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Contribution of Quadriceps Weakness to Fragility Fracture: A Prospective Study

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ABSTRACT

The association between muscle weakness and fracture is not well understood. This study sought to examine the contribution of muscle strength at baseline and change in muscle strength to the observed risk of fragility fracture in older people. The study involved 595 men and 1066 women aged 60+ years (median 69 years) who had been followed for a median of 11 years (range, 4 to 22 years). Quadriceps isometric muscle strength (MS) measured at baseline and biennially was adjusted for height. Femoral neck bone mineral density (FNBMD) was measured by DXA. Low-trauma fracture was ascertained from X-ray reports and interview. The relationship between baseline MS and serial MS and fracture assessed by time-invariant and time-variant Cox's regression models was expressed as hazard ratio (HR) and 95% confidence interval (CI). During the follow-up period, 282 (26%) women and 89 (15%) men sustained a fragility fracture. From age 60 years, women lost 0.28 kg/m (1.6%) of MS per year, whereas men lost 0.39 kg/m (1.5%) of MS per year. In the time-variant model, using serial MS, each 1 SD (4.7 kg/m) lower MS was associated with a 27% increase in the risk of fracture in women (HR 1.27; 95% CI, 1.11 to 1.43); and 46% increase in men (HR 1.46; 95% CI, 1.22 to 1.75). After adjusting for FNBMD, age and prior fracture, history of fall and smoking, HR per SD of lower MS was 1.13 (95% CI, 0.99 to 1.28) for women and 1.35 (95% CI, 1.18 to 1.64) for men. These data indicate that muscle weakness is an independent determinant of fracture risk in men, but not in women. This sex difference suggests that apart from mechanical load effect of muscle on bone, there are other muscle-bone interactions that need to be investigated in future studies. The accuracy of fracture risk prediction for men may be improved by incorporating muscle strength. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: QUADRICEPS STRENGTH; OSTEOPOROSIS; FRACTURE; BONE MINERAL DENSITY; TIME-VARIANT ANALYSIS

Introduction

Fragility fractures represent a burden to the population as well as to the individual.[1] At the population level, fracture incidence increases with advancing age, imposing a significant healthcare cost. Fracture-related economic costs in the United States were estimated at $17 billion for 2005, and these costs are predicted to rise by almost 50% by 2025.[2] At the individual level, people with a preexisting fracture are at risk of refracture and risk of premature mortality. Women and men who have sustained a fracture have a 2.0-fold and 3.5-fold increased risk of a subsequent fracture, respectively.[3] The 5-year mortality risk after a fracture increases above expected rate from 1.3 to 22.3 per 100 person-years.[1] The mortality from a subsequent fracture even doubles the mortality from the initial fracture.[4] Therefore, prevention is an important measure to address the accelerated prevalence of fracture among the growing older population. Identification of determinants of fragility fracture risk is the first and essential step leading to developing and applying preventive strategies.

An individual's risk of fracture depends on the balance between bone mechanical strength and the force imposed on the bone. Bone mechanical strength is characterized by the structure of bone tissues and bone mineral density (BMD),[5] which is a primary determinant of fracture risk.[6] Each 1 SD decrease in BMD is associated with a 2.4-fold and 2.0-fold increase in fracture risk in women and men, respectively.[6] Low BMD per se, however, does not account for all fracture cases.[7] In fact, about 50% of women and 70% of men with a fracture do not have osteoporosis by BMD alone.[8]

Muscle weakness is another important risk factor for fracture.[6] Both muscle and bone are affected by several factors, including genetic,[9–11] hormonal,[12–15] and lifestyle factors.[16–20] Muscle strength plays an important role in the maintenance of bone

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health, as it provides load on the bone and is positively associated with BMD.[21–23] However, current understanding about the influence of muscle strength on fragility fracture risk among elderly people is limited.

Muscle strength is a dynamic trait, in the sense that it changes with age.[24] Muscle strength, as measured by grip strength, declines at annual rates from 2.2% to 3.1% depending on gender and age.[25] Muscle strength can also be modified by altered physical activity (eg, exercise and disuse) or nutritional status.[26,27] Therefore, muscle strength measured close to the time of fracture might predict fracture risk better than strength measured years before a fracture.

We hypothesized that not only low muscle strength but also a decline in muscle strength would be associated with an increased risk of fragility fracture. The present study was designed to test this hypothesis by analyzing the association between fracture risk and measures of muscle strength at a point in time (baseline muscle strength) and at several time points (serial muscle strength).

Subjects and Methods

Participants and settings

The participants were women and men aged 60 years or above (at the study entry) who were participating in the Dubbo Osteoporosis Epidemiology Study. This ongoing longitudinal population-based study commenced in 1989 in Dubbo (Australia). Dubbo was selected as the study setting because of its relative isolation, centralized health services, stable population, and its age- and gender- representation of the general Australian population. The study is ongoing; however, the data for this analysis was extracted on September 29, 2013.

At the starting time, the study involved 1581 men and 2095 women from all 4005 Dubbo residents aged 60 and older.[1] The study protocol was approved by the St Vincent's Hospital human research ethics committee. Further details of the population and study design have been published elsewhere.[28,29]

Measurements of muscle strength and risk factors

Quadriceps strength was measured as the maximal isometric muscle contraction in the leg that participants identified as dominant, using a horizontal Pocket Balance spring scale (Rebuere, Remscheid, Germany). The dominant leg was ascertained by asking if the participant was left- or right-handed, then the relevant leg was used. The gauge was attached to the participant using a strap placed on the mid-shin of a seated participant whose knee and hip were at right angles. The gauge was then attached to the base of the chair so that it was perpendicular with the shin. The participant was asked to perform a maximum extension of their leg a total of three times, with the highest value being used for analysis. In order to maintain the joint angles during the test procedure, participants were asked to hold firmly onto the chair and not to lift their pelvis off the seat. The reason for using the greatest of three attempts was to allow the participant to familiarize themselves with the technique and to obtain the maximum leg strength. The gauge was calibrated to a maximum 50 kg of force. The measurement was taken for each participant at his or her biannual visits to the study clinic. In order to investigate the pattern of changes in muscle strength over time using the mixed-effects model, we only included participants who had attended at least three visits during the follow-up period. This limitation has resulted in 595 men and 1066 women in the analysis. The median of the number of visits was four (range, 3 to 10). Because measured muscle strength may be affected by the leg length, ie, longer leg length, the higher value of muscle strength, we used height-adjusted muscle strength (kg/m), which henceforth is referred to as muscle strength (MS). The interobserver variability for muscle strength measurement, as measured by intraclass correlation coefficient, ranged between 0.94 and 0.98.[30–32]

BMD (g/cm^2) was measured at the lumbar spine and femoral neck by dual-energy X-ray absorptiometry (DXA) using a LUNAR DPX densitometer (GE-LUNAR, Madison, WI, USA). The reliability of this method, as published previously, as measured by the reliability coefficient of BMD at the femoral neck is 0.98.[33] In this analysis we used femoral neck BMD in the analysis because it is less likely affected by age-related degenerative changes than the lumbar spine.

At baseline, age, anthropometric data (ie, weight and height), smoking (as ever or present smoker), and physical activity were recorded. Physical activity was assessed using the questionnaire similar to that used in the Framingham Massachusetts Heart Study.[34] The questionnaire asked participants to report their average number of hours per day spent in each of five levels of activity, ranging from basal to heavy level. Each level was then multiplied by an intensity factor based on the approximate oxygen consumption for that level. The sum of all resulting products gave the physical activity index, which is expressed as metabolic equivalents (METs). Fracture history prior to baseline was collected by a nurse coordinator using a structured questionnaire. History of falls was also ascertained by the nurse coordinator at each biennial visit. The coordinator asked participants about the number of falls and fall circumstance during the last 2 years prior to the visit. In this study, we used information of fall (eg, yes/no) in the last visit closer to the time of fracture.

Fracture ascertainment

The incidence of a fragility fracture was ascertained during the follow-up period, which started from the time of the first quadriceps strength measurement up to March 15, 2013. Fracture was ascertained from X-ray reports. An interview, direct or via phone, was then conducted by a trained nurse to obtain the circumstance of the fracture. Fractures due to high trauma, such as motor vehicle accident, or pathological factors (eg, cancer, or Paget's disease) were excluded. Fracture of the skull, fingers, and toes were not included in the analysis. All eligible fractures were categorized as hip; vertebral; and nonhip, nonvertebral fractures.

Statistical analysis

The magnitude of associations between muscle strength and fracture risk was estimated using the Cox's proportional hazards model. In this model, fracture and the time to fracture were considered the outcome, whereas muscle strength was the primary risk factor. Covariates considered in the model were gender, age, baseline BMD, and prior fracture. Two forms of muscle strength were measured: strength measured at baseline only and strength measured at several follow-up points, which henceforth will be referred to as baseline and time-variant strength. To include time-variant strength in a proportional hazard model, we constructed data in counting process format, which presents a specific strength measurement time for a

specific individual in a row. Thus, the number of rows for a specific individual was equivalent to the number of muscle strength measurements that person took. In this format, an individual would have his or her muscle strength varying at different measurement points.

For time-invariant analysis, the hazard function for fracture risk at time t can be expressed as follows:

$$h_i(t) = h_0 e^{(\text{baselinestrength})}$$

where h_0 is the baseline hazard function and $e^{(\text{baselinestrength})}$ is the coefficient associated with the risk factor. When the risk factor changes with time, the model becomes:

$$h_i(t) = h_0 e^{\text{strength}(t)}$$

where *strength(t)* is strength measured at time *t*. The model uses the last strength measurement before the fracture to estimate the hazard of fracture. Thus, hazard of fracture would be estimated with more accuracy when time-variant strength was used because the model used as much data as possible.

The change of muscle strength over time was assessed using the individual growth model. This model also allows us to test a hypothesis of differences in quadriceps strength change between genders. All statistical analyses were conducted with the Statistical Analysis System (SAS; SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

The study included 1066 women and 595 men who had been followed for a median of 11 years (range, 4 to 22 years). During the follow-up, there were 282 initial fractures in women and 89 in men over 12,618 and 7313 person-years at risk, respectively. These yielded an average fracture incidence of 22 per 1000 person-years (95% confidence interval [CI], 20 to 25) in women and 12 per 1000 person-years (95% CI, 10 to 15) in men. Among 282 (26%) fractures in women, there were 41 (14.5%) hip, 113 (40.1%) vertebral, and 128 (45.4%) nonhip, nonvertebral fractures. The 89 (15.0%) fractures in men were composed of 14 (15.7%) hip, 36 (40.5%) vertebral, and 39 (43.8%) nonhip, nonvertebral fractures.

Men and women who subsequently fractured were significantly older, and had lower weight and lower FNBMD at baseline than those who did not fracture. Women who fractured had a higher prevalence of prior fracture than those who did not. Men who fractured had lower baseline muscle strength compared to men without a fracture (Table 1).

Change in quadriceps strength

At baseline, height-adjusted muscle strength (MS) for women was (mean ± SD) 15.1 ± 4.7 kg/m and for men was 23.0 ± 4.7 kg/m. Women with a fracture had MS of 14.8 ± 4.4 kg/m, which was not significantly different from that of their nonfracture counterparts (15.2 ± 4.7 kg/m; $p = 0.1968$) (Fig. 1). Men with a fracture (21.8 ± 5.1 kg/m) had significantly lower baseline muscle strength than men without a fracture (23.2 ± 4.6 kg/m; $p = 0.0077$).

To investigate the pattern of annual change of muscle strength, we conducted individual growth analysis, which takes into account individual differences over time. Women at age 60 years had 17.7 kg/m (95% CI, 17.3 to 18.1) MS, whereas men at the same age had 26.9 kg/m (95% CI, 26.3 to 27.4) MS. The difference in MS between women and men was statistically significant ($p < 0.0001$). In women, the absolute annual change was –0.28 kg/m, equivalent to a rate of decline of 1.6% per year. In men, the absolute annual change was –0.39 kg/m, equivalent to a rate of decline of 1.5% per year (Table 2). The difference in the absolute (but not relative) annual change between women and men was statistically significant ($p < 0.0001$). Gender accounted for 49% of the individual differences in mean of MS, and 20% of the individual differences in the absolute annual change in MS. This is consistent with the significant difference in absolute annual change in MS between the genders.

MS as a predictor of fracture risk

In either gender, there was significant association between fracture risk and advancing age, lower baseline muscle strength, serial muscle strength, lower baseline FNBMD, and higher baseline weight (Table 3). Current smoking was associated with increased risk of fracture in men (HR 1.65; 95% CI, 1.06 to 2.59), but not in women (HR 1.12; 95% CI, 0.86 to 1.44).

The cumulative incidence of fracture significantly decreased with increasing tertiles of baseline MS in men but not in women (Fig. 2). In unadjusted models, lower baseline MS and serial MS were both significantly associated with increased fracture risk

Table 1. Baseline Characteristics of 595 Men and 1066 Women in the Study Stratified by Subsequent Fracture Occurrence

	Women		Men	
	Fracture	Nonfracture	Fracture	Nonfracture
n (%)	282 (26.5)	784 (73.5)	89 (15.0)	506 (85.0)
Age at baseline (years)	**71.0 ± 5.8**	**68.2 ± 5.4**	**71.7 ± 5.5**	**69.3 ± 4.7**
Height at baseline (cm)	159.8 ± 5.7	160.3 ± 5.6	172.6 ± 6.1	173.4 ± 6.3
Weight at baseline (kg)	**66.9 ± 11.5**	**69.7 ± 12.8**	**78.1 ± 12.8**	**83.3 ± 13.0**
FNBMD at baseline (g/cm^2)	**0.77 ± 0.11**	**0.85 ± 0.13**	**0.90 ± 0.14**	**0.96 ± 0.14**
MS at baseline (kg/m)	14.8 ± 4.4	15.2 ± 4.7	21.8 ± 5.1	23.2 ± 4.6
PA (METs)	31.21 ± 3.0	30.85 ± 2.5	32.9 ± 5.2	33.3 ± 5.2
History of falls = yes, *n* (%)	107 (37.9)	287 (36.6)	34 (38.2)	148 (29.3)
Smoking = yes, *n* (%)	84 (29.8)	215 (27.4)	61 (68.5)	298 (58.9)
Prior fracture = yes, *n* (%)	**54 (19.2)**	**103 (13.1)**	7 (7.9)	48 (9.5)

Values are means ± SD, unless otherwise specified. The difference between fracture and nonfracture groups was tested by the independent Student's *t* test (for continuous data) and chi-square test (for categorical data). Bold values indicate $p < 0.05$ within gender.

FNBMD = femoral neck bone mineral density; MS = muscle strength (quadriceps); PA = physical activity; MET = metabolic equivalent.

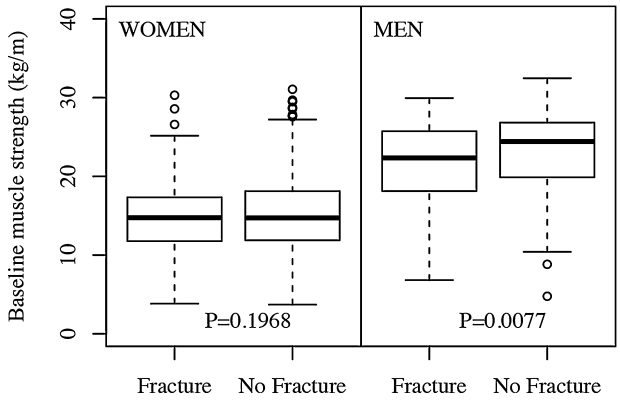

Fig. 1. Baseline muscle strength (quadriceps) in men and women, stratified by fracture status. Median, third and first quartile, and maximum and minimum values are represented by line inside the box, upper edge and lower edge of the box, and endpoints of upper and lower whiskers, respectively.

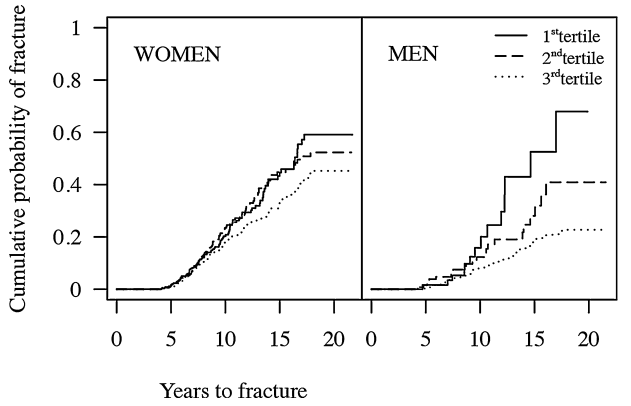

Fig. 2. Cumulative probability of fracture stratified by tertiles of baseline muscle strength (quadriceps).

(Table 4). After further adjusting for age and FNBMD, in men the association between fracture and baseline MS and serial MS remained significant; however, in women the association changed, represented by a change in HR (95% CI) from 1.18 (1.05 to 1.33) to 1.09 (0.97 to 1.24) for baseline MS, and from 1.27 (1.12 to 1.43) to 1.13 (0.99 to 1.28) for serial MS. Further adjusting for prior fracture, history of falls and smoking did not alter the results for baseline MS or serial MS.

The inclusion of MS together with age and BMD improved the model's discrimination for men. In men, the concordance index for the model with age and FNBMD was 0.676, and this statistic was increased to 0.70 when MS was included in the model. In women, MS did not improve the concordance index over and above the basic model with age and BMD.

The analysis for body mass index–adjusted muscle strength yielded similar results. Each SD (0.32 kg/kg/m^2) decrease in body mass index–adjusted muscle strength was associated with an increased hazard of fracture (HR 1.26; 95% CI, 1.05 to 1.51) in men but not in women (HR 1.13; 95% CI, 1.0 to 1.3).

Table 2. MS and Change in MS

	Women	Men
MS at age 60 years (kg/m)	17.7 (17.3 to 18.1)*	26.9 (26.3 to 27.4)*
Annual change (kg/m)	−0.28 (−0.31 to −0.26)*	−0.39 (−0.43 to −0.35)*
Annual rate of change (%)	−1.6 (−1.8 to −1.5)	−1.5 (−1.6 to −1.3)

Values are in the units labeled (95% confidence interval).
MS = muscle strength.
*$p < 0.0001$.

Table 3. Association Between Baseline Risk Factors and Risk of Fracture: Univariate Cox's Regression Analysis

		Women	Men
Variables	Unit	HR (95% CI)	HR (95% CI)
Age at baseline	+5 (years)	**1.35 (1.23–1.5)**	**1.62 (1.32–1.99)**
MS at baseline	−4.7 (kg/m)	**1.18 (1.05–1.33)**	**1.47 (1.21–1.79)**
Time-variant MS	−4.7 (kg/m)	**1.27 (1.11–1.43)**	**1.46 (1.22–1.75)**
FNBMD at baseline	−0.14 (g/cm^2)	**1.74 (1.5–2.0)**	**1.66 (1.31–2.10)**
Height at baseline	−6 (cm)	1.09 (0.96–1.23)	1.11 (0.91–1.36)
Weight at baseline	−13 (kg)	**1.19 (1.04–1.36)**	**1.41 (1.11–1.79)**
Physical activity	−5 (METs)	0.83 (0.68–1.02)	1.11 (0.89–1.37)
Prior fracture	(yes)	**1.58 (1.17–2.14)**	0.90 (0.42–1.95)
History of falls	(yes)	0.95 (0.75–1.22)	1.34 (0.87–2.05)
Smoking	(yes)	1.12 (0.86–1.44)	**1.65 (1.06–2.59)**

Women: $n = 1066$, 282 fractures; Men: $n = 595$, 89 fractures. Bold values indicate $p < 0.05$.
HR = hazard ratio; CI = confidence interval; MS = muscle strength (quadriceps); FNBMD = femoral neck bone mineral density; MET = metabolic equivalent.

Table 4. Association Between Risk of Fracture and Baseline and Serial MS, Stratified by Gender: Cox's Regression Analysis

	Women		Men	
	Baseline MS	Serial MS	Baseline MS	Serial MS
Univariate	**1.18 (1.05–1.33)**	**1.27 (1.12–1.43)**	**1.47 (1.21–1.79)**	**1.46 (1.22–1.75)**
Age adjusted	1.11 (0.98–1.26)	**1.17 (1.03–1.33)**	**1.41 (1.15–1.73)**	**1.35 (1.12–1.63)**
Age and FNBMD adjusted	1.09 (0.97–1.24)	1.13 (0.99–1.28)	**1.46 (1.19–1.80)**	**1.37 (1.14–1.66)**
Multivariate[a]	1.08 (0.96–1.23)	1.13 (0.99–1.28)	**1.45 (1.18–1.79)**	**1.35 (1.12–1.64)**

Values are HR (95% CI). Women: $n = 1066$, 282 fractures; Men: $n = 595$, 89 fractures. All HRs are per −4.7 kg/m (1 standard deviation) of MS. Bold values indicate $p < 0.05$.

MS = muscle strength (quadriceps); FNBMD = femoral neck bone mineral density; HR = hazard ratio; CI = confidence interval.

[a]HR was adjusted for baseline age and FNBMD, fracture prior to baseline, history of falls, and smoking.

Further analysis by fracture site revealed that in women, each SD decrease in baseline MS was associated with a 38% increase in the risk of vertebral fracture (HR 1.38; 95% CI, 1.14 to 1.68), but it was not associated with hip fracture (HR 1.12; 95% CI, 0.83 to 1.59), or nonhip, nonvertebral fracture (HR 1.06; 95% CI, 0.89 to 1.27) (Table 5). In men, the risk of hip fracture and of vertebral fracture increased with every SD decrease of baseline and serial MS. The association remained virtually unchanged after adjusting for baseline age, baseline FNBMD, prior fracture, history of falls, and smoking. For nonhip, nonvertebral fracture in men, lower baseline MS, but not change in MS, was significantly associated with greater risk of fracture.

Discussion

The relationship between skeletal muscle strength and fracture has not been well documented. In this longitudinal population-based study, we have shown that skeletal muscle strength (as measured by quadriceps strength) declined with advancing age in both women and men, and this reduction was associated with an increased risk of fracture in both sexes.

Other studies examining muscle strength loss with the aging process found that the rate loss ranged between 1.5% and 5% per year,[35–37] which is similar to the rate of loss from our study. However, our data further suggest that the absolute loss was significantly higher in men than in women. Importantly, we found that a decrease in muscle strength was associated with increased fracture risk in both sexes. However, after adjusting for age and bone density, the association remained significant in men but not in women. This sex-related difference may be explained by a differential effect of lean mass between men and women. In a previous study,[38] compared to fat mass, lean mass was found to exert a greater effect on FNBMD in men; but in postmenopausal women, fat mass exerted a greater effect on bone density than lean mass. Moreover, in postmenopausal women, greater fat mass was associated with greater BMD after adjusting for the body size.[39] In this study, we have shown that despite the identical annual rate of lean muscle loss, the absolute loss was significantly higher in men than in women, suggesting that the absolute amount of muscle strength loss is more relevant to fracture risk.

The underlying etiology of the association between muscle strength and fracture is not known. However, a number of hypotheses could be proposed to account for the relationships. A recent study has found that low grip strength is associated with impaired microarchitecture at the distal radius in older men.[22] Other possible pathways include reduced muscle mass per se, increased falls frequency, decreased BMD, and insufficient gonadal hormones; all of which could predispose an individual to a higher risk of fracture.

Muscle weakness increases the risk of falls.[40,41] In turn, falls within the previous 12 months increases the risk of fracture.[42] Falls increases the risk of hip fracture by 1.4-fold to 1.6-fold[42] and the risk of any fragility fracture 2.1-fold.[8] In our study, adjusting for falls slightly attenuated but did not change the significance of the association between muscle strength and fracture. Reduction in muscle strength has been related to BMD loss in several studies.[21,43,44] A study in postmenopausal women reported that muscle strength measured at hip accounted for 26% of total BMD variance.[44] Another study,

Table 5. Association Between Risk of Fracture and Baseline and Serial MS, Stratified by Gender and Fracture Type

	Women		Men	
	Baseline MS	Serial MS	Baseline MS	Serial MS
Univariate analysis				
Hip fracture	1.12 (0.83–1.53)	**1.65 (1.17–2.35)**	**1.85 (1.13–3.0)**	**1.84 (1.13–2.99)**
Vertebral fracture	**1.38 (1.14–1.68)**	**1.33 (1.09–1.62)**	**1.52 (1.10–2.09)**	**1.61 (1.21–2.16)**
NHNV fracture	1.06 (0.89–1.27)	1.18 (0.98–1.42)	**1.43 (1.05–1.94)**	**1.32 (1.00–1.74)**
Multivariate analysis[a]				
Hip fracture	0.94 (0.69–1.30)	1.31 (0.92–1.87)	**1.76 (1.07–2.90)**	**1.70 (1.08–2.67)**
Vertebral fracture	**1.25 (1.02–1.53)**	1.13 (0.92–1.39)	**1.43 (1.02–2.00)**	**1.50 (1.11–2.04)**
NHNV fracture	1.01 (0.85–1.36)	1.11 (0.92–1.34)	**1.42 (1.03–1.96)**	1.21 (0.91–1.61)

Values are HR (95% CI). Cox's regression analysis (Women: $n = 1066$, 41 hip, 113 vertebral, and 128 non-hip, nonvertebral fractures; Men: $n = 595$, 14 hip, 36 vertebral, and 39 non-hip, nonvertebral fractures). All HRs are per −4.7 kg/m (1 standard deviation) of MS. Bold values indicate $p < 0.05$.

MS = muscle strength (quadriceps); NHNV = non-hip, nonvertebral; HR = hazard ratio; CI = confidence interval.

[a]HR was adjusted for baseline age and FNBMD, fracture prior to baseline, history of falls, and smoking.

however, found an association in older men but not in older women.[43]

In men, muscle strength both measured at baseline and measured repeatedly predicted fracture risk independent of other risk factors. In women, however, the association between fracture risk and baseline strength was mediated by age and FNBMD and there was no statistically significant association between fracture risk and either baseline or repeated measurements of strength. This discrepancy might be an indication of gender specificity in fracture prediction; ie, that prediction would be improved if measurements of muscle strength were included for men.

The present findings should be interpreted within the study's strengths and weaknesses. The study was based on a large sample size of individuals who had been well characterized and followed up for a long time. To our knowledge, this is the first study that has used serial longitudinal measurements (up to 10 measurements), taking into account individual differences to predict the change of muscle strength. This is also the first study that has determined the association between muscle strength and fracture risk using the serial measurement of strength instead of baseline strength alone. However, the maximal measurement of MS at 50 kg may be lower than the maximal performance of men. This could result in the underestimation of the association between MS and fracture risk in men. Furthermore, the modest number of fractures in men reduces power to detect associations, especially for site-specific fracture analysis. However, for any fracture, the main outcome of the study, 89 fracture cases in men were statistically sufficient for these analyses.

Moreover, our method of muscle strength measurement has some benefits and weaknesses. The method is simple and quick, highly suitable to large-scale study. However, the method only measures isometric muscle contraction, not concentric/eccentric muscle contraction, which may also be functionally relevant. Isometric strength assesses strength in a finite range, whereas the changes in strength may differ in different parts of the range, particularly near full extension where quadriceps weakness can contribute to falls, which in turn contribute to fracture risk. The test requiring non-weight bearing may not entirely represent the contribution of quadriceps weakness to falls that happen during weight-bearing activities. Quadriceps muscle strength does not reflect other muscles such as other antigravity muscles.

Fracture risk assessment tools available at the moment, such as FRAX,[45] Garvan's Fracture Risk Calculator,[7] or QFracture-Score,[46] have not yet included muscle strength as a predictor. Results of this study suggest that the incorporation of muscle strength data in a fracture prediction model may improve the predictive accuracy of the model, and help making informed decision concerning the diagnosis and treatment of osteoporosis.

In summary, we have found that muscle strength is an independent determinant of fracture risk in men. In women, the association is mediated by age and FNBMD. Measurements of quadriceps strength could be used in conjunction with existing fracture risk calculation algorithms to improve the accuracy of fracture risk assessment in men. These findings have important implications for approaches to the prevention of osteoporosis and fracture in the general population.

Disclosures

JAE has served as consultant on the Scientific Advisory Boards of Amgen, Aspen, Merck Sharp & Dohme, Novartis, and Sanofi-Aventis; he was the Editor-in-Chief for the *Journal of Bone and Mineral Research* from 2003 to 2007 and was a committee member of the Department of Health and Aging, Australian Government, and Royal Australasian College of General Practitioners. JRC has given educational talks for Amgen, Merck Sharp & Dohme, Novatis, and Sanofi-Aventis; she has received travel expenses from Merck Sharp & Dohme, Amgen, and Aspen. TVN has received honoraria for consulting and speaking in symposia sponsored by Merck Sharp & Dohme, Roche, Servier, Sanofi-Aventis, and Novartis. JAE, TVN, and JRC have received grants from Sanofi and BUPA. TVN has received an NHMRC project grant. The remaining authors state that they have no conflicts of interest.

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Authors' roles: TVN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: HMP, JRC, JAE, and TVN. Study conduct: HMP and TVN. Data collection: TVN, JRC, and JAE. Data analysis: HMP and TVN. Data interpretation: HMP, NDN, JRC, JAE, and TVN. Drafting manuscript: HMP and TVN. Revising manuscript content: HMP, NDN, JRC, JAE, and TVN. Approving final version of manuscript: HMP, NDN, JRC, JAE, and TVN.

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