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ABSTRACT

Measures of muscle mass, strength, and function predict risk of incident fractures, but it is not known whether this risk information is additive to that from FRAX (fracture risk assessment tool) probability. In the Osteoporotic Fractures in Men (MrOS) Study cohorts (Sweden, Hong Kong, United States), we investigated whether measures of physical performance/appendicular lean mass (ALM) by DXA predicted incident fractures in older men, independently of FRAX probability. Baseline information included falls history, clinical risk factors for falls and fractures, femoral neck aBMD, and calculated FRAX probabilities. An extension of Poisson regression was used to investigate the relationship between time for five chair stands, walking speed over a 6 m distance, grip strength, ALM adjusted for body size (ALM/height²), FRAX probability (major osteoporotic fracture [MOF]) with or without femoral neck aBMD, available in a subset of n = 7531), and incident MOF (hip, clinical vertebral, wrist, or proximal humerus). Associations were adjusted for age and time since baseline, and are reported as hazard ratios (HRs) for first incident fracture per SD increment in predictor using meta-analysis. 5660 men in the United States (mean age 73.5 years), 2764 men in Sweden (75.4 years), and 1987 men in Hong Kong (72.4 years) were studied. Mean follow-up time was 8.7 to 10.9 years. Greater time for five chair stands was associated with greater risk of MOF (HR 1.26; 95% CI, 1.19 to 1.34), whereas greater walking speed (HR 0.85; 95% CI, 0.79 to 0.90), grip strength (HR 0.77; 95% CI, 0.72 to 0.82), and ALM/height² (HR 0.85; 95% CI, 0.80 to 0.90) were associated with lower risk of incident MOF. Associations remained largely similar after adjustment for FRAX, but associations between ALM/height² and MOF were weakened (HR 0.92; 95% CI, 0.85 to 0.99). Inclusion of femoral neck aBMD markedly attenuated the association between ALM/height² and MOF (HR 1.02; 95% CI, 0.96 to 1.10). Measures of physical performance predicted incident fractures independently of FRAX probability. Whilst the predictive value of ALM/height² was
Introduction

The place of falls as a major risk factor for fracture is well established; the majority of hip fractures occur as a result of a fall from standing height or less.\(^\text{1,2}\) There is also substantial evidence that risk factors related specifically to falls risk, such as physical performance, function, and muscle indices, are also related to the risk of incident fracture.\(^\text{3–5}\) Current clinical approaches to risk assessment are increasingly based on clinical risk factors, with or without aBMD, through fracture risk calculators. FRAX (fracture risk assessment tool) is the most commonly used fracture risk assessment tool worldwide,\(^\text{6}\) but unlike other tools such as QFracture or the GARVAN calculator,\(^\text{7–9}\) it does not include falls as a specific input risk factor\(^\text{2,10}\) because of the inconsistent data across the 12 derivation and 11 validation cohorts.\(^\text{11}\) We have previously demonstrated that prior falls predict the risk of incident falls\(^\text{12}\) and fractures\(^\text{13}\) independently of FRAX probability. Although the predictive value of falls-related risk factors for incident fracture have been demonstrated individually,\(^\text{4,5}\) it has not been established whether specific falls risk factors, such as physical performance, might give information independent of the reporting of prior falls themselves. We therefore undertook a meta-analysis of the three Osteoporotic Fractures in Men (MrOS) cohorts (United States, Sweden, Hong Kong) to investigate whether the predictive value of four measures (time for five chair stands, walking speed over a distance of 6 m, grip strength, and appendicular lean mass [ALM]) for incident fracture was independent of FRAX probability, history of falls, or aBMD.

Subjects and Methods

Participants

Details of the MrOS cohort studies have been published previously.\(^\text{12–15}\) Briefly, MrOS is a multicenter study of community-dwelling men aged 65 years or older from three countries, recruited and evaluated using similar criteria. To be eligible for the study, subjects had to be able to walk without aid. In the MrOS Hong Kong study, 2000 Chinese men, aged 65 to 92 years, were enrolled between August 2001 and February 2003.\(^\text{16}\) All were Hong Kong residents of Asian ethnicity. Stratified sampling was adopted to ensure that 33% of subjects were included in each of the following age groups: 65 to 69, 70 to 74, and ≥75 years. Recruitment notices were placed in housing estates and community centers for the elderly. In the MrOS Sweden study, 3014 men, aged 69 to 81 years, were enrolled between October 2001 and December 2004.\(^\text{12,17}\) The cohort comprised men from the cities of Malmö, Gothenburg, and Uppsala, identified and recruited using national population registers. More than 99% were of Caucasian ethnicity. The participation rate in the MrOS Sweden study was 45%. In the MrOS United States study, 5994 men, aged 65 to 100 years, were enrolled at six sites between March 2000 and April 2002.\(^\text{18,19}\) Each US clinical site designed and customized strategies to enhance recruitment of its population. Common strategies included mailings from the Department of Motor Vehicles, voter registration and participant databases, common seniors’ newspaper features and advertisements, and targeted presentations. Self-defined racial/ethnic ancestry was ascertained through questionnaires at baseline.

Exposure variables

At baseline, height (cm) and weight (kg) were measured, and BMI was calculated as kg/m\(^2\). The international MrOS questionnaire\(^\text{18}\) was administered at baseline to collect information about current smoking habits, number and type of medications, fracture history, family history of hip fracture, past medical history (rheumatoid arthritis), and high consumption of alcohol (three or more glasses of alcohol-containing drinks per day), calculated from the reported frequency and amount of alcohol use. Previous fracture at baseline was documented as all fractures after the age of 50 years regardless of trauma. Glucocorticoid exposure was documented in MrOS as at least 3 times per week in the month preceding the baseline assessment. Apart from glucocorticoid use and rheumatoid arthritis (both FRAX input variables), there was no information on secondary causes of osteoporosis and the “Secondary Osteoporosis” input variable for FRAX probability calculation was set to “No” for all men. Self-reported falls during the 12 months preceding the baseline were recorded by questionnaire (past falls). Time for five chair stands, walking speed over 6 m (at usual pace), and grip strength using JAMAR dynamometers (Sammons Preston Rolyan, Bolingbrook, IL, USA) were assessed at the baseline visit. Areal bone mineral density (aBMD) was measured at the femoral neck and ALM from whole body scans using Hologic QDR 4500 A or W (Hologic, Bedford, MA, USA) or Lunar Prodigy (GE Lunar Corp., Madison, WI, USA) depending on the center, with cross calibration of instruments for aBMD. A T-score was calculated using NHANES (National Health and Nutrition Examination Survey) young women as a reference value.\(^\text{20,21}\) A 10-year probability of fracture (FRAX major osteoporotic fracture: hip, humerus, vertebral, or forearm sites) was calculated using the clinical risk factors described above, with and without femoral neck aBMD entered into country-specific FRAX models.

Fracture and death outcomes

Hong Kong.\(^\text{22}\) Incident fractures were captured via subject follow-up through a phone call or a visit to the research center. All fracture sites (hip, wrist, skull/face, ribs, shoulder, arm, wrist, vertebra, tibia, fibula, foot, metatarsal toes, hand, fingers, and pelvis) were recorded. Pathological fractures were excluded. All incident fractures reported by participants were then confirmed by X-rays or medical records. Deaths were verified by death certificates.

Sweden.\(^\text{23}\) Central registers covering all Swedish citizens were used to identify the subjects and the time of death for all
subjects who died during the study; these analyses were performed after the time of fracture validation. At the time of fracture evaluation, the computerized X-ray archives in Malmö, Gothenburg, and Uppsala were searched for new fractures occurring after the baseline visit using the unique personal registration number allocated to every Swedish citizen. All additional fractures reported by the study subject after the baseline visit were confirmed by physician review of radiology reports. Fractures reported by the study subject, but not confirmed by radiographic report, were not included.

United States:$^{118}$ If a participant reported a fracture, study staff conducted a follow-up telephone interview to determine the date and time the fracture had occurred, a description of how the fracture occurred, the type of trauma that resulted in the fracture, the participant’s location and activities at the time of the fracture, symptoms just before or coincident with the fracture, and source of medical care for the fracture. All reported fractures were centrally verified by a physician adjudicator through medical records obtained from the participant’s physician. Deaths were verified through state death certificates.

Statistical methods

Clinical outcomes comprised any fracture, osteoporotic fracture (defined according to Kanis et al., 2001$^{24}$ as clinical vertebral, ribs, pelvis, humerus, clavicle, scapula, sternum, hip, other femoral fractures, tibia, fibula, distal forearm/wrist), major osteoporotic fracture (MOF: hip, clinical vertebral, humerus, or wrist/forearm), and hip fracture. An extension of Poisson regression models$^{255}$ was used to study the association between predictors, FRAX, prior falls, aBMD, and the future risk of fracture. All associations were adjusted for age and time since baseline. In contrast to logistic regression, the Poisson regression uses the length of each individual’s follow-up period and the hazard function is assumed to be $\exp(\beta_0 + \beta_1 \times \text{current time from baseline} + \beta_2 \times \text{current age} + \beta_3 \times \text{variable of interest})$. The observation period of each participant was divided into intervals of one month. One fracture per person and time to the first fracture were counted; events were censored if they occurred after the time of first fracture, loss to follow-up, death, or end of follow-up. To correct for body size, ALM for each individual was divided by the square of their height. We initially investigated the predictive value of each of the four exposures (chair stand time, walking speed, grip strength, appendicular lean mass, and incident fracture risk).

Associations between chair stand time, walking speed, grip strength, appendicular lean mass, and incident fracture risk

Table 2 summarizes the associations between each of the four predictors (chair stand time, walking speed, grip strength, and ALM divided by height$^2$, adjusted only for age and follow-up time), and the fracture outcomes. Thus, across all cohorts, greater time for five chair stands was associated with a greater risk of MOF (HR 1.26; 95% CI, 1.19 to 1.34), whereas greater walking speed (HR 0.85; 95% CI, 0.79 to 0.90), grip strength (HR 0.77; 95% CI, 0.72 to 0.82) and ALM/height$^2$ (HR 0.85; 95% CI, 0.80 to 0.90) were associated with a lower risk of incident MOF. Results for any fracture, osteoporotic fracture, and hip fracture outcomes were very similar, as were associations by cohort.

Independent predictive value of exposures after adjustment for prior falls or FRAX probability

The results of models additionally including prior fall or FRAX (MOF with or without aBMD) are documented in Table 3. The associations between each of the four exposures and any of the fracture outcomes remained very similar with adjustment for prior falls. The inclusion of FRAX (MOF without aBMD (using the subset of 7531 for whom FRAX probability could be calculated)) very slightly attenuated the magnitude of the HRs; in contrast, although inclusion of FRAX (MOF with aBMD) led to a modest attenuation of HRs in general, those for any fracture (HR 0.95; 95% CI, 0.90 to 1.01) and osteoporotic fracture (HR 0.95; 95% CI, 0.89 to 1.01) with ALM/height$^2$ became nonsignificant, and that between ALM/height$^2$ and MOF was also attenuated (HR 0.92; 95% CI, 0.85 to 0.99). Adjustment for BMI or physical activity also did not materially alter the magnitude of the relationships and associations for ALM were similar to those for ALM/height$^2$. However, with ALM/BMI as the exposure, the patterns were again of similar direction, but were attenuated such that none of the models achieved statistical significance (summarized in Supplementary Table 1).
Table 1. Baseline Characteristics and Fracture Outcomes of Study Participants by Country

|                      | Hong Kong | Sweden | USA   |
|----------------------|-----------|--------|-------|
| Proportion of whole cohort | 99%       | 92%    | 94%   |
| n                     | 1987      | 2764   | 5660  |
| Person-years          | 19,592    | 24,102 | 61,456|
| Age [mean (range)], years | 72.4 (65–92) | 75.4 (70–81) | 73.5 (64–100) |
| BMI                   | 23.5 ± 3.1| 26.3 ± 3.5 | 27.4 ± 3.8 |
| Previous fracture     | 14%       | 35%    | 22%   |
| Family history hip fracture | 5%     | 13%    | 17%   |
| Smoker                | 12%       | 8%     | 3%    |
| Glucocorticoids       | 1%        | 2%     | 2%    |
| Rheumatoid arthritis  | 1%        | 1%     | 5%    |
| Excess alcohol        | 1%        | 2%     | 4%    |
| aBMD FN T-score       | −1.4 ± 0.9 | −0.9 ± 1.0 | −0.6 ± 1.1 |
| Time 5 stands (s)     | 12.7 ± 3.9 | 13.4 ± 4.2 | 11.1 ± 3.3 |
| Walk speed (m/s)      | 1.0 ± 0.2 | 1.3 ± 0.3 | 1.2 ± 0.2 |
| Fall                  | 15%       | 16%    | 20%   |
| Grip strength (kg)    | 33.9 ± 6.7 | 43.1 ± 7.8 | 41.8 ± 8.4 |
| ALM (kg)              | 20.2 ± 2.8 | 24.3 ± 3.2 | 24.3 ± 3.5 |
| Height (cm)           | 163 ± 5.7 | 175 ± 6.5 | 174 ± 6.8 |
| ALM/height²           | 7.6 ± 0.9 | 7.9 ± 0.8 | 8.0 ± 0.9 |
| FRAX MOF without aBMD | 6.9 ± 2.9 | 13.5 ± 6.1 | 9.1 ± 4.8 |
| FRAX hip without aBMD | 3.4 ± 2.5 | 7.5 ± 5.5 | 3.6 ± 3.9 |
| FRAX MOF with aBMD    | 6.6 ± 3.2 | 11.4 ± 6.7 | 7.8 ± 4.5 |
| FRAX hip with aBMD    | 3.0 ± 2.6 | 5.5 ± 6.0 | 2.4 ± 3.4 |
| FU (hip fx: mean (SD), years) | 9.9 (2.8) | 8.7 (2.9) | 10.9 (3.8) |
| Any fx                | 11%       | 22%    | 19%   |
| Osteoporotic fx       | 9%        | 19%    | 15%   |
| MOF fx                | 7%        | 16%    | 10%   |
| OWH fx (MOF)          | 4%        | 12%    | 5%    |
| Hip fx                | 3%        | 7%     | 4%    |

Data are hazard ratios (HRs) for fracture (fx) per 1 SD increase in predictor (HR/SD), adjusted for age and follow-up time. Statistically significant associations (p < 0.05) are in bold.

FN = femoral neck; ALM = appendicular lean mass; FU = follow-up; FRAX = fracture risk assessment tool; fx = fracture; MOF = major osteoporotic fracture; OWH = osteoporotic fracture without hip fracture.

Table 2. Associations Between Exposures and Risk of Incident Fracture

|                      | Any fx          | Ost fx          | MOF fx           | Hip fx           |
|----------------------|-----------------|-----------------|------------------|------------------|
| Time 5 chair stands  |                 |                 |                  |                  |
| HK                   | 1.13 (0.99, 1.30) | 1.19 (1.02, 1.38) | 1.24 (1.04, 1.46) | 1.20 (0.93, 1.55) |
| SW                   | 1.14 (1.06, 1.24) | 1.21 (1.11, 1.31) | 1.21 (1.10, 1.33) | 1.38 (1.19, 1.60) |
| US                   | 1.17 (1.10, 1.24) | 1.18 (1.10, 1.26) | 1.20 (1.10, 1.42) | 1.38 (1.21, 1.58) |
| Total                | 1.15 (1.10, 1.21) | 1.19 (1.13, 1.25) | 1.26 (1.19, 1.34) | 1.36 (1.24, 1.49) |
| Walking speed        |                 |                 |                  |                  |
| HK                   | 0.84 (0.73, 0.97) | 0.80 (0.68, 0.94) | 0.78 (0.65, 0.93) | 0.57 (0.44, 0.75) |
| SW                   | 0.86 (0.79, 0.93) | 0.84 (0.77, 0.91) | 0.84 (0.76, 0.92) | 0.72 (0.62, 0.84) |
| US                   | 0.95 (0.89, 1.02) | 0.93 (0.86, 1.00) | 0.87 (0.79, 0.95) | 0.73 (0.63, 0.84) |
| Total                | 0.91 (0.86, 0.95) | 0.88 (0.83, 0.93) | 0.85 (0.79, 0.90) | 0.70 (0.64, 0.77) |
| Grip strength        |                 |                 |                  |                  |
| HK                   | 0.76 (0.66, 0.88) | 0.77 (0.66, 0.91) | 0.75 (0.63, 0.90) | 0.71 (0.54, 0.93) |
| SW                   | 0.79 (0.73, 0.86) | 0.78 (0.71, 0.85) | 0.76 (0.69, 0.84) | 0.69 (0.59, 0.80) |
| US                   | 0.86 (0.81, 0.92) | 0.80 (0.74, 0.86) | 0.78 (0.71, 0.86) | 0.74 (0.64, 0.86) |
| Total                | 0.83 (0.79, 0.86) | 0.79 (0.75, 0.83) | 0.77 (0.72, 0.82) | 0.72 (0.65, 0.79) |
| ALM/Height²          |                 |                 |                  |                  |
| HK                   | 0.88 (0.76, 1.01) | 0.84 (0.72, 0.99) | 0.82 (0.69, 0.98) | 0.74 (0.56, 0.97) |
| SW                   | 0.85 (0.78, 0.92) | 0.84 (0.76, 0.91) | 0.82 (0.75, 0.91) | 0.84 (0.72, 0.98) |
| US                   | 0.91 (0.85, 0.96) | 0.92 (0.85, 0.99) | 0.89 (0.81, 0.97) | 0.91 (0.79, 1.04) |
| Total                | 0.89 (0.84, 0.93) | 0.88 (0.83, 0.93) | 0.85 (0.80, 0.90) | 0.86 (0.78, 0.95) |

Data are hazard ratios (HRs) for fracture (fx) per 1 SD increase in predictor (HR/SD), adjusted for age and follow-up time. Statistically significant associations (p < 0.05) are in bold.

HK = Hong Kong; SW = Sweden; US = United States; fx = fracture; Ost = osteoporotic; MOF = major osteoporotic fracture.
Independent predictive value of exposures after adjustment for femoral neck aBMD

Inclusion of femoral neck aBMD T-score (Table 3) had a very modest attenuating effect on predictive value of chair stand time, walking speed, and grip strength, but completely removed associations between ALM/height and fracture reported in previous studies are mixed, with no association between ALM/height and fracture. The associations we have observed are consistent with those for femoral neck aBMD directly, or as part of FRAX, markedly attenuated (albeit with a slightly attenuated effect size), the inclusion of aBMD without femoral neck aBMD, femoral neck aBMD. Statistically significant associations (p < 0.05) are in bold.

fx = fracture; Ost = osteoporotic; MOF = major osteoporotic fracture; FU = follow-up; FRAX = fracture risk assessment tool; FN = femoral neck.

Interactions with age and follow-up time

In models incorporating age or follow-up time as interaction terms, there was no evidence that either variable influenced the predictive value of any of the four exposures. Thus, for chair stand time, the HR for any fracture was 1.08 (95% CI, 0.98 to 1.19) at age 70 years and 1.15 (95% CI, 1.08 to 1.21) at 80 years, p interaction = 0.12. The HR for any fracture with walking speed was 0.88 (95% CI, 0.81 to 0.95) at 1 year after baseline and 0.89 (95% CI, 0.87 to 1.01) at 10 years after baseline, p interaction = 0.28. All other interaction terms were p > 0.30.

Discussion

We have demonstrated, in this large population cohort of older men, that physical performance (chair stand time, walking speed, grip strength) and ALM predict incident fracture risk independently of FRAX probability and history of prior falls. Though chair stand time, walking speed, and grip strength also predicted fracture risk independently of femoral neck aBMD

Table 3. Associations Between Exposures and Risk of Incident Fracture

| Exposure (SD) | Adjustment | Any fx | Ost fx | MOF fx | Hip fx |
|--------------|------------|--------|--------|--------|--------|
| Time 5 chair stands | Age, FU time | 1.15 (1.10, 1.21) | 1.19 (1.13, 1.25) | 1.26 (1.19, 1.34) | 1.36 (1.24, 1.49) |
| + prior falls | 1.15 (1.09, 1.20) | 1.18 (1.12, 1.24) | 1.24 (1.17, 1.31) | 1.34 (1.23, 1.47) |
| or + FRAX wo aBMD | 1.13 (1.07, 1.20) | 1.17 (1.10, 1.24) | 1.26 (1.17, 1.35) | 1.31 (1.17, 1.46) |
| or + FRAX with aBMD | 1.12 (1.06, 1.19) | 1.16 (1.09, 1.23) | 1.24 (1.15, 1.34) | 1.29 (1.15, 1.44) |
| or + FN aBMD | 1.16 (1.11, 1.21) | 1.19 (1.13, 1.25) | 1.26 (1.19, 1.34) | 1.35 (1.23, 1.48) |

Walking speed

| Age, FU time | 0.91 (0.86, 0.95) | 0.88 (0.83, 0.93) | 0.85 (0.79, 0.90) | 0.70 (0.64, 0.77) |
| + prior falls | 0.91 (0.87, 0.95) | 0.88 (0.83, 0.93) | 0.85 (0.80, 0.90) | 0.71 (0.65, 0.79) |
| or + FRAX wo aBMD | 0.88 (0.83, 0.93) | 0.85 (0.80, 0.91) | 0.82 (0.76, 0.88) | 0.70 (0.62, 0.78) |
| or + FRAX with aBMD | 0.89 (0.84, 0.95) | 0.85 (0.80, 0.91) | 0.83 (0.77, 0.90) | 0.71 (0.63, 0.80) |
| or + FN aBMD | 0.90 (0.86, 0.94) | 0.87 (0.83, 0.92) | 0.84 (0.79, 0.89) | 0.71 (0.65, 0.78) |

Grip strength

| Age, FU time | 0.83 (0.79, 0.86) | 0.79 (0.75, 0.83) | 0.77 (0.72, 0.82) | 0.72 (0.65, 0.79) |
| + prior falls | 0.83 (0.79, 0.88) | 0.79 (0.75, 0.84) | 0.78 (0.73, 0.83) | 0.72 (0.65, 0.80) |
| or + FRAX wo aBMD | 0.84 (0.79, 0.89) | 0.81 (0.76, 0.87) | 0.79 (0.73, 0.85) | 0.74 (0.66, 0.84) |
| or + FRAX with aBMD | 0.85 (0.80, 0.90) | 0.83 (0.77, 0.89) | 0.81 (0.75, 0.87) | 0.76 (0.68, 0.86) |
| or + FN aBMD | 0.86 (0.82, 0.90) | 0.83 (0.78, 0.88) | 0.82 (0.77, 0.87) | 0.79 (0.71, 0.87) |

ALM/Height

| Age, FU time | 0.89 (0.84, 0.93) | 0.88 (0.83, 0.93) | 0.85 (0.80, 0.90) | 0.86 (0.78, 0.95) |
| + prior falls | 0.88 (0.84, 0.93) | 0.88 (0.83, 0.93) | 0.86 (0.80, 0.91) | 0.86 (0.78, 0.95) |
| or + FRAX wo aBMD | 0.93 (0.88, 0.99) | 0.93 (0.87, 0.99) | 0.89 (0.82, 0.96) | 0.91 (0.81, 1.02) |
| or + FRAX with aBMD | 0.95 (0.90, 1.01) | 0.95 (0.89, 1.01) | 0.92 (0.85, 0.99) | 0.95 (0.85, 1.07) |
| or + FN aBMD | 1.01 (0.96, 1.06) | 1.02 (0.96, 1.08) | 1.02 (0.96, 1.10) | 1.12 (1.01, 1.23) |

Data are hazard ratios (HRs) for fracture (fx) per 1 SD change in predictor (HR/SD), adjusted for age, follow-up time, and additional adjustment for either prior falls, FRAX MOF without femoral neck aBMD, FRAX MOF with femoral neck aBMD, femoral neck aBMD. Statistically significant associations (p < 0.05) are in bold.

test
same instrument, namely DXA, and were moderately correlated with a Pearson correlation coefficient ranging from 0.29 (USA) to 0.43 (Hong Kong). It is well established that soft tissue can influence the measurement of aBMD, potentially through a magnification artifact associated with a thicker body where BMI is higher, and through altered edge detection. This phenomenon has been particularly discussed in terms of adipose tissue; the effect of muscle mass, which is not specifically measured by DXA (it is derived as the tissue that is not fat or bone), has been much less thoroughly considered. Interestingly, the effect was very similar when ALM rather than ALM/height$^2$ was used (data not shown), suggesting that it is not solely a result of size adjustment, although both ALM and ALM/height$^2$ are strongly related to body size. The marked attenuation of associations using ALM/BMI is likely to be a consequence of ALM being a component of body weight (together with fat mass and bone mass), with BMI calculated as weight divided by height squared. Importantly, aBMD is calculated from equations incorporating soft tissue mass; thus the possibility of measurement artifact must be considered. Assessment of muscle using an alternative modality, such as pQCT, might offer a potential route to clarification of this issue.

We studied three well-characterized cohorts drawn from general populations with standardized assessments and prospective recording of fractures. However, there are some limitations that should be considered in the interpretation of our findings. First, the population studied was male, and of a narrow age range (64 to 99 years), thus limiting the generalizability of our findings. Second, the definition of glucocorticoid use differed from those usually specified for incorporation into FRAX. Third, there was no information on causes of secondary osteoporosis (other than rheumatoid arthritis and glucocorticoids), and this variable was therefore set to null. The effect of these considerations on our findings is uncertain, but may have led to an underestimation of risk by FRAX. Fourth, we were limited to DXA measures of lean mass, so that both lean and bone measures were obtained from the same scanner—DXA only approximates muscle mass. Finally, we did not specifically investigate any additional effect of multiple falls, and did not have information on the severity of a past fall, or whether a past fall was associated with injury, hence limiting our ability to identify events potentially most likely to be associated with a fracture outcome.

Although these results clearly demonstrate that measures such as chair stand time, walking speed, grip strength, and ALM offer risk information over and above FRAX with aBMD, how these might be incorporated into clinical assessment will require further investigation. An important consideration is whether the specific component of risk informed by each of these measures is amendable to intervention. Thus far, there are no medications licensed for the improvement of any of these measures, and there is no evidence for the efficacy of currently used antiosteoporosis therapies among individuals selected on the basis of such risk factors. Indeed, there is scant evidence that nonpharmacological interventions, for example, alterations to diet and/or physical activity to improve physical performance, actually reduce fracture risk. For the moment then, these measures are most likely to be of adjunctive use in clinical decision making, perhaps to guide interventions for those close to intervention thresholds derived from FRAX and aBMD assessment, but also as the basis for directed nonpharmacological therapeutic approaches focused, for example, on reducing the risk of falls. They may also be particularly relevant in older frail patients, who are often assessed in the context of multidisciplinary falls/frailty clinics.
In conclusion, we have demonstrated that physical performance (chair stand time, walking speed, grip strength) and ALM are predictive of incident fractures, independently of prior falls and FRAX probability. The observation that inclusion of aBMD in the models markedly attenuated the predictive value of ALM requires further investigation to differentiate a true effect from artifact caused by DXA technology. Although our findings support the consideration of these measures in fracture risk assessment, further prospective studies in cohorts with wider age ranges, other ethnicities, and most importantly, women, are now warranted to replicate and extend these findings, ideally to establish the potential for their inclusion as a modifier of FRAX probability.

Disclosures

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References

1. Masud T, Morris RO. Epidemiology of falls. Age and ageing. 2001 Nov;30 Suppl 4:3–7. Epub 2002 Jan 5.
2. Masud T, Binkley N, Boonen S, Hannan MT. Official positions for FRAX (R) clinical regarding falls and fracture: can falls and frailty be used in FRAX(R)? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom. 2011 Jul–Sep; 14(3):194–204. Epub 2011 Aug 4.
3. Cauley JA, Harrison SL, Cawthon PM, et al. Objective measures of physical activity, fractures and falls: the osteoporotic fractures in men study. J Am Geriatr Soc. 2013 Jul;61(7):1080–8. Epub 2013 Jul 17.
4. Cawthon PM, Blackwell TL, Marshall LM, et al. Physical performance and radiographic and clinical vertebral fractures in older men. J Bone Miner Res. 2014 Sep;29(9):2101–8. Epub 2014 Jul 22.
5. Cawthon PM, Fullman RL, Marshall L, et al. Physical performance and risk of hip fractures in older men. J Bone Miner Res. 2008 Jul;23(7):1037–44. Epub 2008 Feb 28.
6. Kanis JA, Harvey NC, Cooper C, Johansson H, Oden A, McCloskey EV. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteopor. 2016 Dec;11(1):25. Epub 2016 Jul 29.
7. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFRACTURE.Scores. BMJ. 2009;339:b4229.
8. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007 Aug;18(8):1109–17. Epub 2007 Mar 21.
9. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int. 2008 Oct;19(10):1431–44. Epub 2008 Mar 8.
10. Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int. 2011;22(9):2395–411.
11. McCloskey EV, Kanis JA, Oden A, et al. A meta-analysis of the association between falls and hip fracture risk. Osteoporos Int. 2012;23(Suppl 2):S80–1.
12. Harvey NC, Johansson H, Oden A, et al. FRAX predicts incident falls in elderly men: findings from MrOs Sweden. Osteoporos Int. 2016 Jan;27(1):267–74. Epub 2015 Sep 24.
13. Harvey NC, Oden A, Orwell E, et al. Falls predict fractures independently of FRAX probability: a meta-analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res. 2018 Mar;33(3):510–16.
14. Karlsson MK, Ribom E, Nilsson JA, et al. Inferior physical performance tests in 10,998 men in the MrOS study is associated with recurrent falls. Age Ageing. 2012 Nov;41(6):740–6. Epub 2012 Aug 28.
15. Rosengren BE, Ribom EL, Nilsson JA, et al. Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk. Age Ageing. 2012 May;41(3):339–44. Epub 2012 Feb 9.
16. Lau EM, Leung PC, Kwok T, et al. The determinants of bone mineral density in Chinese men-results from Mr. Os (Hong Kong), the first cohort study on osteoporosis in Asian men. Osteoporos Int. 2006;17(2):297–303.
17. Mellstrom D, Johnell O, Ljunggren O, et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res. 2006 Apr;21(4):529–35. Epub 2006 Apr 7.
18. Orwell E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study—a large observational study of the determinants of fracture in older men. Contemp Clin Trials. 2005 Oct;26(5):569–85. Epub 2005 Aug 9.
19. Blank JB, Cawthon PM, Carrión-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemporary clinical trials. 2005 Oct;26(5):557–68. Epub 2005 Aug 9.
20. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998(8)(5):468–89.
21. Kanis JA, Adachi JD, Cooper C, et al. Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. Osteoporos Int. 2013 Nov;24(11):2763–4. Epub 2013 Jul 13.
22. Kwok T, Khoo CC, Leung J, et al. Predictive values of calcaneal quantitative ultrasound and dual energy X ray absorptiometry for non-vertebral fracture in older men: results from the MrOS study (Hong Kong). Osteoporos Int. 2012 Mar;23(3):1001–6. Epub 2011 Apr 30.
23. Ohlsson C, Mellstrom D, Carlzon D, et al. Older men with low serum IGF-1 have an increased risk of incident fractures: the MrOS Sweden study. J Bone Miner Res. 2011 Apr;26(4):865–72. Epub 2011 Mar 25.
24. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12(5):417–27.
25. Breslow NE, Day NE. Statistical methods in cancer research. IARC Scientific Publications No. 32. 1987;Vol. II. p. 131–5.
26. Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): development and evaluation. J Clin Epidemiol. 1993 Feb;46(2):153–62. Epub 1993 Feb 1.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep;327(7414):557–60. Epub 2003 Sep 6.
28. Ensrud KE, Blackwell TL, Cauley JA, et al. Objective measures of activity level and mortality in older men. J Am Geriatr Soc. 2014 Nov;62(11):2079–87. Epub 2014 Nov 5.
29. Chan BK, Marshall LM, Winters KM, Faulkner KA, Schwartz AV, Orwoll ES. Incident fall risk and physical activity and physical performance among older men: the Osteoporotic Fractures in Men Study. Am J Epidemiol. 2007;165(6):696–703.
30. Cawthon PM, Blackwell TL, Cauley J, et al. Evaluation of the usefulness of consensus definitions of sarcopenia in older men: results from the Observational Osteoporotic Fractures in Men Cohort Study. J Am Geriatr Soc. 2015 Nov;63(11):2247–59. Epub 2015 Oct 28.
31. McLean RR, Kiel DP, Berry SD, et al. Lower lean mass measured by dual-energy X-ray absorptiometry (DXA) is not associated with increased risk of hip fracture in women: the Framingham Osteoporosis Study. Calcif Tissue Int. 2018 Jan. Epub 2018 Jan 7.
32. Hars M, Biver E, Chevalley T, et al. Low Lean mass predicts incident fractures independently from FRAX: a prospective cohort study of recent retirees. J Bone Miner Res. 2016 Nov;31(11):2048–56. Epub 2016 Jun 3.
33. Harris R, Chang Y, Beavers K, et al. Risk of fracture in women with sarcopenia, low bone mass, or both. J Am Geriatr Soc. 2017 Dec;65(12):2673–78. Epub 2017 Sep 30.
34. Malkov S, Cawthon PM, Peters KW, et al. Hip fractures risk in older men and women associated with DXA-derived measures of thigh subcutaneous fat thickness, cross-sectional muscle area, and muscle density. J Bone Miner Res. 2015 Aug;30(8):1414–21. Epub 2015 Feb 4.
35. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. Rheumatology (Oxford). 2008 Jul;47(Suppl 4):iv2–8. Epub 2008 Jul 2.
36. Dual energy x-ray absorptiometry for bone mineral density and body composition assessment. IAEA Human Health Series No. 15. Vienna: International Atomic Energy Authority; 2010.
37. Cameron ID, Gillespie LD, Robertson MC, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;12:CD005465. Epub 2012 Dec 14.
38. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9:CD007146. Epub 2012 Sep 14.