Original Article

Association of Muscle Weakness with Post-Fracture Mortality in Older Men and Women: A 25 Year Prospective Study†

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Short title: Quadriceps weakness and post-fracture mortality

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Disclosure

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Abstract

Osteoporotic fracture increases the risk of premature mortality. Muscle weakness is associated with both increased fracture risk and low BMD. However, the role of muscle strength in post-fracture mortality is not well understood. This study examines the change of muscle strength measured at quadriceps (QS) before and after fracture, and defines the relationship between muscle strength and post-fracture mortality.

The study involved 889 women and 295 men (who were participating in the Dubbo Osteoporosis Study) who had at least one low trauma fracture (ascertained from X-ray reports) after the age of 50. Median follow-up time was11 years (range: 1-24). To determine the change in muscle strength before and after a fracture, we selected a subset of 344 women and 99 men who had had at least two muscle strength measurements before the fracture event, and a subset of 407 women and 105 men who had had at least two measurements after the fracture.

During the follow-up period, 366 (41.2%) women and 150 (50.9%) men died. The annual rate of decrease in height-adjusted muscle strength before fracture was 0.27 kg/m (1.85%) in women and 0.40kg/m (1.79%) in men. Strength loss after fracture was not significantly different from that before fracture. In women, after adjusting for baseline age and BMD, each SD (5 kg/m) lower height-adjusted pre- and post-fracture quadriceps strength was associated with a 27% [HR(95%CI): 1.27(1.07-1.50)] and 18% [HR(95%CI): 1.18(1.01-1.38)] increase in post-fracture mortality risk, respectively. Similarly, in men, each SD (5kg/m) lower height-adjusted pre-and post-fracture QS was associated with increased mortality before fracture [HR(95%CI): 1.33(1.09-1.63)] and after fracture [HR(95%CI): 1.43(1.16-1.78)]. Muscle weakness accounted for 15% (95%CI: 0.05-0.24) of premature deaths after fracture in women and 23% (95%CI: 0.11-0.35) in men.

These results indicate that in the older individuals, lower muscle strength is an independent risk factor for post-fracture mortality.

Keywords: muscle strength, post-fracture mortality, mixed model, premature mortality, population attributable risk.

Introduction

From the public health view point, fragility fracture is a significant burden on the population, because it is highly prevalent and it is associated with serious consequences. In women, the lifetime risk of fracture at the hip, the most serious type of fracture, is one in six, which is higher than the lifetime risk of invasive breast cancer.[1, 2] The risk of hip fracture in aged men is about one-third of that in women.[1] More importantly, a fracture is associated with an increased risk of premature mortality in both women and men.[3] With the on-going aging of the population, the impact of fragility fracture is projected to become more pronounced.

Factors that account for this premature mortality risk following a fracture have not been well established. Studies investigating these factors have predominantly focused on hip fracture due to the high mortality incidence following this kind of fracture. Co-morbidities and low bone mineral density have been reported to be associated with post-hip fracture mortality[4, 5], but they could not explain the excess mortality post fracture.

Muscle strength declines with advancing age at the rate of 1.6% per year in the general older population.[6] This decline in muscle strength has been reported to be associated with an increased fracture risk.[6, 7] However, among those who are at risk of a fracture the pattern of muscle strength decline is not clear. Also, it is not known whether muscle strength decline is exacerbated in those who experience a fragility fracture.

In addition, although muscle weakness increases fracture risk [6, 7] and fracture in turn increases the risk of premature mortality,[3, 8, 9] the relationship of muscle weakness to mortality after a fracture is not well understood. People with a low-trauma hip or vertebral fracture have an increased risk of premature mortality with the highest risk during the first year after fracture, and a notably increased risk persisting for several years after the event.[3, 8, 10, 11] Muscle weakness has been shown to be associated with premature mortality in the general population.[12, 13] The excess risk of mortality in people with fracture could be contributed to by an increased prevalence of muscle weakness or an

increased effect of muscle weakness on premature mortality. Attributable risk estimates can give insight into contributors to the excess mortality in people with fragility fracture by quantifying the proportion of risk of premature mortality that is attributable to muscle weakness.

Furthermore, increased mortality after fragility fracture is gender-specific. [14] Men are about 2-fold more likely to die after fracture than women.[15] Understanding gender-specific skeletal muscle changes and their association with post-fracture mortality could help in understanding the gender difference in mortality after fracture.

In this study, we tested three hypotheses: (1) muscle strength declines in those who are progressing to a fragility fracture; (2) muscle strength loss is increased after a fragility fracture; and (3) low muscle strength (before and/or after a fragility fracture) is associated with post-fracture mortality.

Study Design and Methods

Participants and Settings

The study involved all participants who had at least one low traumatic fracture since the age of 50 and had been taking part in Dubbo Osteoporosis Epidemiology Study (DOES). DOES is an ongoing longitudinal population-based study, which commenced in 1989 in Dubbo, Australia. Dubbo has a relatively stable population and its own radiological services, thus constituting an ideal setting for the epidemiological study of fracture. The details of DOES have been published elsewhere.[16-19] The study protocol was approved by the St Vincent's Hospital human research ethics committee. In 1989, approximately 2100 women and 1600 men aged 60 years or over were living in Dubbo City.[18] At its beginning (1989), DOES involved over 60% of this population.[4] By its nature, the study did not involve those who were institutionalized. The second phase of the study which started around 2000 continued to recruit individuals who reached 60 years of age from the general population. Hence, at the time the data were extracted (31st August, 2015), there were 2318 women and 1424 men in DOES. **Muscle strength measurement was expected to be done for all those participants. However, due to time strain, which happened randomly, or due to some**

participants was too weak to perform the test, there were 5% of those women and men had no strength measurement. The remaining 2200 women and 1359 men had at least one muscle strength measurement. Therefore, this group was the "input" population on which further criteria was applied to select the final sample. In this study, due to a change in measurement protocol, from "input" population, we included only those with strength measurements from 1992 resulting in 2004 women and 1191 men. Among those with eligible strength measurements, 889 women and 295 men had experienced at least one fracture after the age of 50. For the main aim of this study, to investigate the association between muscle strength and post-fracture mortality, this whole fracture cohort was used. In addition, to investigate the change of muscle strength before and after fracture, two subgroups of this fracture cohort were used. One subgroup, henceforth referred to as the pre-fracture subgroup, consisted of 344 women and 99 men who had at least two muscle strength measurements before fracture. The other subgroup, referred to as the post-fracture subgroup, consisted of 407 women and 105 men who had at least two muscle strength measurements after fracture. There were 73 women and 17 men who belonged to both subgroups. The framework for the study design is outlined in Figure 1.

The median follow-up time for the whole fracture cohort was 11 years (range: 1 to 24 years). The median follow-up time for the pre-fracture and post-fracture subgroups were 15 (range: 3 to 24 years) and 11 years (range: 2 to 24 years), respectively.

Fracture ascertainment

For those participants who fractured after the age of 50 but before entering the study, their fractures were identified by recall. Fracture occurred after age 50 and before baseline accounts for 4% of all fractures and the analysis excluding these cases yielded a similar result. Fractures occurring after participants had entered the study were ascertained from X-ray reports from the two and, at some times, three radiological services in Dubbo as previously reported.[20] Following identification of a fracture, an interview, direct or via phone, was then conducted by a trained nurse to obtain the circumstance of the fracture. For ethical reasons,

we could not take X-ray for the whole cohort, and could therefore not ascertain the incidence of asymptomatic vertebral fractures. Vertebral fractures reported in this paper were mainly clinical fractures. Fractures resulting from high trauma, such as motor vehicle accidents, or pathological factors (e.g., bone-related cancer, or Paget's disease) were excluded. Fractures of the skull, fingers and toes were not included in the analysis. All eligible fractures were categorized as hip, vertebral or non-hip, non-vertebral fractures.

Ascertainment of death

Ascertainment of death was performed by systematically searching funeral director lists, local newspapers and Dubbo media reports. Deaths certificates were obtained from the New South Wales Registry of Births, Deaths, and Marriages.

Measurements of Muscle Strength and Risk Factors

Quadriceps strength was defined as the maximal isometric muscle contraction measured in the participant's self-identified dominant leg, using a horizontal spring gauge. Details of the measurement have been published elsewhere.[6] The maximum value of force that could be measured was 50 kg. The measurement was taken approximately biannually for each participant. The median number of measurements was 3 (range: 1 to 10) for the whole cohort, and was 3 (range: 2 to 9) and 3 (range: 2 to 10) for the pre- and post-fracture subgroups. As measured muscle strength may be affected by leg length, we used height adjusted muscle strength (kg/m), which henceforth is referred to as muscle strength (MS).This measurement method has a reliability coefficient of 0.75.[21]

Bone mineral density (g/cm^2) was measured at the femoral neck by dual-energy X-ray absorptiometry using a LUNAR DPX, or later on Prodigy 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.[22]

At baseline, age, anthropometric data (i.e. weight and height), falls history (within one year prior to baseline), smoking status (past or present), physical activity and co-morbidities were collected by a trained nurse. Co-morbidities were classified as follows: cancer (non-bone related, bladder, bowel,

cervix, uterus, gastro-intestine, liver and melanoma), diabetes (type I and type II), cardiovascular disease (ischemic heart disease, mitral valve incompetence, myocardial infarction, stroke, transient ischemic attacks, pulmonary embolus, pulmonary oedema, cardiac arrhythmia, and carotid insufficiency), hypertension, neurological disease (Alzheimer, dementia, depression, and epilepsy), rheumatoid arthritis and respiratory disease (asthma and emphysema). Number of co-morbidities was a sum of the presence of these co-morbidities minus hypertension.

Physical activity was assessed at the same time as the first muscle strength measurement. In cases where this information was not available, we took physical activity values from one of the two visits prior to when muscle strength was first measured. In these cases, the gap between physical activity information and muscle strength measurement was at most five years. Physical activity index was calculated as the average number of hours per day spent in each of five levels of activity, with weighting factors based on associated oxygen consumption for each activity according to the Framingham Study.[23] Details of physical activity data collection and calculation has been published elsewhere.[24]

Statistical Analysis

The change in muscle strength over time was assessed using an individual growth model. **A simple linear regression model was fitted for each individual. In this model, muscle strength was considered the outcome and time as a dependent variable; thus the estimated intercept and gradient are estimates of the baseline and annual rate of change, respectively. The residual variance is an estimate of within-subject variance. The collection of gradients across individuals was then subject to further analyses of association with potential predictors.[25]**

The association between baseline muscle strength and post-fracture mortality risk was investigated initially using Kaplan-Meier survival curves with participants stratified into tertiles of muscle strength. The association then was assessed using the Cox's proportional hazards model.

In order to estimate the proportion of death attributable to muscle weakness, we estimated partial population attributable risk (PAR_p).[26] This population attributable risk for muscle weakness represents the proportion of deaths that could be deferred if muscle weakness was eliminated from the population; or in other words, if those with muscle weakness instead had their muscle strength in the normal ranges. We also estimated full PAR (PAR_f),[26] which is the proportion of deaths that would be deferred if all the risk factors (except for age) identified in parsimonious models were considered eliminated. In order to calculate PAR_p and PAR_f, cutoffs to define threshold for all risk factors were required. The cutoff for muscle strength was defined as the value equivalent to the first tertile of the range. This cutoff was 11.11 kg/m for women and 17.44 kg/m for men. While no internationally recognized thresholds exist for this measure, **our choice for this cutoff was based on the following information: 1) people in the lowest tertile of muscle strength had a significantly higher risk of fracture[6]and 2) Kaplan-Meier survival curves (Figure 2) showed that those people who were at the lowest muscle strength tertile had significantly lower survival probability. The same method was applied to define the cutoff for physical activity index.** Age from 70 and BMD T-score less than -2.5 were used as thresholds for age and femoral neck BMD.

All analyses were performed separately for men and women, and conducted with SAS software.[27] Graphs were constructed in R[28] using the packages *ggplot2*[29], *survival*[30, 31]and *KMsurv.*[32]

Results

Fracture Cohort

Among 889 first-recorded low-trauma fractures in women, there were 89 (10.0%) hip, 298 (33.5%) vertebral and 502 (56.5%) non-hip, non-vertebral fractures. The 295 first-recorded low-trauma fractures in men were comprised of 36 (12.2%) hip, 101 (34.2%) vertebral and 158 (53.6%) non-hip, non-vertebral fractures. The mean age at fracture was 75 years (SD: 9 years) for both men and women. The mean age at baseline was 72 years (SD:7) for women and 73 (SD: 7) for men.

Compared to men, women had lower height-adjusted MS [13.2 kg/m (SD: 4.8) vs. 20.2 kg/m (SD: 5.9), P<0.0001], and lower FNBMD [0.76 g/cm^2 (SD: 0.13) vs. 0.88 g/cm^2 (SD: 0.15), P<0.0001]. There was no difference in the distribution of co-morbidities between women and me, except for cardiovascular disease where men had higher prevalence than women.

In the subgroups of those who had at least two measurements of muscle strength, at baseline, women in the post-fracture group were significantly older, shorter and had lower MS than those in the pre-fracture group. These differences were not observed in men (Table 1).

Incidence of mortality

During the follow-up period, 366 (41.2%) women and 150 (50.9%) men died over 10,925 and 3,186person-years at risk, respectively. These yielded an average mortality rate of 34 per 1,000 person-years (95% confidence interval (95% CI): 31, 38) in women and 47 per 1,000 person-years (95% CI: 40, 55) in men.

In women, compared to survivors, those who died were significantly older, shorter, less physically active, and also had lower weight, BMI, FNBMD and MS at baseline. These differences, except for height and physical activity, were also observed in men. Diabetes was more prevalent in men who died while respiratory disease was more prevalent in women who died. (Table 2)

When analyzed by fracture type, the risk of mortality following a hip fracture was highest (67% for women and 64% for men), followed by mortality risk among individuals with a clinical vertebral fracture (37% for women and 46% for men). The risk of mortality among individuals with non–hip and non–vertebral fractures was similar to that for those with vertebral fracture.

Muscle strength change before and after fracture

Analyses for determining muscle strength change were performed in subgroups of men and women who had at least 2 muscle strength measurements before and/or after fracture. Two parameters of muscle strength before and after fracture were estimated: predicted strength at age 70 and annual absolute loss of strength from this age, which was to calculate the relative annual rate loss.

In women, for those whose muscle strength had been taken before fracture, strength at age 70 was 14.6 kg/m (95%CI: 14.1, 15.0) and annual absolute loss was 0.27 kg/m (95%CI: -0.32, -0.23), equivalent to an annual rate loss of 1.85%/year (95%CI: -2.20, -1.57). For women whose muscle strength was measured after fracture, muscle strength loss was not significantly different from that before fracture (Table 3).

In men, all muscle parameters taken before or after fracture were greater than those in women. Before fracture, men at age 70 had a muscle strength of 22.3 kg/m (95%CI: 21.3, 23.3) and annual absolute loss of 0.40 kg/m (95%CI: -0.50, -0.29), equivalent to an annual rate loss of 1.79%/year (95%CI: -2.24, -1.30). Strength and rate of loss of strength were not significantly different between before versus after fracture (Table 3).

Subgroup analysis of those with different fracture types revealed that there were no significant differences in the absolute decline of muscle strength before and after fracture for all fracture types in both women and men (Table 4). However, among women with vertebral fracture, muscle strength after fracture was significantly lower than that before fracture while strength loss after fracture was significantly higher than the loss before fracture.

Muscle weakness as a predictor of post-fracture mortality risk

Survival probability was lowest in those whose muscle strength was in the lowest tertile of their gender matched group, regardless of fracture type (Figure 2).

In both genders, there were significant independent associations between lower muscle strength and post-fracture mortality risk as well as for advancing age, lower weight, lower FNBMD, lower BMI

and low levels of physical activity (Table 5). Lower height and history of falls were associated with increased risk of post-fracture mortality in women but not in men. Hypertension was protective against post-fracture mortality in men (Table 5).

After adjustment for age, the association between muscle strength and post-fracture mortality was attenuated but still significant. After adjustment for other risk factors, i.e. age, FNBMD, BMI, physical activity, smoking, history of falls and the illnesses, each SD lower muscle strength was associated with increased risk of post-fracture mortality of 19% [HR(95%CI):1.19 (1.05, 1.34)] in women and 39% [HR(95%CI): 1.39 (1.18, 1.64)] in men (Figure 3).

In the most parsimonious model, predictors of post-fracture mortality risk for women were low muscle strength, older age, low femoral neck BMD, low level of physical activity and rheumatoid arthritis. If all those predictors, except age which is un-modifiable, were all eliminated, 48% of the premature mortality in these women would be delayed [PAR_f (95%CI): 0.48 (0.25-0.65)]. By contrast, if only low muscle strength was eliminated while other predictors stayed the same, then 15% of the premature mortality among these women would be delayed [PAR_p (95%CI): 0.15 (0.05-0.24)]; suggesting that muscle weakness contributes to roughly one third of the premature mortality. In men, muscle strength and age remained in the most parsimonious model. As age is un-modifiable, we obtained PAR for muscle strength only. If low muscle strength was eliminated from these men, then 23% of premature deaths [PAR_p (95%CI): 0.23 (0.11-0.35)] would be deferred.

We also investigated the association between post-fracture mortality risk and muscle strength measured before and after fracture. In both men and women, muscle strength before and after fracture both were associated with mortality; however, the effect size for strength before fracture was larger than that for strength after fracture (Table 6). Full adjustment for all potential predictors was not conducted due to insufficient number of events per predictor.

Further analysis by fracture site revealed that, after adjusting for age, each SD decrease in MS was associated with an increase in the risk of mortality following vertebral and non-hip,

non-vertebral fractures for both men and women (Figure 4). However, this association was not observed for mortality following hip fractures. The adjustment for all possible risk factors was not conducted because of the small number of **deaths** in each subgroup following specific types of fracture.

Discussion

Post-fracture mortality remains a puzzle as debate centers on whether the relationship between fracture and mortality is causal. **In this study, we have demonstrated that muscle strength declined with advancing age, and low muscle strength was associated with an increased risk of post-fracture mortality. This association was independent of baseline femoral neck BMD, BMI, history of falls, smoking, physical activity, and the number and type of co-morbidities.**

Decline in skeletal muscle strength with advancing age in the general population has been previously reported,[6, 33] including in our previous study using the Dubbo Osteoporosis Epidemiology Study.[6] In that study we found that muscle strength at quadriceps declined at an annual rate of 1.6% for both older women and men. The current study extends the findings of the previous study by taking into account the fracture event so that the reduction in muscle strength can be compared before and after fracture. Interestingly, we have found that there was no difference in the annual loss of strength measured before and after fracture. Also, this finding did not differ between fracture types. The annual absolute loss was higher in men (0.39 kg/m) than in women (0.27 kg/m); however, as men had higher strength, they had an overall lower rate of relative loss than women (1.7% in men compared to 1.9% in women)

The underlining aetiology of skeletal muscle strength decline with advancing age is not well understood. One study showed that loss of muscle mass was a determinant of muscle strength reduction in older adults; however, gaining muscle mass did not prevent aging-related declines in muscle strength.[33)] Studies at the cellular and molecular levels have reported sex-specific structural alterations associated with aging. Men have been reported to have fewer fibers with large cross-section areas (CSA) while women showed reduced fiber size across the CSA range.[34] In addition,

the increase of isometric tension and myofilament lattice stiffness and the reduction of phosphorylation of the fast myosin regulatory light chain and myosin actin cross-bridge kinetics are age-related molecular changes which were most notable in women.[35] These sex-specific age-related alterations may explain in part the gender differences in the age-related reduction of muscle strength.

The association between low muscle strength and mortality risk has been well established for the general population.[12, 13, 36-38] In the present study, we specifically investigated this association in a cohort of those who had sustained a fragility fracture as previous studies have shown higher premature mortality risk in this population.[3, 8, 9] In a general population of those aged 80 and above years old, those with the highest tertile of handgrip strength had a 38% lower sex-adjusted risk of all caused mortality.[13])Our study has shown that each SD decrease in quadriceps strength was associated with increased risk of mortality after a fracture by28% in women and 36% in men after adjusting for age, FNBMD and co-morbidities. The contribution of muscle weakness to post-fracture mortality could be explained in part through a falls mechanisms as muscle weakness increases the risk of falls,[39] which in turn increases the risk of fracture and fracture-related premature mortality.[3, 9, 11] However, in this study, the whole cohort had suffered fractures and there was still a strong association between muscle weakness and premature mortality. Therefore, this association suggests a pathway independent of fracture. **Fall was a potential confounder as it is associated with both muscle strength and mortality. However, in the multivariable analysis, we found that fall did not alter the magnitude of association between low muscle strength and post-fracture mortality, suggesting that the association was independent off fall.**

This study, for the first time, has estimated the proportion of post-fracture mortality attributable to muscle weakness by using partial population attributable risk. Muscle weakness is attributable for 19% (95%CI: 0.11-0.27) of premature deaths after fracture in women and 27% (95%CI: 0.15-0.39) in men. From the public health perspective, an intervention which could significantly improve

muscle strength in those people to bring them to normal strength group may delay death for 2 out of every 10 women and 3 out of every 10 men.

The finding from this study provides insight into the gender difference in increased mortality risk after fragility fracture. It is well documented that while fragility fracture is less prevalent in older men than older women, mortality after fracture is more frequent in older men than in older women.[14, 15] In the present study, low muscle strength was associated with higher mortality risk and absolute strength loss is much greater in men than in women.

A novel feature of our study is that the association between muscle strength and mortality risk was examined following different types of fragility fractures. The age-adjusted association between muscle strength and mortality risk following vertebral or non-hip non-vertebral fractures was similar to that following all types of fracture. This may be explained by the finding that muscle strength and its annual rate loss did not differ between different types of fractures.

The mechanisms by which low muscle strength may be linked to increased post-fracture mortality are not known. In our **previous** study,[6] we reported that low muscle strength was associated with increased risk of fragility fracture. Hence, the increased risk of death following fragility fracture in those with low muscle strength may be due to low strength itself or due to an interaction between low strength and fracture. Thus, taking into account the impact of low muscle strength on fragility fracture and on mortality after a fragility fracture, an intervention to increase muscle strength in the older people may be a good target for both fracture and premature mortality risk reduction.

This study has several limitations. The participants were Caucasian so the findings may not be generalizable to different ethnicities. **The morbidity data were self-reported and this could potentially introduce misclassification bias into the analysis. Moreover, there was no information concerning disease severity which could compromise the estimate of the magnitude of association. The analysis did not take into account the possible effect of vitamin D which could also be a potential confounder.** The association between muscle strength and

mortality found was overall independent of other risk factors, though this was not examined in detail for the different types of fracture due to the small numbers of specific types of fracture.

In summary, muscle strength at quadriceps declines with advancing age but this reduction is not increased after a fragility fracture. Lower muscle strength is a determinant of premature mortality following a fragility fracture at all sites for both men and women, albeit not significantly for hip fracture in women. As low muscle strength is also associated with an increased risk of fragility fracture, early intervention to improve muscle strength in the older population may have an effect on reducing both fracture and premature mortality risk.

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Figure legends

Figure 1. Sampling frame

Figure 2. Survival probability after fracture stratified by tertiles of muscle strength. First, second and third tertiles are represented by solid, dashed and dotted lines, respectively. Upper panels contain data for women and lower panels for men. NHNV is non-hip, non-vertebral fracture. Cutoffs for the first tertile are 11.11 kg/m for women and 17.44 kg/m for men; for second tertile, cutoffs are 15.09 kg/m for women and 23.39 kg/m for men.

Figure 3. Association between risk factors and post-fracture mortality: multivariate Cox's regression analysis (Women: n = 889, 366 deaths; Men: n = 295, 150 deaths). The dots represent hazard ratios (HRs). The area between the whiskers represents the 95%CI. All HRs are per -5 kg/m (approximately one standard deviation) decrease in muscle strength. BMD: femoral neck bone mineral density. Multivariate HRs were adjusted for baseline age, FNBMD, BMI, history of fall, smoking, physical activity and illnesses. Upper panel is for women, lower panel is for men.

Figure 4. Association between quadriceps strength and risk of post-fracture mortality, stratified by gender: Cox's regression analysis in specific fracture types. Hazard ratios (HRs), 95%CI, and a HR of 1.0 are represented by dotted lines, area between whiskers and the dashed vertical line, respectively. All HRs are per -5 kg/m (approximately one standard deviation) decrease in muscle strength. NHNV: non-hip, non-vertebral fracture.

Tables

Table 1. Characteristics of women and men in pre- and post- fracture subgroups

	Women		**Men**	
	Pre-Fx	**Post-Fx**	**Pre-Fx**	**Post-Fx**
N	345	399	96	103
Age at baseline (years)	**71 (6)**	**72 (7)**	73 (6)	72 (6)
Height at baseline (m)	**1.60 (0.6)**	**1.59 (0.6)**	1.72 (0.6)	1.71 (0.7)
Weight at baseline (kg)	68 (13)	67 (13)	78 (12)	80 (13)
FNBMD at baseline (g/cm^2)	0.78 (0.12)	0.76 (0.12)	0.90 (0.14)	0.88 (0.14)
MS at baseline (kg/m)	**14.4 (4.4)**	**13.6 (4.7)**	21.8 (5.4)	21.0 (5.7)

Values are means (SD). FNBMD: Femoral neck bone mineral density. Fx: Fracture. MS: Muscle strength (quadriceps). The difference between pre- and post-fracture groups was tested by the independent Student's test. Bold-faced values indicate $P<0.05$ within sex. Baseline is the time of the first MS measurement for each group.

Table 2. Baseline **c**haracteristics of 889 women and 295 men in the study stratified by survival status

	Women		**Men**	
	Survivor	**Deceased**	**Survivor**	**Deceased**
N (%)	523 (58.8)	366 (41.2)	145 (49.2)	150 (50.9)
Age at baseline (years)	**69.7 (5.8)**	**75.9 (7.0)**	**70.6 (5.9)**	**75.3 (6.8)**
Height at baseline (m)	**1.60 (0.6)**	**1.58 (0.07)**	1.72 (0.7)	172 (0.06)
Weight at baseline (kg)	**69.6 (13.1)**	**63.2 (11.8)**	**81.7 (13.6)**	**76.5 (13.7)**
BMI (kg/m^2)	**27.2 (4.9)**	**25.4 (4.3)**	**27.6 (3.8)**	**25.9 (4.0)**
Physical activity (METs)*	**30.5 (2.3)**	**29.9 (2.8)**	31.5 (4.0)	30.6 (3.5)
FNBMD at baseline (g/cm^2)	**0.79 (0.11)**	**0.71 (0.13)**	**0.90 (0.14)**	**0.86 (0.16)**
MS at baseline (kg/m)	**13.9 (4.6)**	**12.2 (4.9)**	**21.3 (5.4)**	**19.1 (0.5)**
Smoking (yes,(%))	172 (32.9)	122 (33.3)	89 (61.4)	104 (69.3)
Fall (yes,(%))	239 (46.1)	188 (51.7)	59 (41.0)	58 (38.7)
Respiratory disease (yes,(%))	**82 (15.7)**	**40 (10.9)**	19 (13.1)	20 (13.3)
Hypertension (yes, (%))	274 (52.4)	191 (52.2)	76 (52.4)	61 (40.7)
Rheumatoid arthritis (yes, (%))	22 (4.21)	22 (6.0)	3 (2.1)	4 (2.7)
Neurological disease (yes, (%))	45 (8.6)	37 (10.1)	14 (9.7)	11 (7.3)
Cardiovascular disease (yes, (%))	161 (30.8)	124 (33.9)	61 (42.1)	71 (47.3)
Non-bone related cancer (yes, (%))	63 (12.1)	34 (9.3)	13 (9.0)	11 (7.3)
Diabetes (yes, (%))	53 (10.1)	29 (7.9)	**24 (16.6)**	**13 (8.7)**
Number of illness (yes, (%))				
0	225 (43.0)	168 (45.9)	45 (31.0)	49 (32.7)
1	197 (37.7)	126 (34.4)	70 (48.3)	75 (50.0)
2	76 (14.5)	57 (15.6)	26 (17.9)	23 (15.3)

≥ 3	25 (4.8)	15 (4.1)	4 (2.76)	3 (2.0)

Values are means (SD), unless otherwise specified. The difference between survivors and deceased was tested by the independent Student's test (for continuous data) and chi-square test (for categorical data). FNBMD: Femoral neck bone mineral density; MS: Muscle strength (quadriceps). BMI: body mass index. METs: metabolic equivalents. Bold-faced values indicate $P<0.05$ within sex.

Table 3. Muscle strength and change in muscle strength

	Pre-fracture muscle strength	**Post-fracture muscle strength**
Women (N)	**344**	**407**
MS at age 70 (kg/m)	14.6 (14.1, 15.0)	14.3 (13.9, 14.7)
Annual change (kg/m)	-0.27 (-0.32, -0.23)	-0.26 (-0.29, -0.22)
Annual rate of change (%)	-1.85 (-2.20, -1.57)	-1.82 (-2.03, -1.53)
Men (N)	**99**	**105**
MS at age 70 (kg/m)	22.3 (21.3, 23.3)	21.7 (20.7, 22.7)
Annual change (kg/m)	-0.40 (-0.50, -0.29)	-0.44 (-0.54, -0.35)
Annual rate of change (%)	-1.79 (-2.24, -1.30)	-2.02 (-2.49, -1.61)

MS: muscle strength. Values in brackets are 95% confidence interval.

Table 4. Differences between muscle strength and change in muscle strength before and after fracture stratified by fracture type

	Hip fracture	Vertebral fracture	NHNV fracture
Women (N)	63	233	382
Difference in MS at age 70 (kg/m)	1.97 (-0.87, 4.80)	**-1.12 (-2.07, - 0.17)**	0.51 (-0.12, 1.14)
Difference in annual change (kg/m)	-0.14 (-0.38, 0.10)	**0.12 (-0.01, 0.22)**	0.01 (-0.08, 0.06)
Men (N)	20	61	106
Difference in MS at age 70 (kg/m)	-2.15 (-8.25, 3.36)	-0.84 (-3.46, 1.78)	1.36 (-0.45, 3.16)
Difference in annual change (kg/m)	0.09 (-0.50, 0.67)	0.12 (-0.13, 0.36)	-0.08 (-0.28, 0.11)

MS: muscle strength (quadriceps). NHNV: non-hip, non-vertebral. Values in brackets are 95% confidence interval. Bold face indicates $P < 0.05$.

Table 5. Association between risk factors and post-fracture mortality: univariate Cox's regression analysis (Women: *n* = 889, 366 deaths; Men: *n* = 295, 150 deaths)

Variables	Unit	**Women**	**Men**
		Hazard ratio (95%CI)	Hazard ratio (95%CI)
MS at baseline	-5 (kg/m)	**1.58 (1.42-1.76)**	**1.54 (1.34-1.77)**
Age at baseline	+5 year	**1.86 (1.72-2.01)**	**1.68 (1.49-1.90)**
Height at baseline	-6 cm	**1.37 (1.24-1.51)**	1.12 (0.97-1.30)
Weight at baseline	-13 kg	**1.48 (1.31-1.67)**	**1.25 (1.06-1.48)**
BMI	-4 kg/m^2	**1.22 (1.11-1.35)**	**1.24 (1.04-1.48)**
Physical activity	-4 METs	**1.67 (1.37-2.04)**	**1.30 (1.05-1.60)**
FNBMD at baseline	-0.14 g/cm^2	**1.93 (1.69-2.20)**	**1.22 (1.06-1.42)**
Smoking	(yes)	1.06 (0.86-1.32)	1.29 (0.91-1.82)
Fall history	(yes)	**1.43 (1.16-1.75)**	1.12 (0.81-1.56)
Respiratory disease	(yes)	0.72 (0.52-1.01)	0.98 (0.61 -1.57)
Hypertension	(yes)	0.88 (0.72-1.09)	**0.65 (0.47-0.90)**
Rheumatoid arthritis	(yes)	1.38 (0.89-2.12)	1.08 (0.40-2.92)
Neurological disease	(yes)	1.02 (0.73-1.43)	0.94 (0.51-1.73)
Cardiovascular disease	(yes)	0.95 (0.76-1.17)	0.98 (0.71-1.34)
Bone-unrelated cancer	(yes)	0.86 (0.60-1.22)	0.78 (0.42-1.45)
Diabetes	(yes)	0.86 (0.59-1.26)	0.79 (0.44-1.40)
Number of illness *	(yes)		
1		0.80 (0.64-1.01)	0.90 (0.62-1.29)
2		0.87 (0.65-1.18)	0.80 (0.48-1.32)
≥ 3		0.79 (0.46-1.34)	0.88 (0.27-2.82)

* Compare to those without any co-morbidity. FNBMD: Femoral neck bone mineral density. MS: Muscle strength (quadriceps). BMI: body mass index. METs: metabolic equivalents. Bold-faced values indicate $P<0.05$.

Table 6. Association between pre- and post-fracture muscle strength and risk of post-fracture mortality, stratified by gender: Cox's regression analysis (women with MS measured before fracture: *n* = 463, 193 deaths; women with MS measured after fracture: *n* = 426, 173 deaths; men with MS measured before fracture: *n* = 147, 82 deaths; men with MS measured after fracture: *n* = 148, 68 deaths)

	Women		**Men**	
	Hazard ratio (95%CI) for pre-fracture muscle strength	Hazard ratio (95%CI) for post-fracture muscle strength	Hazard ratio (95%CI) for pre-fracture muscle strength	Hazard ratio (95%CI) for post-fracture muscle strength
Univariate	**1.53 (1.29-1.80)**	**1.53 (1.32-1.77)**	**1.46 (1.19-1.79)**	**1.60 (1.32-1.94)**
Age adjusted	**1.31 (1.10-1.55)**	**1.23 (1.05-1.43)**	**1.31 (1.08-1.61)**	**1.50 (1.23-1.83)**
Age and BMD adjusted	**1.27 (1.07-1.50)**	**1.18 (1.01-1.38)**	**1.33 (1.09-1.63)**	**1.43 (1.16-1.78)**

Hazard ratio is per -5 kg/m (approximately one standard deviation) decrease in quadriceps muscle strength. BMD: femoral neck bone mineral density. Bold-faced values indicate P<0.05.

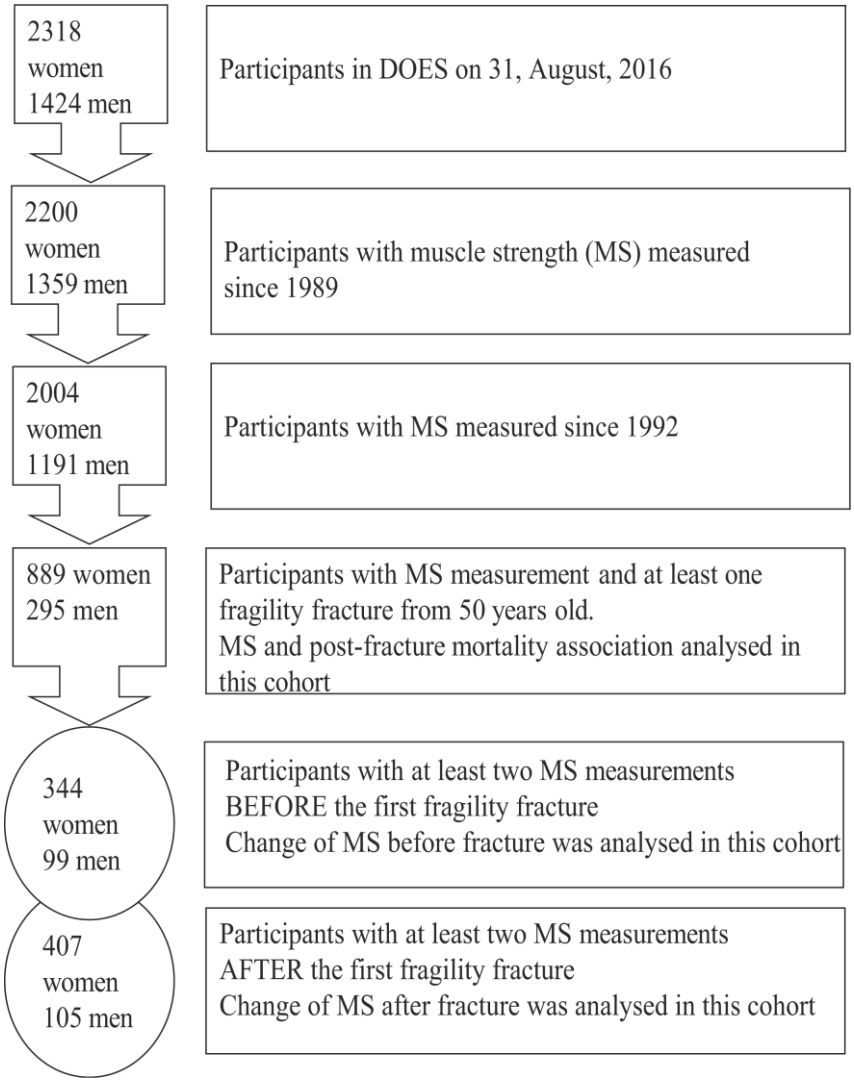

Figure 1

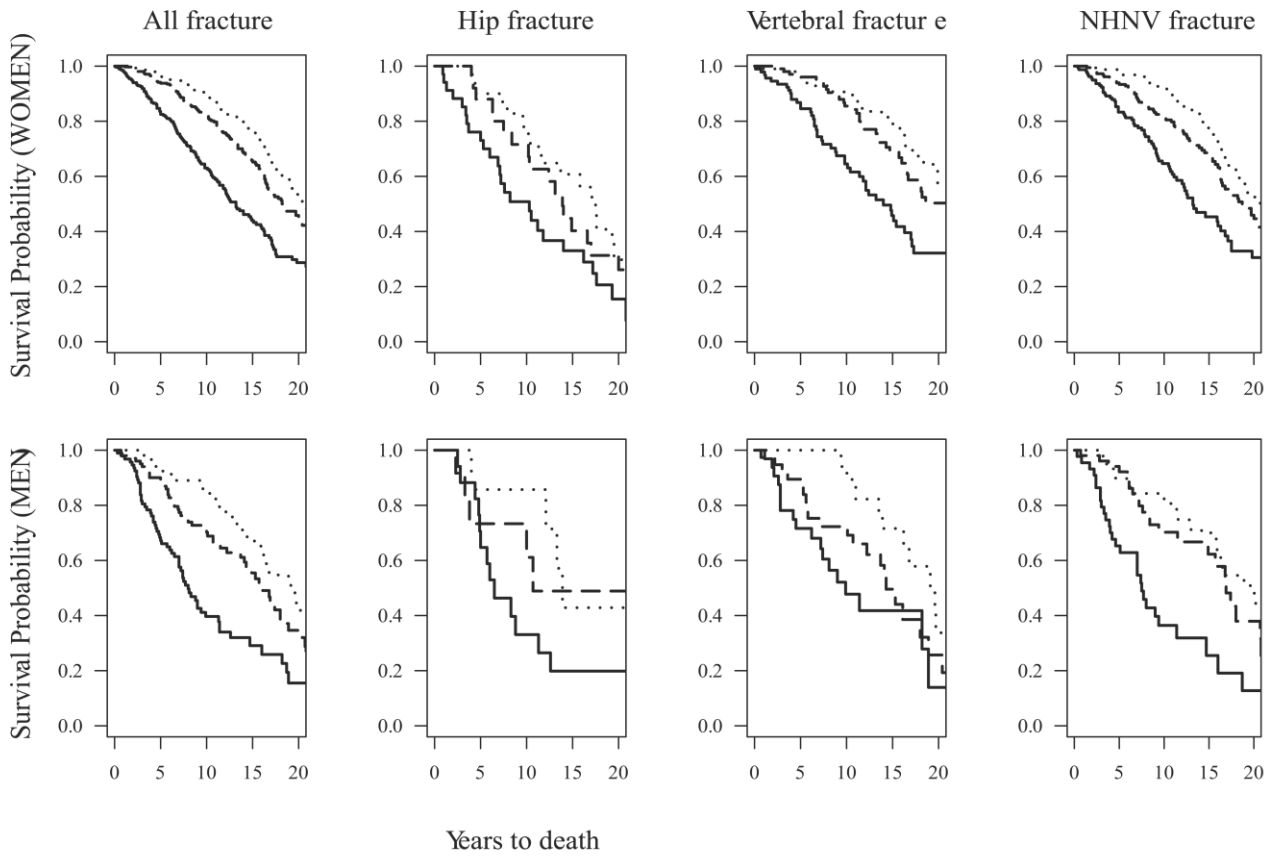

Figure 2

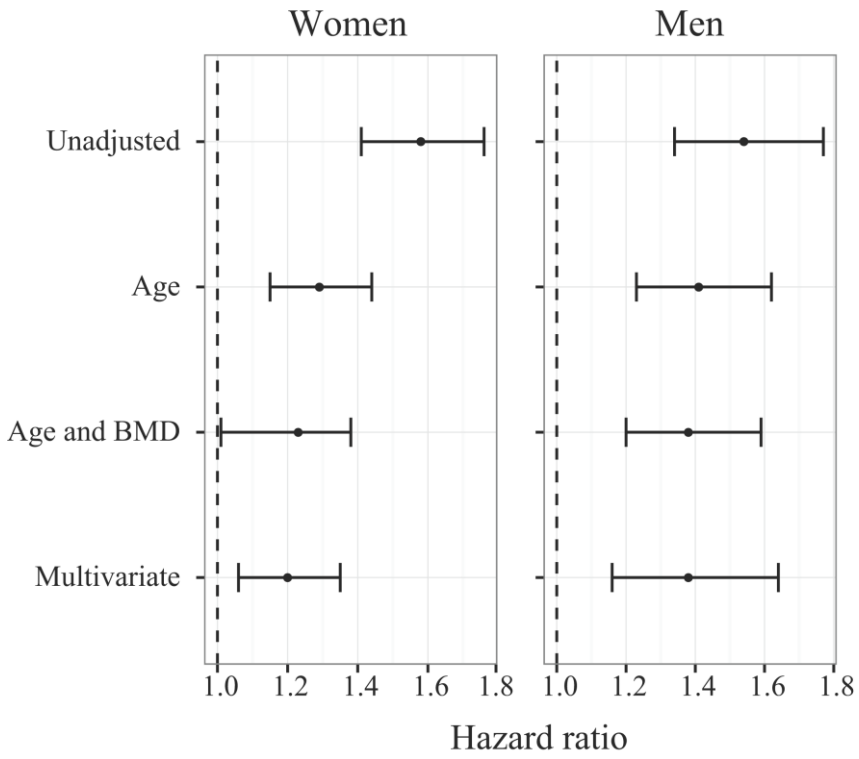

Figure 3

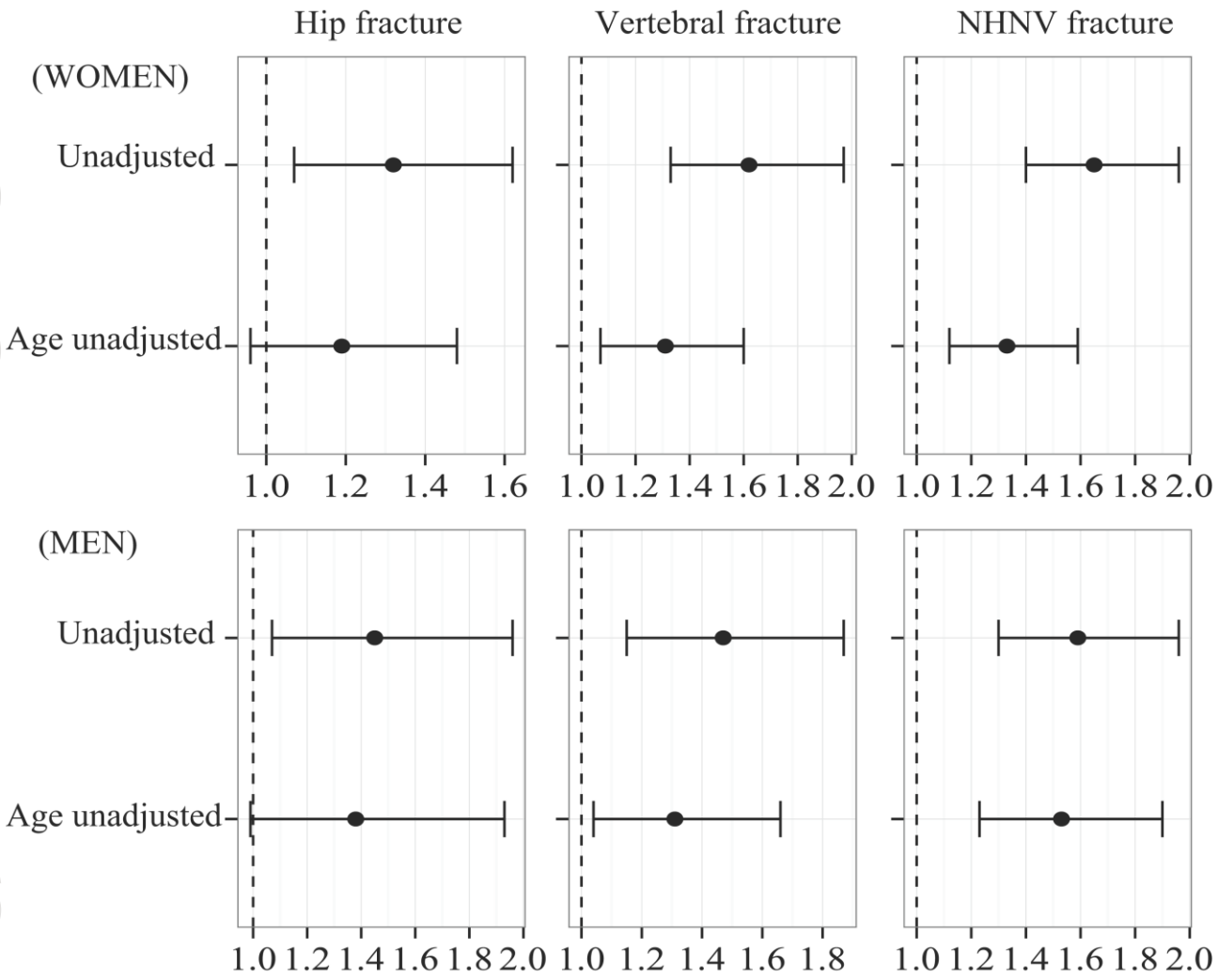

Figure 4