for the outcome or found in the age-adjusted models to be associated with clinically significant risk of subsequent fracture ( $\geq 20\%$ ) and mortality ( $\geq 10\%$ ). Age, FN BMD, smoking, index fracture site, falls, prior fracture, hypertension, physical activity, health rating, CHF, COPD, and rheumatoid arthritis were included in the models that assessed subsequent fracture. Models that assessed mortality were additionally adjusted for BMI, living alone, alcohol consumption, cancer, stroke, MI, low thyroid, diabetes, and kidney disease.

Muscle strength and performance measurements were included in the models as continuous variables with the hazard ratios (HRs) reported per 1-SD decrement in grip strength and gait speed or increment in chair stands time with their corresponding 95% confidence intervals (CIs). Because chair stands time was not normally distributed, it was log-transformed. Proportional hazards assumption was assessed statistically and graphically using Schoenfeld residuals and there was no evidence of assumption violation. Categorical analyses (per quartile) were also performed.

### The association between the rate of decline in muscle strength and performance and the risk of mortality

For the analyses of postfracture mortality, the annualized change in muscle strength and performance was calculated using linear mixed-effects models with random slopes and intercepts. The individual slope is an estimate of the annual change (decline or increase) considering the population-level effect on the overall change. We included men with at least one measurement available after the index fracture in addition to the index measurement. However, only measurements taken at least 6 months after the index fracture date were considered. Therefore, fewer men (339, 295, and 263 men) were included in the analysis of the rate of decline in grip strength, gait speed, and rate of increase in chair stands time, respectively.

The association between the annualized deterioration in muscle strength and physical performance and mortality was assessed using Cox proportional hazard models where the calculated annual changes were included as continuous variables to assess the risk of mortality per SD decline of grip strength, gait speed, and SD increase in chair stands annual change. Follow-up time was calculated from the index fracture date until the date of death, termination of participation, or end of study, whichever came first (Fig. S1).<sup>(47)</sup> As the distribution of the rate of increase in chair stands was not normally distributed, it was log-transformed. Age-adjusted and multivariable-adjusted models were constructed with additional adjustment for the index value of muscle strength and physical performance.

### Sensitivity analyses

We conducted two sensitivity analyses. The first sensitivity analysis aimed to assess the association of inability to perform muscle strength and performance tests on the risk of subsequent fracture and mortality. We separately assessed the association of inability to perform grip strength ( $n = 22$ ), gait speed ( $n = 48$ ), chair stands ( $n = 75$ ), unable to perform one test ( $n = 91$ ), and unable to perform multiple tests ( $n = 26$ ) versus those who were able to complete the three tests ( $n = 684$ ) who represented the comparator group in all models.

In a second sensitivity analysis, we completed the main analyses in all men with muscle strength and performance assessed prior to the index fracture, regardless of the length of time between the muscle strength or performance assessment and the index fracture date (ie, we additionally included those whose grip strength ( $n = 115$ ), gait speed ( $n = 117$ ), or chair stands ( $n = 112$ ) was only assessed more than 5 years prior to the index fracture date).

All analyses were conducted using SAS software (SAS Institute Inc, Cary, NC, USA). Two-sided  $p$ -value  $< 0.05$  was considered to be significant.

## Results

The analytical cohort included 830 men with at least one measurement available for muscle strength and performance measured within 5 years prior to index fracture date (Fig. 1). Among these men there were 170 (20.5%) hip, 102 (12.3%) clinical vertebral, 322 (38.8%) proximal, and 236 (28.4%) distal fractures. Their mean  $\pm$  SD age at fracture was  $81.7 \pm 6.6$  years with a preindex fracture median grip strength (IQR) of 36 (32–42) kg, gait speed of 1.14 (0.99–1.32) m/s, and chair stands time of 12.0 (9.9–14.5) seconds (Table 1).

Men excluded from the primary analysis due to missing data (refused or were unable to perform the tests) had lower BMI, were older, less physically active, less likely to report excellent/good health, and more likely to experience falls and CHF. They also had worse strength and/or performance in their other available tests. Most importantly, although they were less likely to sustain a subsequent fracture, they were more likely to die than those with full data available.

### The association between index measurements of strength and performance and the risk of subsequent fracture

During the median follow-up period of 3.7 years (IQR, 1.3–8.1), 201 men (24.2%) sustained a subsequent low-trauma fracture, yielding an incidence rate of 4.7 subsequent fractures/1000 person-years (95% CI, 4.1–5.4). Men with subsequent fracture had slightly faster gait, but similar grip strength and chair stands performance to those who did not sustain a subsequent fracture. Men who sustained a subsequent fracture were also younger, had lower BMD  $T$ -scores, and were more physically active than those who did not sustain a subsequent fracture (Table S1).<sup>(47)</sup>

Grip strength, gait speed, and chair stands measurements were not associated with subsequent fracture risk in the age-adjusted or multivariable-adjusted models (Fig. 2). Considering the competing risk of mortality did not change the results (data not shown). The categorical analysis of muscle strength and physical performance (as quartiles) showed that the worst quartile of chair stands test, but not grip strength and gait speed, was associated with a nonsignificant 15% increase in the risk of

**Table 1.** Characteristics of Men Included in the Analysis at Index Fracture Time According to Data Availability

| Characteristics                              | Grip strength cohort ( <i>n</i> = 810) | Gait speed cohort ( <i>n</i> = 778) | Chair stands cohort ( <i>n</i> = 712) |
|--|--|-------------------------------------|---------------------------------------|
| Index fracture site, <i>n</i> (%)            |  |                                     |                                       |
| Hip  | 164 (20.2)                             | 147 (18.9)                          | 129 (18.1)                            |
| Vertebral                                    | 101 (12.5)                             | 94 (12.1)                           | 85 (11.9)                             |
| Proximal                                     | 316 (39.0)                             | 306 (39.3)                          | 282 (39.6)                            |
| Distal                                       | 229 (28.3)                             | 231 (29.7)                          | 216 (30.3)                            |
| Age (year), mean ± SD                        | 81.7 ± 6.6                             | 81.3 ± 6.4                          | 81.1 ± 6.4                            |
| BMI (kg/m <sup>2</sup> ), mean ± SD          | 26.9 ± 4.1                             | 26.9 ± 4.0                          | 26.8 ± 3.9                            |
| FN BMD <i>T</i> -score, mean ± SD            | −1.19 ± 1.04                           | −1.16 ± 1.02                        | −1.17 ± 1.00                          |
| Prior fractures, <i>n</i> (%) <sup>a</sup>   | 203 (25.1)                             | 191 (24.6)                          | 173 (24.3)                            |
| History of falls, <i>n</i> (%)               | 323 (39.9)                             | 300 (38.6)                          | 267 (37.5)                            |
| Parent history of hip fracture, <i>n</i> (%) | 115 (14.2)                             | 113 (14.5)                          | 104 (14.6)                            |
| Glucocorticoids, <i>n</i> (%)                | 74 (9.1)                               | 73 (9.4)                            | 65 (9.1)                              |
| Smoking (current), <i>n</i> (%)              | 26 (3.2)                               | 25 (3.2)                            | 24 (3.4)                              |
| Alcohol (heavy), <i>n</i> (%) <sup>b</sup>   | 32 (4.0)                               | 32 (4.1)                            | 31 (4.4)                              |
| Living alone (no), <i>n</i> (%)              | 686 (84.7)                             | 656 (84.3)                          | 605 (85.0)                            |
| Health rating (good/excellent), <i>n</i> (%) | 662 (81.7)                             | 641 (82.4)                          | 596 (83.7)                            |
| Physical activity, mean ± SD                 | 125.0 ± 70.7                           | 129.3 ± 70.1)                       | 132.6 ± 69.0                          |
| Muscle parameter, median (IQR)               |  |                                     |                                       |
| Grip strength (kg) <sup>c</sup>              | 36.0 (32.0–42.0)                       | 36.0 (32.0–42.0)                    | 38.0 (32.0–42.0)                      |
| Gait speed (m/s) <sup>d</sup>                | 1.14 (0.99–1.32)                       | 1.14 (0.99–1.32)                    | 1.17 (1.02–1.33)                      |
| Chair stands time (seconds) <sup>e</sup>     | 12.0 (9.9–14.4)                        | 11.9 (9.8–14.3)                     | 12.0 (9.9–14.5)                       |
| Comorbidities, <i>n</i> (%)                  |  |                                     |                                       |
| Kidney disease                               | 109 (13.5)                             | 106 (13.6)                          | 98 (13.8)                             |
| Non-skin cancer                              | 219 (27.0)                             | 205 (26.3)                          | 191 (26.8)                            |
| Stroke                                       | 78 (9.6)                               | 66 (8.5)                            | 58 (8.1)                              |
| MI   | 153 (18.9)                             | 141 (18.1)                          | 129 (18.1)                            |
| CODP   | 113 (14.0)                             | 110 (14.1)                          | 100 (14.0)                            |
| Hypertension                                 | 416 (51.4)                             | 392 (50.4)                          | 360 (50.6)                            |
| CHF  | 64 (7.9)                               | 59 (7.6)                            | 52 (7.3)                              |
| Low thyroid                                  | 79 (9.8)                               | 77 (9.9)                            | 70 (9.8)                              |
| Diabetes                                     | 114 (14.1)                             | 109 (14.0)                          | 95 (13.3)                             |
| Rheumatoid arthritis                         | 69 (8.5)                               | 69 (8.9)                            | 58 (8.1)                              |

FN BMD = femoral neck bone mineral density; SD = standard deviation.

<sup>a</sup>Prior low trauma fractures after the age of 50 years and before enrollment in the study.

<sup>b</sup>Heavy alcohol consumption ≥3 standard drinks/day.

<sup>c</sup>There were missing data on grip strength *n* = 20 in the analytical cohort, *n* = 20 in the gait speed dataset, and *n* = 15 in the chair stands dataset.

<sup>d</sup>There were missing data on gait speed *n* = 52 in the analytical cohort, *n* = 52 in the grip strength dataset, and *n* = 13 in the chair stands dataset.

<sup>e</sup>There were missing data on chair stands *n* = 118 in the analytical cohort, *n* = 113 in the grip strength dataset, and *n* = 79 in the gait speed dataset.

subsequent fracture, compared to the best performing quartile (Table S3).<sup>(47)</sup>

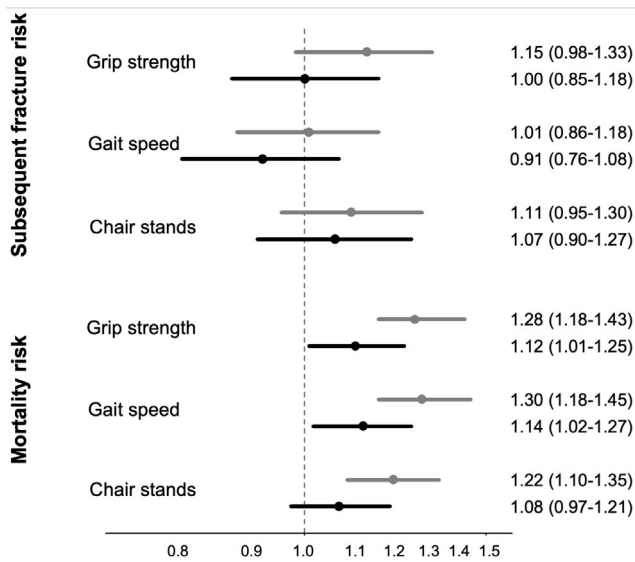
There were 22, 48, and 75 men who were unable to do grip strength, gait speed, or chair stand, respectively. In total, 91 men were unable to do a single test and 26 were unable to do multiple tests. Generally, men who were unable to perform the tests had higher rates of subsequent fracture than those who were able. The sensitivity analysis suggested that there was an association of poor muscle performance with increased risk of subsequent fracture particularly for those who were unable to do the chair stands test (age adjusted HR 1.59; 95% CI, 0.98–2.56) and those who were unable to perform multiple tests (age adjusted HR 2.03; 95% CI, 0.95–4.35) (Table S4).<sup>(47)</sup>

The second sensitivity analysis that included participants who had measurements taken more than 5 years prior to index fracture date incorporated an additional 115, 117, and 112 men to the grip strength, gait speed, and chair stands cohort, respectively. This analysis showed similar magnitude of association with subsequent fracture to the primary analysis (Table S5).<sup>(47)</sup>

The association between index measurements of strength and performance measurements and the risk of mortality after fracture

During a median (IQR) of 5.1 (1.8–9.6) years of follow-up, 536 men (64.6%) died postfracture, yielding a mortality rate of 10.6 deaths/1000 person-years (95% CI, 9.8–11.5). Men who died after the index fracture had significantly lower grip strength, slower gait speed, and longer chair stands time than those who survived. Furthermore, men who died after the index fracture were significantly older, less physically active, and were less likely to report excellent/good health. They had lower BMD *T*-score and were more likely to report history of stroke, hypertension, and rheumatoid arthritis prior to the index fracture than those who survived (Table S2).<sup>(47)</sup>

After adjustment for age and other risk factors, each SD decrement in grip strength (8.5 kg) and gait speed (0.25 m/s), and each SD increment in chair stand time (1.34 seconds) were associated with increased risk of postfracture mortality of 12% (HR 1.12; 95% CI, 1.01–1.25) for grip strength, 14% (HR 1.14; 95% CI, 1.02–1.27) for gait speed, and 8% (HR 1.08; 95% CI,

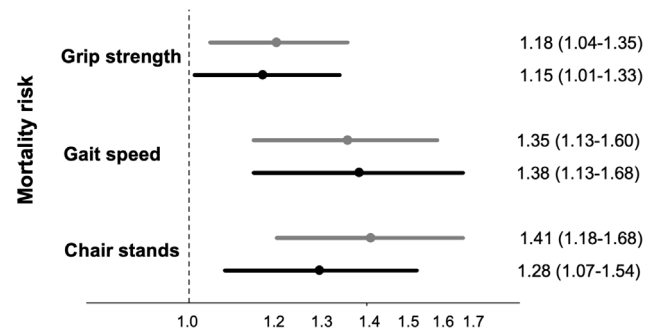


**Fig. 2.** Association between index muscle strength and physical performance measurements and the risk of subsequent fracture and mortality after fracture. Data presented as hazard ratios (95% confidence interval) per SD change in predictor (grip strength: 8.5-kg decrease, gait speed: 0.25-m/s decrease, and chair stands: 1.34-second increase). Multivariable-adjusted models that assessed subsequent fracture risk accounted for age, FN BMD, prior fracture, falls, physical activity, smoking, index fracture site, health rating, COPD, CHF, rheumatoid arthritis, and hypertension at time of the index fracture. Multivariable-adjusted models that assessed mortality risk accounted for age, BMI, living alone, physical activity, smoking status, alcohol consumption, FN BMD, falls, prior fractures, index fracture site, health rating, cancer, stroke, MI, COPD, hypertension, CHF, low thyroid, diabetes, kidney disease, and rheumatoid arthritis at time of the index fracture. Grip strength cohort included 810 men, 194 had subsequent fracture and 521 died. Gait speed cohort included 778 men, 193 had subsequent fracture and 492 died. Chair stands cohort included 712 men, 180 had subsequent fracture and 441 died.

0.97–1.21) for chair stands (Fig. 2). The categorical analysis of muscle strength and physical performance showed that compared to the best performing quartiles, the worst quartiles of grip strength, gait speed, and chair stands test were associated with 28%, 37%, and 14% increased mortality risk, respectively, albeit not statistically significant for all tests (Table S3).<sup>(47)</sup>

The first sensitivity analysis showed that men who were unable to perform the tests had higher rates of mortality than those who were able to complete all tests. Inability to perform the tests was associated with greater risk of mortality (age-adjusted HR 1.24; 95% CI, 0.76–2.01 for grip strength; HR 2.01; 95% CI, 1.44–2.81 for gait speed; HR 1.89; 95% CI, 1.45–2.47 for chair stands (Table S4)).<sup>(47)</sup> Notably, inability to perform multiple tests was associated with twofold increased risk of mortality (HR 2.09; 95% CI, 1.38–3.18).

The second sensitivity analysis, which included participants who had measurements taken more than 5 years prior to index fracture, showed a similar magnitude of association of the risk of mortality to the primary analysis for grip strength and gait speed (Table S5).<sup>(47)</sup> However, the association for chair stands increased slightly from 8% to 12% and became significant (Table S5).<sup>(47)</sup>



**Fig. 3.** Association between annual decline in muscle strength and physical performance post fracture and mortality risk. Hazard ratios are presented per 1-SD change in the annual decline of grip strength, gait speed, and chair stands time. All associations are significant associations ( $p < 0.05$ ). Age-adjusted models and multivariable-adjusted models were adjusted for the corresponding index measurement. Multivariable-adjusted models accounted for age, BMI, living alone, physical activity, smoking status, alcohol consumption, FN BMD, falls, prior fractures, index fracture site, health rating, cancer, stroke, MI, COPD, hypertension, CHF, low thyroid, diabetes, kidney disease, and rheumatoid arthritis at time of the index fracture. Grip strength cohort included 339 men, 189 men died. Gait speed cohort included 295 men, 151 men died. Chair stands cohort included 263 men, 132 men died.

### The association between decline in strength and performance and mortality risk

Men who died had significantly greater annual rate of deterioration in their muscle strength and performance than those who survived. Compared to those who survived, men who died had higher annual rates of decline, relative to the index measurement, in grip strength (median [IQR]: 2.07% [1.78%–2.45%] versus 1.88% [1.63%–2.15%]), higher annual rates of decline in gait speed (2.26% [1.93%–2.60%] versus 1.91% [1.53%–2.25%]), and higher annual rates of increase in chair stands time (3.99% [2.41%–5.68%] versus 3.06% [2.41%–5.68%]) (data not shown).

Greater deterioration in muscle strength and performance was significantly associated with increased mortality risk independent to the index value and other covariates (multivariable-adjusted HR 1.15; 95% CI, 1.01–1.33 for each SD decline in grip strength, HR 1.38; 95% CI, 1.13–1.68 for gait speed, and HR 1.28; 95% CI, 1.07–1.54 for each SD increase chair stand time; Fig. 3).

Notably, the index measurements of grip strength and gait speed remained significantly associated with mortality after incorporating the rate of decline to the models (index grip HR 1.32; 95% CI, 1.09–1.61, index gait speed HR 1.34; 95% CI, 1.07–1.67). However, the association between the index chair stands measurement and mortality risk was attenuated (HR 0.84; 95% CI, 0.66–1.06) after incorporating its annual rate of increase.

## Discussion

In this cohort of community-dwelling older men, we have demonstrated that grip strength, gait speed, and chair stands tests, assessed within 5 years prior to index fracture, were not associated with subsequent fracture. However, they were associated

with increased risk of mortality after fracture after taking into account age, comorbidities, and other potential confounders. Furthermore, the annual decline in muscle strength and performance following fracture was associated with increased risk of mortality. Inability to perform one or more of these tests was associated with a trend toward a higher risk of subsequent fracture and with an even higher risk (24%–109%) of mortality. Therefore, regular assessments of muscle strength and performance in clinical practice settings should be considered in order to identify those for whom intervention may be beneficial.

To our knowledge, no previous studies have assessed the association between muscle strength and performance measurements and the risk of subsequent fracture among community-dwelling older adults with an index fracture. Men who sustained a subsequent fracture were younger, had lower BMD *T*-scores, and were more physically active than those who did not. That suggests that those who sustained a subsequent fracture might be more likely to engage in behavior that would place them at higher risk for fracture. Measurements of muscle strength and performance, assessed prior to fracture time, were not associated with the risk of subsequent fracture, although our results suggest that those who were unable to do the tests may have had a higher subsequent fracture risk. This finding was unexpected and contrary to our hypothesis. A potential explanation could be that because all men in this study had sustained an index fracture, the difference in muscle strength and performance measurements between those who sustained a subsequent fracture and those who did not was not large enough to show any difference in the risk of subsequent fracture. Increased gait speed is a marker for increased physical activity,<sup>(48)</sup> such as walking for exercise, which in turn might increase the risk of fracture. Because muscle strength and performance predict index fracture, the distribution of these performance factors was skewed toward the lower end. Furthermore, the time to subsequent fracture was short (median, 3.20; IQR, 1.39–5.95). Further studies with longer follow-up time, or assessment of muscle strength and physical performance nearest to the index fracture date, are warranted to confirm our findings.

The effect of muscle strength assessed prior to fracture on the risk of mortality following a fracture has only been reported in two relatively small studies.<sup>(30,31)</sup> A previous study that included 18 men and 64 women aged 75–80 years reported a relative risk of mortality of 4.40 (95% CI, 1.40–13.80) for the lowest tertile of baseline knee extension strength, compared to those in the highest tertile.<sup>(31)</sup> Another prospective study that included 295 men and 889 women (mean age 75 years) reported a 19% and 39% increase in mortality risk in women and men, respectively, for each SD lower baseline quadriceps strength.<sup>(30)</sup> In the current study we reported a weaker association (12% increased risk) between each grip strength SD decrement and mortality. One explanation for this difference may be the different study design.

In the previous studies, authors assessed muscle strength measurements at baseline (average of 2.4–3.0 years before the fracture), whereas in the current study, muscle strength was assessed closer to the fracture. Another explanation could be that the previous studies explored different tests for muscle strength. Quadriceps strength declines faster than grip strength<sup>(49)</sup> and has been reported to be more clinically relevant to gait and physical function,<sup>(50)</sup> and hence, perhaps to mortality, compared to grip strength.<sup>(51)</sup>

However, to our knowledge, there have been no previous studies examining the role of gait speed and chair stands measurements, assessed prior to fracture, to the risk of mortality. We found that each SD decrement in gait speed and each 1-SD

increment in chair stand time measurements were respectively associated with 14% and 8% increased mortality risk. The contribution of chair stands did not reach the significance level, probably due to the smaller numbers of men included because the sensitivity analysis that included an additional 112 men showed significant association (12% increased mortality risk).

The current study also demonstrated that men with greater annual decline in grip strength, gait speed, or increase in chair stands time following fracture were at 15% to 38% higher risk of mortality (assessed per SD decrement/increment), independent of the index value and other potential covariates. This is consistent with a previous study where the changes in quadriceps strength assessed before and after the index fracture were significantly associated with postfracture mortality in men.<sup>(30)</sup> The associations found in our study were more pronounced than that of the index values. Furthermore, the association between the index measurement of chair stands and mortality was attenuated and became nonsignificant after accounting for its decline. Whether the index fracture contributed to this decline in these measures requires more investigation. However, these results suggest that rehabilitation after fracture may be particularly important to maintain muscle strength and performance in older people.

The mechanisms by which poor muscle strength and performance and their decline increase mortality after fracture are not known. Whether loss of muscle strength and performance following a fracture mediates postfracture mortality or whether poor muscle strength and performance reflect worse generalized health status warrants further exploration. On the other hand, some physiological processes (including inflammation and endocrine dysfunction) may cause declines in muscle strength and performance as well as increased risk of mortality.<sup>(29)</sup>

The study has several strengths. First, both subsequent fracture and mortality were investigated prospectively in a relatively large cohort of men recruited from the community. Second, objective, reliable, and repeated measurements of muscle strength and performance were assessed and analyzed. Third, fractures and mortality were centrally adjudicated, thus limiting measurement error in the assessment of these events. Finally, index measurements were utilized within 5 years prior to index fracture and repeated measurements were utilized at least 6 months after index fracture, ensuring that assessments would be close to fracture time and very unlikely to be affected by the acute fracture event. Nonetheless, a few limitations should be noted. First, our study cohort consisted of older primarily white men who must have been able to walk without aid, and thus our findings may not be generalizable to men of other races/ethnicities, less mobile, or institutionalized men. Second, there was a potential selection bias because only men with measurements available within 5 years prior to index fracture were included. However, the sensitivity analysis that included men with measurements taken more than 5 years prior to index fracture showed similar results, indicating the robustness of our analysis. In addition, the MrOS men were largely not osteoporotic by *T*-score. It is unknown if these results would be similar in men with BMD *T*-score osteoporosis. Finally, the association between rate of change and subsequent fracture risk could not be assessed due to the small number of subsequent fractures and small number of repeated measurements preceding subsequent fracture. Further studies with bigger cohorts and more frequent measurements of grip strength or walking speed might help investigate this association in more depth. However, MrOS is one of the largest studies of fracture risk in older men, so it is not clear if such analyses would be possible in another cohort.

In summary, muscle strength and performance, measured prior to index fracture were not significantly associated with subsequent fracture risk. However, these measures and their rate of decline following fracture were important determinants of mortality risk. Single and repeated assessments of strength and performance may be useful in clinical practice settings as indicators of overall health and for targeting individuals at higher risk of death after fracture. Future interventions should be evaluated to identify who may benefit from exercise interventions designed to improve muscle strength and physical performance after fracture.<sup>(52,53)</sup> However, it remains to be seen whether improvement in these parameters can reduce fracture associated mortality.

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## Author contributions

**Dima A. Alajlouni:** Conceptualization; formal analysis; methodology; validation; writing – original draft; writing – review and editing. **Dana Bliuc:** Conceptualization; methodology; supervision; validation; visualization; writing – review and editing. **Thach S Tran:** Conceptualization; methodology; supervision; validation; visualization; writing – review and editing. **Robert D. Blank:** Conceptualization; visualization; methodology; writing – review and editing. **Peggy M Cawthon:** Data curation; funding acquisition; investigation; project administration; resources; writing – review and editing. **Kristine E. Ensrud:** Data curation; funding acquisition; project administration; resources; writing – review and editing. **Nancy E. Lane:** Data curation; funding acquisition; project administration; resources; writing – review and editing. **Eric S. Orwoll:** Data curation; funding acquisition; project administration; resources; writing – review and editing. **Jane A. Cauley:** Data curation; funding acquisition; project administration; resources; writing – review and editing. **Jacqueline R Center:** Conceptualization; funding acquisition; methodology; project administration; supervision; visualization; writing – review and editing.

## Conflicts of interest

DAA, DB, TST, PMC, KE, NL, ESO, and JAC reported no competing interests. RB has been a consultant for Bristol Myers Squibb, served on an advisory board for Amgen, received authorship royalties from Wolters Kluwer, received an editorial stipend from Elsevier, received travel support from Amgen, and owns stock in Abbott Labs, Abbvie, Amgen, JangoBio, and Procter & Gamble. JRC has received support from Amgen for attending educational meetings, received advisory board honoraria from Amgen and Bayer, and received educational talks honoraria from Amgen.

## Data availability

MrOS data is publicly available at <https://mrosonline.ucsf.edu>. Data related to the study results is available on request from the authors. Supplementary material is available in “figshare” at <https://doi.org/10.6084/m9.figshare.19710679.v1>

## Peer review

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