**Measures of physical performance and muscle strength as predictors of fracture risk independent of FRAX, falls and BMD: A meta-analysis of the Osteoporotic Fractures in Men (MrOS) Study**

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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® probability. We investigated, in the Osteoporotic Fractures in Men (MrOS) Study cohorts (Sweden, Hong Kong, USA), whether measures of physical performance/ appendicular lean mass 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 BMD, and calculated FRAX probabilities. An extension of Poisson regression was used to investigate the relationship between time for 5 chair stands, walking speed over 6m, grip strength, appendicular lean mass (ALM) adjusted for body size (ALM/height2), FRAX probability [major osteoporotic fracture (MOF) with or without femoral neck BMD, available in a subset of n=7531], and incident MOF (hip, clinical vertebral, wrist or proximal humerus). Associations were adjusted for age, time since baseline, and are reported as hazard ratio (HR) for first incident fracture per SD increment in predictor, using meta-analysis. 5660 men in USA (mean age 73.5 years); 2764 in Sweden (75.4 years); and 1987 in Hong Kong (72.4 years) were studied. Mean follow-up time was 8.7-10.9 years. Greater time for 5 chair stands was associated with greater risk of MOF [HR:1.26(95%CI:1.19,1.34)], whereas greater walking speed [HR:0.85(95%CI:0.79,0.90), grip strength [HR:0.77(95%CI:0.72,0.82)] and ALM/height2 [HR:0.85(95%CI:0.80,0.90)] were associated with lower risk of incident MOF. Associations remained largely similar after adjustment for FRAX, but that between ALM/height2 and MOF was weakened [HR:0.92(95%CI:0.85,0.99]. Inclusion of femoral neck BMD markedly attenuated the association between ALM/height2 and MOF [HR:1.02(95%CI:0.96,1.10)]. Measures of physical performance predict incident fractures independently of FRAX probability. Whilst the predictive value of ALM/height2 being substantially reduced by inclusion of BMD requires further study, these findings support the consideration of physical performance in fracture risk assessment.

**Key words:** Osteoporosis; epidemiology; FRAX; falls; fracture; interaction

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**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.(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.(3-5) Current clinical approaches to risk assessment are increasingly based on clinical risk factors, with or without BMD, through fracture risk calculators. FRAX® is the most commonly used fracture risk assessment tool worldwide(6) but, unlike other tools such as QFracture or the GARVAN calculator,(7-9) does not include falls as a specific input risk factor(2,10) due to the inconsistent data across the 12 derivation and 11 validation cohorts.(11) We have previously demonstrated that prior falls predict the risk of incident falls(12) and fractures(13) independently of FRAX probability. Although the predictive value of falls-related risk factors for incident fracture have been demonstrated individually,(4,5) it has not been established whether the risk information so provided will be independent of that obtained through FRAX and BMD. This is an important consideration, because if these measures were to provide no additional information over and above current fracture risk assessment, then there would be little to be gained from their measurement as part of fracture risk stratification. Furthermore, it is not clear 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 (US, Sweden, Hong Kong) to investigate whether the predictive value of four measures (time for 5 chair stands, walking speed over 6m, grip strength and appendicular lean mass) for incident fracture was independent of FRAX probability, history of falls or BMD.

**Methods**

*Participants*

Details of the Osteoporotic Fractures in Men (MrOS) cohort studies have been published previously,(12-15) but briefly, MrOS is a multicentre 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, 2,000 Chinese men, aged 65–92 years, were enrolled between August 2001 and February 2003.(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: 65–69, 70–74 and ≥75 years. Recruitment notices were placed in housing estates and community centres for the elderly. In the MrOS Sweden Study, 3014 men, aged 69–81 years, were enrolled between October 2001 and December 2004.(12,17) The cohort comprised men from the cities of Malmo, 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 65–100 years, were enrolled at 6 sites between March 2000 and April 2002.(18,19) Each US clinical site designed and customised strategies to enhance recruitment of its population. Common strategies included mailings from the Department of Motor Vehicles, voter registration and participant databases, common senior newspaper features and advertisement and targeted presentations. Self-defined racial/ethnic ancestry was ascertained through questionnaires at baseline.

*Exposure variables*

At baseline, height (centimeters) and weight (kilograms) were measured, and BMI was calculated as kilograms per square meter. The international MrOS questionnaire(18) was administered at baseline to collect information about current smoking, number and type of medications, fracture history, family history of hip fracture, past medical history (rheumatoid arthritis) and high consumption of alcohol (3 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. For glucocorticoid exposure, this was documented in MrOS as use 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 5 chair stands, walking speed over 6m (at usual pace) and grip strength using JAMAR dynamometers (Sammons Preston Rolyan, Bolingbrook, IL, US) were assessed at the baseline visit. Areal bone mineral density (BMD) was measured at the femoral neck, and appendicular lean mass from whole body scans, using Hologic QDR 4500 A or W (Hologic, Bedford, MA) or Lunar Prodigy (GE Lunar Corp., Madison, WI) depending on the centre, with cross calibration of instruments for BMD. A T-score was calculated using NHANES young women as a reference value.(20,21) 10-year probability of fracture [FRAX major osteoporotic fracture (hip, humerus, vertebral or forearm sites)] was calculated using clinical risk factors described above with and without femoral neck BMD entered into country-specific FRAX models.

*Fracture and death outcomes*

*Hong Kong:(22)* Incident fractures were captured via subject follow-up through phone call or visit to the research centre. 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-ray or medical record. Deaths were verified by death certificates.

*Sweden:(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, and these analyses were performed after the time of fracture validation. At the time of fracture evaluation, the computerized X-ray archives in Malmo, Goteborg, 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 possible to confirm by radiographic report were not included.

*US:(18)* 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(25) was used to study the association between predictors, FRAX, prior falls, BMD 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(β0 + β1 · current time from baseline + β2 · current age + β3 · 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, and time at risk was censored at the time of first fracture, loss to follow-up, death or end of follow up. To correct for body size, appendicular lean mass for each individual was divided by the square of their height. We initially investigated the predictive value of each of the 4 exposures (chair stand time, walking speed, grip strength and appendicular lean mass/height2, allstandardized to be normally distributed with mean=0 and SD=1) adjusted only for age and follow-up time. Subsequently, we used multivariable models to investigate the predictive value of these indices independent of FRAX, prior falls or BMD (entered into the model as femoral neck T-score). Additionally we investigated whether inclusion of BMI or levels of physical activity [Physical Activity Scale for the Elderly (PASE) questionnaire(26)] modified the associations, and also explored the predictive value of ALM/BMI. In further analyses, we investigated interactions with age and time since baseline, in which age and time were used as continuous variables and examples given at specific ages and times. The association between predictive factors and risk of fracture are described as a hazard ratio (HR) per 1 standard deviation change in predictor together with 95% confidence intervals (CI). Two-sided p-value were used for all analyses and p<0.05 considered to be significant. Analyses were undertaken separately within each cohort and then the β-coefficients from each cohort were weighted according to the variance, and merged to determine the weighted mean of the coefficient and its standard deviation (fixed-effects meta-analysis, since heterogeneity was low to moderate as assessed by I2).(27) The risk ratios are then given by e(weighted mean coefficient).

**Results**

*Characteristics of participants*

The study cohort consisted of 10,411 men who had information on the key exposures, together with prior falls and femoral neck BMD: 5660 men in USA (mean age 73.5 years; mean follow-up 10.9 years); 2764 men in Sweden (mean age 75.4 years; mean follow-up 8.7 years); and 1987 men in Hong Kong (mean age 72.4 years; mean follow-up 9.9 years). The frequency of past falls was similar across the cohorts at 20%, 16%, and 15% respectively. Previous fracture were more commonly reported in Sweden (35%) than in USA (22%) and Hong Kong (14%). Consistent with the known country-specific epidemiology of fracture, the highest mean FRAX probability [major osteoporotic fracture (MOF) with BMD] was observed in Sweden (11.4%), followed by USA (7.8%) and Hong Kong (6.6%). 61 men (0.6%) were unable to complete the chair stand test. Summary statistics for the key exposure variables are presented in Table 1, which summarises the baseline characteristics of the individuals by country cohort.

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

Table 2 summarises the associations between each of the 4 predictors (chair stand time, walking speed, grip strength and appendicular lean mass divided by height2, adjusted only for age and follow-up time), and the fracture outcomes. Thus, across all cohorts, greater time for 5 chair stands was associated with greater risk of MOF [HR:1.26(95%CI:1.19,1.34)], whereas greater walking speed [HR:0.85(95%CI:0.79,0.90), grip strength [HR:0.77(95%CI:0.72,0.82)] and ALM/height2 [HR:0.85(95%CI:0.80,0.90)] were associated with 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 BMD) 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 BMD (using the subset of 7531 for who FRAX probability could be calculated)] very slightly attenuated the magnitude of the hazard ratios; in contrast, whilst inclusion of FRAX (MOF with BMD) led to modest attenuation of hazard ratios in general, those for any fracture [HR: 0.95 (95%CI: 0.90, 1.01) and osteoporotic fracture (HR: 0.95 (95%CI: 0.89, 1.01) with ALM/height2 became non-significant, and that between ALM/height2 and MOF was also attenuated [HR: 0.92 (95%CI:0.85, 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/height2. 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. (Summarised in Online Supplementary Table 1).

*Independent predictive value of exposures after adjustment for femoral neck BMD.*

Inclusion of femoral neck BMD 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/height2 and each of the non-hip fracture outcomes (HRs 1.01 to 1.02). Furthermore, the HR for hip fracture inverted to suggest a detrimental effect of increasing lean mass on hip fracture risk after adjustment for BMD [HR: 1.12; 95%CI: 1.01, 1.23)]. Figure 1 summarises the effect of the different adjustments, using the participants in whom FRAX data were available.

*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 4 exposures. Thus, for chair stand time, the HR for any fracture was 1.08 (95%CI: 0.98, 1.19) at age 70 years and 1.15 (95%CI: 1.08, 1.21) at 80 years, p interaction=0.12. The HR for any fracture with walking speed was 0.88 (95%CI: 0.81, 0.95) at 1 year after baseline and 0.94 (0.87, 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 appendicular lean mass predict incident fracture risk independently of FRAX probability and history of prior falls. Whilst chair stand time, walking speed and grip strength also predicted fracture risk independently of femoral neck BMD (albeit with a slightly attenuated effect size), inclusion of BMD directly, or as part of FRAX, markedly attenuated associations between appendicular lean mass and incident fracture.

There are several studies across a range of cohorts that demonstrate the predictive value of measures such as chair stand time, walking speed, grip strength for fractures. The associations we have observed are consistent with those for physical performance, fractures and falls derived using a different analytic methodology in the US MrOS cohort.(3-5,28,29) In the present analysis however, we have, across the three MrOS cohorts, extended such findings by demonstrating that the associations between these risk factors and incident fracture are independent of key clinical factors such as prior falls, BMI and FRAX probability. Associations between appendicular lean mass and fracture reported in previous studies is mixed, with no association between ALM/height2 and hip fracture in the U.S. MrOS cohort,(30) or women in the Framingham study,(31) while a study in Swiss retirees found that low lean mass was a risk factor for clinical fractures.(32)

The attenuation (and indeed inversion for hip fracture) of the relationships between appendicular lean mass and incident fracture by the inclusion of femoral neck BMD are intriguing. A similar finding was observed in the Women’s Health Initiative,(33) and in the Health ABC study,(34) with the authors of this latter study suggesting that excess lean in excess of bone mass might be a pro-fracture state. However, this would seem to be at odds with the general adaptation of bone to muscle,(35) and excess lean mass or power over bone strength seems unlikely in older men (compared with younger athletes for example). In contrast, in the Swiss GERICO study, adjustment of low lean mass for BMD did not substantially attenuate associations with incident fracture.(32) Importantly, both the measure of lean mass and BMD are derived from the same instrument, namely DXA, and were moderately correlated with a Pearson correlation coefficient ranging from 0.29 (US) to 0.43 (Hong Kong). It is well established that soft tissue can influence the measurement of BMD, potentially through magnification artifact associated with a thicker body where BMI is higher, and through altered edge detection.(36) This phenomenon has been particularly discussed in terms of adipose tissue, and the effect of muscle mass, which is not specifically measured by DXA (it is derived as the tissue which is not fat or bone), has been much less thoroughly considered. Interestingly the effect was very similar when ALM rather than ALM/height2 was used (data not shown), suggesting that it is not solely a result of size adjustment although both ALM and ALM/height2 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, BMD is calculated from equations incorporating soft tissue mass,(36) and 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.(18) Firstly, the population studied was male, and of a narrow age range (64-99 years), so limiting generalizability of our findings. Secondly, the definition of glucocorticoid use differed from those usually specified for incorporation into FRAX. Thirdly 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. Fourthly, we were limited to DXA measures of lean mass, so that both lean and bone measures were obtained from the same scanner and 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, so limiting our ability to identify events potentially most likely to be associated with a fracture outcome.

Whilst these results clearly demonstrate that measures such as chair stand time, walking speed, grip strength and appendicular lean mass offer risk information over and above FRAX with BMD, 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 anti-osteoporosis therapies amongst individuals selected on the basis of such risk factors. Indeed, there is scant evidence that non-pharmacological interventions, for example alterations to diet and/or physical activity to improve physical performance, actually reduce fracture risk.(37,38) 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 BMD assessment, but also as the basis for directed non-pharmacological therapeutic approaches focused, for example, on reducing the risk of falls.(37,38) 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 appendicular lean mass are predictive of incident fractures, independently of prior falls and FRAX probability. The observation that inclusion of BMD in the models markedly attenuated the predictive value of appendicular lean mass requires further investigation to differentiate a true effect from artifact caused by the DXA technology. Whilst 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.

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**Author Roles**

All authors contributed to manuscript drafting, review and finalisation. NCH wrote the first draft of the manuscript and oversaw its preparation; HJ and AO undertook statistical analysis; EO and JL designed and implemented MrOS US, and provided data; MK, BR, OL, CO, DM designed and implemented MrOS Sweden, and provided data; TK designed and implemented MrOS Hong Kong, and provided data; CC contributed expertise on fracture epidemiology; EM and JAK oversee FRAX and provided FRAX methodology; EVM is guarantor.

**Disclosures**

All authors have no disclosures in relation to this manuscript.

References

1. Masud T, Morris RO. Epidemiology of falls. Age and ageing. Nov 2001;30 Suppl 4:3-7. Epub 2002/01/05.

2. Masud T, Binkley N, Boonen S, Hannan MT. Official Positions for FRAX(R) clinical regarding falls and frailty: 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. Jul-Sep 2011;14(3):194-204. Epub 2011/08/04.

3. Cauley JA, Harrison SL, Cawthon PM, Ensrud KE, Danielson ME, Orwoll E, et al. Objective measures of physical activity, fractures and falls: the osteoporotic fractures in men study. J Am Geriatr Soc. Jul 2013;61(7):1080-8. Epub 2013/07/17.

4. Cawthon PM, Blackwell TL, Marshall LM, Fink HA, Kado DM, Ensrud KE, et al. Physical performance and radiographic and clinical vertebral fractures in older men. J Bone Miner Res. Sep 2014;29(9):2101-8. Epub 2014/07/22.

5. Cawthon PM, Fullman RL, Marshall L, Mackey DC, Fink HA, Cauley JA, et al. Physical performance and risk of hip fractures in older men. J Bone Miner Res. Jul 2008;23(7):1037-44. Epub 2008/02/28.

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. Archives of osteoporosis. Dec 2016;11(1):25. Epub 2016/07/29.

7. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. 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. Aug 2007;18(8):1109-17. Epub 2007/03/21.

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. Oct 2008;19(10):1431-44. Epub 2008/03/08.

10. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al. Interpretation and use of FRAX in clinical practice. OsteoporosInt. 10.1007/s00198-011-1713-z doi 2011;22(9):2395-411.

11. McCloskey EV, Kanis JA, Oden A, Johansson H, Diez Perez A, Eisman JA, et al. A meta-analysis of the association between falls and hip fracture risk. . Osteoporos Int. 2012;23(Suppl. 2):S80-S1.

12. Harvey NC, Johansson H, Oden A, Karlsson MK, Rosengren BE, Ljunggren O, et al. FRAX predicts incident falls in elderly men: findings from MrOs Sweden. Osteoporos Int. Jan 2016;27(1):267-74. Epub 2015/09/24.

13. Harvey NC, Oden A, Orwoll E, Lapidus J, Kwok T, Karlsson M, et al. Falls predict fractures independently of FRAX probability: A meta-analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res. 2017;In press.

14. Karlsson MK, Ribom E, Nilsson JA, Ljunggren O, Ohlsson C, Mellstrom D, et al. Inferior physical performance tests in 10,998 men in the MrOS study is associated with recurrent falls. Age Ageing. Nov 2012;41(6):740-6. Epub 2012/08/28.

15. Rosengren BE, Ribom EL, Nilsson JA, Mallmin H, Ljunggren O, Ohlsson C, et al. Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk. Age Ageing. May 2012;41(3):339-44. Epub 2012/02/09.

16. Lau EM, Leung PC, Kwok T, Woo J, Lynn H, Orwoll E, 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. OsteoporosInt. 2006;17(2):297-303.

17. Mellstrom D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res. Apr 2006;21(4):529-35. Epub 2006/04/07.

18. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, 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. Oct 2005;26(5):569-85. Epub 2005/08/09.

19. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemporary clinical trials. Oct 2005;26(5):557-68. Epub 2005/08/09.

20. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, 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, Clark P, Cummings SR, Diaz-Curiel M, et al. Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. Osteoporos Int. Nov 2013;24(11):2763-4. Epub 2013/07/26.

22. Kwok T, Khoo CC, Leung J, Kwok A, Qin L, Woo 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. Mar 2012;23(3):1001-6. Epub 2011/04/30.

23. Ohlsson C, Mellstrom D, Carlzon D, Orwoll E, Ljunggren O, Karlsson MK, et al. Older men with low serum IGF-1 have an increased risk of incident fractures: the MrOS Sweden study. J Bone Miner Res. Apr 2011;26(4):865-72. Epub 2011/03/25.

24. Sims I. Many more eligible for bisphosphonates after NICE lowers threshold to 1%. PULSE; 2017.

25. Breslow NE, Day NE. Statistical Methods in Cancer Research. IARC Scientific Publications No 32. 1987;Volume 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. Feb 1993;46(2):153-62. Epub 1993/02/01.

27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. Sep 06 2003;327(7414):557-60. Epub 2003/09/06.

28. Ensrud KE, Blackwell TL, Cauley JA, Dam TT, Cawthon PM, Schousboe JT, et al. Objective measures of activity level and mortality in older men. J Am Geriatr Soc. Nov 2014;62(11):2079-87. Epub 2014/11/05.

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. AmJEpidemiol. 2007;165(6):696-703.

30. Cawthon PM, Blackwell TL, Cauley J, Kado DM, Barrett-Connor E, Lee CG, 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. Nov 2015;63(11):2247-59. Epub 2015/10/28.

31. McLean RR, Kiel DP, Berry SD, Broe KE, Zhang X, Cupples LA, 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. Jan 5 2018. Epub 2018/01/07.

32. Hars M, Biver E, Chevalley T, Herrmann F, Rizzoli R, Ferrari S, et al. Low Lean Mass Predicts Incident Fractures Independently From FRAX: a Prospective Cohort Study of Recent Retirees. J Bone Miner Res. Nov 2016;31(11):2048-56. Epub 2016/06/03.

33. Harris R, Chang Y, Beavers K, Laddu-Patel D, Bea J, Johnson K, et al. Risk of Fracture in Women with Sarcopenia, Low Bone Mass, or Both. J Am Geriatr Soc. Sep 27 2017. Epub 2017/09/30.

34. Malkov S, Cawthon PM, Peters KW, Cauley JA, Murphy RA, Visser M, 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. Aug 2015;30(8):1414-21. Epub 2015/02/04.

35. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. Rheumatology (Oxford). Jul 2008;47 Suppl 4:iv2-8. Epub 2008/07/02.

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, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;12:CD005465. Epub 2012/12/14.

38. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9:CD007146. Epub 2012/09/14.

**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 | 19592 | 24102 | 61456 |
| 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% |
| BMD 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 BMD | 6.9±2.9 | 13.5±6.1 | 9.1±4.8 |
| FRAX hip without BMD | 3.4±2.5 | 7.5±5.5 | 3.6±3.9 |
| FRAX MOF with BMD | 6.6±3.2 | 11.4±6.7 | 7.8±4.6 |
| FRAX hip with BMD | 3.0±2.6  (n=1661) | 5.5±6.0  (n=1732) | 2.4±3.4  (n=4138) |
|  |  |  |  |
| 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% |

fx=fracture; Ost=osteoporotic; MOF=Major Osteoporotic Fracture

**Table 2:** Associations between exposures and risk of incident fracture. Data are Hazard ratio 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **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)** | **1.30 (1.20, 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)** |

HK=Hong Kong; SW=Sweden; US=United States; Fx=fracture; Ost=osteoporotic; MOF=Major Osteoporotic Fracture

**Table 3:** Associations between exposures and risk of incident fracture. Data are Hazard ratio 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 BMD; FRAX MOF with femoral neck BMD; femoral neck BMD. Statistically significant associations (p<0.05) are in bold.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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 BMD | **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/Height2** | 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 BMD | **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 BMD | 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 BMD | 1.01 (0.96, 1.06) | 1.02 (0.96, 1.08) | 1.02 (0.96, 1.10) | **1.12 (1.01, 1.23)** |

**Figure 1:** Associations between exposures and risk of incident fracture. Data are Hazard ratio for fracture per 1 SD change in predictor (HR/SD), adjusted for age, follow-up time, and as specified. (in a subset of 7531 participants: n=1661 HK; 1732 SW; 4138 US).

