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High risk of fall, poor physical function, and low grip strength in men with fracture—the STRAMBO study

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Abstract

Background Several studies assessed the association of prevalent fractures with muscle mass, strength, and physical capacity in men. Clinical impact of these associations is not clear, and they could be influenced by confounders. Our aim was to assess the association of the prevalent fractures with muscle strength, physical function, and the risk of subsequent falls in older men after adjustment for muscle mass and potential confounders.

Methods In a cohort of 890 men aged 50 and older, we assessed appendicular skeletal muscle mass (ASM) by DXA, grip strength, physical function (chair stands, static, and dynamic balance). Relative ASM (RASM) was calculated as ASM / (height)^2. Then, 813 men aged 60 and over were followed up prospectively for 5 years and 144 sustained >1 incident falls. All the analyses were adjusted for lifestyle factors, co-morbidities, and hormones known to influence muscle and physical function.

Results Low leisure physical activity, very high occupational physical activity, Parkinson's disease, diabetes mellitus, low apparent free testosterone concentration (AFTC), as well as Grade 2 and 3 vertebral fractures and multiple fractures were associated with lower grip strength when adjusted for confounders including upper limb RASM. Low leisure physical activity, very high occupational physical activity, diabetes mellitus, prior stroke, low AFTC and 25-hydroxycholecalciferol, high C-reactive protein, vertebral fractures, and non-vertebral fractures were associated with poor physical function (lowest quintile of the score of tests) when adjusted for confounders including lower limb RASM. Grade 2 and 3 and multiple vertebral fractures were associated with twofold higher risk of multiple falls after adjustment for confounders. Men having multiple fractures had a twofold higher risk of multiple falls after adjusting for confounders. In multivariable models, risk of falls increased proportionally to the increasing severity and number of vertebral fractures as well as to the increasing number of all fractures.

Conclusions In older men, Grade 2 and 3 vertebral fractures and multiple vertebral and non-vertebral fractures are associated with lower grip strength, poor physical function, and higher risk of multiple falls after adjustment for multiple confounders. This suggests a real direct association. One fracture can initiate a vicious circle leading to another fracture; thus, patients with fractures need physical therapy regardless of their general health status.

Keywords Muscle strength; Physical performance; Fall; Fragility fracture; Men

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Introduction

Many studies have assessed the relationship between fractures and physical function. Low muscle strength, sedentary lifestyle, and poor physical function are associated with higher risk of fracture.[1–7] Prior fractures are also associated with poor physical function. However, this association has been studied mainly in postmenopausal women,[8–10] whereas data in men are limited. Moreover, studies on vertebral fractures were focused on back pain and disability, impaired back mobility, impairment in activities of daily living, and life quality.[11–17] Furthermore, studies on sequellae of non-vertebral fractures were performed mainly in elderly women or mixed cohorts and were focused on hip fracture.[10,18,19] Some studies on the sequellae of fragility fractures have been carried out in small groups,[13,16,17,20] or are inadequately controlled for potential confounders.[11,14,15,17]

Recent studies show that some conditions, e.g. diabetes mellitus, low grade inflammation, hypogonadism, and vitamin D deficit, are associated with lower muscle strength and higher risk of fall, fracture, frailty, and disability.[21–26] Thus, low muscle strength, poor balance, and high fall risk in a patient with vertebral fracture and diabetes mellitus may be not necessarily because of the vertebral fracture, but all the above (i.e. including fracture) may be the consequences of diabetes. Therefore, analyses accounting for these confounders are necessary for better assessment of the disability related to the fracture itself. Such analyses are also useful for identification of factors which increase disability in subjects with fractures.

Some,[27,28] but not all[29] studies suggest lower lean mass in individuals with prevalent fractures. Low muscle mass and strength may be associated with higher risk of disability, although data are discordant.[30–33] Thus, it is important to check whether the associations remain significant after additional adjustment for muscle mass. The loss of significance after adjustment for muscle mass would suggest that the effect of the factor on the disability may be mediated by its effect on muscle mass.

Therefore, the aim of our study is to assess the association of the prevalent fractures with muscle strength, physical function, and the risk of incident falls in older men after adjustment for muscle mass and other potential confounders.

Materials and methods

Cohort

The STRAMBO study is a prospective cohort study of skeletal fragility in men.[34] It is a collaboration between INSERM (National Institute of Health and Medical Research) and MTRL (Mutuelle des Travailleurs de la Région Lyonnaise), complementary health insurance company open to all citizens. The study obtained authorization from the ethics committee and was performed in agreement with the Helsinki Declarations of 1975 and 1983. Men were recruited in 2006–08 from the MTRL lists. Invitations to participate were sent to randomly selected men aged 20–85 years living in greater Lyon. The response rate was 19%. Informed consent was provided by 1169 men. All men able to give informed consent, to answer the questions, and to participate in the diagnostic tests were included. No exclusion criteria were used. This analysis was performed in 890 men aged 50 and older, because few younger men had had fragility fractures prior to the recruitment. Men aged 60 and older (n = 825) were followed up prospectively for 5 years to collect data on incident falls (our study is focused on the incident fragility fractures which are infrequent before the age of 60 in men). Twelve men were lost to follow-up, and the prospective analysis was performed in 813 men.

Fracture assessment

Vertebral fractures were assessed on the lateral scans of thoracic and lumbar spine obtained in the dorsal decubitus position by the Vertebral Fracture Assessment (VFA) software using the HOLOGIC Discovery A device equipped with the C-arm (Hologic Inc., Bedford, MA, USA).[35] Vertebral fractures were assessed by one reader (PS) using the semi-quantitative method of Genant, as modified for men.[36,37] Vertebral fractures were identified in 98 men who were classified according to the most severe fracture as follows: grade 1 (mild, n = 18), grade 2 (moderate, n = 60), and grade 3 (severe, n = 20). Three vertebral fractures sustained after a major trauma were excluded. Mild deformities supposedly related to other conditions were excluded, specificity being preferred to sensitivity. The intra- and interrater reproducibility of diagnosis and grading of vertebral fracture was excellent: $\kappa = 0.87–0.93$.

Non-vertebral fractures were self-reported. We retained fractures that occurred after the age of 18 and after a fall from a standing position (or equivalent) or less. One hundred men self-reported 119 fractures. Fractures of the face, hand, and toes were excluded. Fractures were not ascertained further. Median time since the last fracture was 9 years. Thirty-nine fractures after severe traumas were excluded. These men were considered ‘no fracture’. Vertebral fractures and skeletal sites of non-vertebral fractures were described previously.[35]

Epidemiologic questionnaire

Men replied to an interviewer-administered epidemiologic questionnaire that covered lifestyle factors and health status. Smoking was assessed as current smoker vs. non-smoker. Alcohol intake was calculated as average amount of alcohol consumed weekly. Leisure physical activity was calculated as the amount of time spent on gardening and participating in leisure sport activity including seasonal activities. The cut-offs (1, 3, and 7 h/week) were closest to the quartiles. Time spent outdoors was calculated as the amount of time spent on walking, gardening, and participating in outdoor leisure sport activity including seasonal ones. Calcium intake was estimated using a food-frequency questionnaire (FFQ) adapted to French alimentary habits.[38] Occupational physical activity was self-reported and classified as weak, average, high, and very high. Diseases (diabetes mellitus, ischemic heart disease, prior myocardial infarction, hypertension, prior stroke, and

Parkinson's disease) were self-reported, classified as present or absent, and not further ascertained.

Biochemical measurements

Testosterone was measured by tritiated radioimmunoassay (RIA) with diethylether extraction.[39] Detection limit was 0.06 nmol/L. Inter-assay coefficient of variation (CV) was 8%. Sex hormone-binding globulin (SHBG) was measured by RIA with intra- and interassay CV of 4% and 5% (CisBioInternational, Gif-sur-Yvette, France).[39] Apparent free testosterone concentration (AFTC) was calculated.[40] 25-Hydroxycholecalciferol (25OHD) was assessed by RIA (DiaSorin, Stillwater, USA) after acetonitrile extraction.[41] Detection limit was 3 ng/mL. Intra- and inter-assay CV were 5–7% and 9–11%. High sensitivity C-reactive protein (CRP) was measured by immunoturbidimetric latex assay (Roche Diagnostics, Mannheim, Germany). Detection limit was 0.15 mg/L. Intra- and inter-assay (CV) were $<$10%.[42]

Dual-energy X-ray absorptiometry (DXA)

Body composition was estimated by DXA using the same device.[43] The body composition software provides values for the masses of lean soft tissue and fat for whole body and specific regions. The limbs were isolated from the trunk by using DXA regional computer-generated lines with manual adjustment. The legs and the arms were defined as soft tissue between a line drawn through and perpendicular to the axis of the femoral neck and the phalange tips and as the soft tissue between the centre of the arm socket and the phalange tips, respectively. Relative appendicular skeletal muscle mass (RASM) was calculated as the sum of lean mass of the four limbs divided by $(\text{height})^2$. Upper limb RASM was calculated as the sum of lean mass of both arms divided by $(\text{height})^2$. Lower limb RASM was calculated as the sum of lean mass of both legs divided by $(\text{height})^2$. Abdominal aortic calcification (AAC) was assessed on the lateral spine scans using the 24-point score described by Kauppila.[44,45]

Grip strength

Grip strength was measured three times by a hand dynamometer (Martin Vigorimeter, Martin Gebrüder GmbH & Co, Tuttlingen, Germany) at the dominant hand.[43] The mean of these three measures was used for the calculations.

Physical performance: clinical tests

Clinical tests were described previously.[46] A man seated on a chair was asked to stand up and sit down from a chair five times.[47] The examiner recorded the number of chair stands and the time required. The inability to perform the test was diagnosed when the man did not complete five chair stands (score 0). For men who accomplished five stands, time was scored 1–4 according to the quartiles (4 for the shortest time, 1 to the longest time). Static balance was evaluated based on standing with feet in the side by side position.[47] Men were evaluated for 10 s with eyes open and for 10 s with eyes closed. The timing was stopped when the participant moved his feet or grasped an object for support or when the time (10 s) had elapsed. For standing balance, the test was scored as follows: unable to stand in the positions (score 0), $<$10 s with eyes open (score 1), 10 s with eyes open and $<$5 s with eyes closed (score 2), 10 s with eyes open and 5–9 s with eyes closed (score 3), and 10 s in each position (score 4). To test dynamic balance, men performed a 10-step tandem walk on a line drawn on the floor, forward and backward.[48] For each part, the examiner recorded the time and the number of steps really performed. The men who did not perform a 10-step tandem walk forward (resp. backward) were scored unable (score 0). For men who accomplished 10 steps, time was scored 1–4 according to the quartiles (4 for the shortest time). The composite score was calculated by adding up the four tests (0–16), e.g. a man who completed three chair stands (score 0), stood 10 s with eyes open and 3 s with eyes closed (score 2), had time of walk forward in the fourth quartile (score 1) and stopped the walk backward after 3 steps (score 0), and had the composite score of 3.

Prospective study

Men aged 60 and older were followed up prospectively. Every year they answered a mail questionnaire concerning the incident falls: date and circumstances of a fall, number of the falls during the given period. Falls were defined as unexpected events in which the men came to rest on the ground or lower level.[49] Falls because of external trauma were excluded.

Statistical methods

We used SAS 9.3 software (Cary, NC, USA). For bivariable comparisons of variables with Gaussian distribution, we used t-test and analysis of variance. For bivariable comparisons of variables with skewed distribution, we used Mann–Whitney test and Kruskal–Wallis test. For bivariable comparisons of class variables, we used chi-square test. Variables significant in the bivariable comparisons were used for adjusting multivariable analyses. As most of the studied variables are correlated with age, all the multivariable models are adjusted for age. Models are adjusted for upper limb RASM or lower limb RASM to assess the effect independent of muscle mass.

Differences in upper limb RASM and grip strength across the class variables were assessed using analyses of covariance adjusted as above. Diseases were dichotomized (yes/no). Other variables were grouped (described in tables). Post hoc comparisons were performed using Dunnet–Hsu's test.

We calculated multivariable adjusted odds ratios (OR) of poor physical function and 95% confidence interval (95%CI) associated with investigated variables using logistic regression. We selected covariates based on the model that provided the highest area under the curve for presence of poor physical function (c statistic). Fall-free survival according to the prevalent fractures (presence, number, severity) was analysed by Cox model after checking the assumption of proportional hazards. Follow-up time was censored (ended) at the first fall, death, last news or 5 years after recruitment, whichever the first. The variables predicting falls with $p < 0.15$ in at least one model (e.g. for vertebral fracture present vs. absent) and variables which changed hazard risk (HR) by >0.04 were retained in the final model: age, height, current smoking, time spent outdoors, calcium intake, prior myocardial infarction, prior stroke, diabetes mellitus, Parkinson's disease, AAC score, AFTC, and C-reactive protein.

Results

Description of the cohort

The 890 men aged 50 and older had data for all variables used in this study. Their average age was 70 years, 179 reported falls during the year preceding the recruitment, 100 reported prior non-vertebral fractures, and 92 had prevalent vertebral fractures (*Table 1*).

Table 1 Descriptive analysis of 890 men aged 50 and older participating in the cross-sectional study

Variable	Mean ± SD
Age (years)	70 ± 9
Body weight (kg)	79 ± 11
Body height (cm)	169 ± 7
BMI (kg/m^2)	27.6 ± 3.6
Upper limb RASM (kg/m^2)	2.56 ± 0.32
Lower limb RASM (kg/m^2)	5.71 ± 0.62
Grip strength (kPa)	71.0 ± 17.7
Current smoking (n,%)	60 (6.6)
Alcohol intake (g/week)	109 [16; 234]*
Calcium intake (mg/d)	767 ± 248
Leisure physical activity (h/week)	3.0 [0.8; 7.0]*
Time spent outdoors (h/week)	7 [4; 10]*
Occupational physical activity (n,%): Low	203 (22.2)
Average	274 (30.0)
High	255 (27.9)
Very high	182 (19.9)
Ischemic heart disease (n,%)	132 (14.4)
History of myocardial infarction (n,%)	54 (5.9)
Hypertension (n,%)	351 (38.4)
Diabetes mellitus (n,%)	115 (12.6)
History of stroke (n,%)	33 (3.6)
Parkinson's disease (n,%)	15 (1.6)
Abdominal aortic calcification	1 [0; 3]*
Physical activity score <9 (n,%)	155 (17.4)
History of falls (n,%)	179 (20.1)
Vertebral fractures (n,%)	92 (10.3)
Non-vertebral fractures (n,%)	100 (11.2)
All fractures (n,%)	168 (18.9)
Total testosterone (nmol/L)	11.8 ± 5.3
Sex hormone-binding globulin (nmol/L)	44.1 ± 22.3
Apparent free testosterone (pmol/L)	243 ± 93
25-Hydroxycholecalciferol (ng/mL)	22 ± 10
C-reactive protein (ng/mL)	1.65 [0.83; 3.18]*

*Median [first quartile, third quartile].

Muscle mass and strength

Grip strength and upper limb RASM correlated positively ($r = 0.24$, $p < 0.01$), also when adjusted for age ($r = 0.12$, $p < 0.001$). After adjustment for confounders (*Table 2*), men in the lowest quartile of leisure physical activity (<1 h/wk) had lower upper limb RASM (3.1%, 0.25SD, $p < 0.005$) and grip strength (4.5%, 0.19SD, $p < 0.05$) vs. men in the upper quartile of physical activity (>7 h/wk). The difference in grip strength lost significance after adjustment for upper limb RASM. Men who had leisure physical activity <1 h/wk had 5.4% lower grip strength (0.22SD, $p < 0.001$) vs. men with physical activity ≥1 h/wk (three groups combined), also after adjustment for upper limb RASM (4.4%, 0.19SD, $p < 0.005$). Very high occupational activity was associated with 6.3% lower grip strength (0.26SD, $p < 0.01$) vs. light activity, also after adjustment for upper limb RASM (7.1%, 0.30SD, $p < 0.005$). Grip strength and upper limb RASM did not vary according to smoking habits or alcohol intake.

Diabetic men had 5.4% lower grip strength vs. non-diabetic men (0.23SD, $p < 0.01$), also when adjusted for upper limb RASM. Men with Parkinson's disease had 14.0% lower grip strength (0.67SD, $p < 0.05$), also when adjusted for upper limb RASM (13.2%, 0.63SD, $p < 0.05$).

Prior myocardial infarction was associated with 6.0% lower grip strength (0.26SD, $p < 0.05$), but this difference lost significance after adjustment for upper limb RASM. Hypertension and prior stroke were not associated with upper limb RASM or grip strength.

Men in the lowest 25OHD quartile had 5.3% lower upper limb RASM (0.44SD, $p < 0.001$) and 5.7% lower grip strength (0.24SD, $p < 0.001$) vs. men in the highest quartile. The

Table 2 Association of upper limb RASM and grip strength with potential determinants in multivariable models

	N	upper limb RASM (kg/m^2)	Grip strength (kPa)	Grip strength (kPa)—adjusted for upper limb RASM
Current and former smoking				
Never (reference)	289	2.55 ± 0.32	69.7 ± 17.8	70.1 ± 17.8
≤6 packet-years	135	2.57 ± 0.31	70.0 ± 16.5	70.2 ± 16.1
>6–15 packet-years	148	2.58 ± 0.32	71.3 ± 19.6	71.4 ± 19.2
>15–28 packet-years	146	2.59 ± 0.34	73.8 ± 17.1[a]	73.4 ± 17.1
>28 packet-years	172	2.54 ± 0.32	72.4 ± 17.4	72.8 ± 17.4
Alcohol drinking				
≤1 unit/wk	239	2.53 ± 0.34	69.3 ± 17.2	70.0 ± 17.0
>1–7 units/wk	241	2.57 ± 0.33	72.4 ± 18.1	72.4 ± 18.1
>7–14 units/wk (ref.)	168	2.61 ± 0.32	71.5 ± 16.9	70.9 ± 16.9
>14 units/wk	242	2.55 ± 0.30	71.8 ± 18.1	72.2 ± 17.8
Leisure physical activity (h/week)				
<1 h/wk	240	2.53 ± 0.32[c]	68.4 ± 16.9[a]	69.1 ± 16.5
1–3 h/wk	245	2.55 ± 0.34	72.3 ± 17.9	72.7 ± 17.9
>3–7 h/wk	185	2.57 ± 0.28	72.7 ± 16.5	72.8 ± 16.9
>7 h/wk (reference)	220	2.61 ± 0.33	71.6 ± 17.7	71.2 ± 17.8
Occupational physical activity				
Light (reference)	199	2.54 ± 0.30	73.1 ± 17.5	73.7 ± 17.4
Moderate	274	2.55 ± 0.30	72.2 ± 16.6	72.5 ± 16.5
Heavy	242	2.57 ± 0.35	70.5 ± 18.0	70.4 ± 18.1[a]
Very heavy	175	2.59 ± 0.34	68.5 ± 17.4[b]	68.5 ± 17.2[c]
History of myocardial infarction				
Yes	47	2.54 ± 0.32	67.1 ± 15.8[a]	67.7 ± 14.9
No (reference)	843	2.56 ± 0.32	71.4 ± 17.7	71.6 ± 17.7
Hypertension				
Yes	333	2.58 ± 0.32	70.9 ± 16.4	71.0 ± 16.1
No (reference)	557	2.55 ± 0.32	71.6 ± 18.3	71.9 ± 18.3
Type 2 diabetes mellitus				
Yes	112	2.56 ± 0.32	67.8 ± 17.0[b]	68.2 ± 16.5[a]
No (reference)	778	2.56 ± 0.32	71.7 ± 17.5	71.9 ± 17.5
History of stroke				
Yes	32	2.56 ± 0.32	68.7 ± 13.3	68.8 ± 13.0
No (reference)	858	2.56 ± 0.32	71.4 ± 18.7	71.6 ± 17.8
Parkinson's disease				
Yes	14	2.51 ± 0.36	61.5 ± 12.2[a]	62.2 ± 12.2[a]
No (reference)	876	2.56 ± 0.32	71.5 ± 17.8	71.7 ± 17.7
C-reactive protein (CRP)				
<1 ng/mL (reference)	282	2.60 ± 0.31	72.7 ± 18.2	72.4 ± 18.2
1 – <3 ng/mL	378	2.57 ± 0.32	71.9 ± 17.3	72.0 ± 17.3
3 – <5 ng/mL	101	2.51 ± 0.33[c]	68.8 ± 16.7	69.8 ± 16.6
≥5 ng/mL	129	2.51 ± 0.33[d]	68.7 ± 17.5[a]	69.8 ± 17.1
Apparent free testosterone concentration (AFTC)				
<192 pmol/L	223	2.51 ± 0.36[d]	70.0 ± 17.4	71.0 ± 17.2
192 – <243 pmol/L	222	2.57 ± 0.31	71.6 ± 18.1	71.5 ± 18.1
243 – <297 pmol/L	225	2.56 ± 0.29	72.0 ± 16.4	72.2 ± 16.4

(Continues)

Table 2 (Continued)

	N	upper limb RASM (kg/m^2)	Grip strength (kPa)	Grip strength (kPa)—adjusted for upper limb RASM
≥297 pmol/L (reference)	220	2.60 ± 0.33	71.8 ± 18.5	71.5 ± 18.4
25-Hydroxycholecalciferol (25OHD)				
<15 ng/mL	201	2.48 ± 0.34^{d}	69.3 ± 17.2^{b}	70.7 ± 16.8
15 – <21 ng/mL	239	2.55 ± 0.32^{b}	71.5 ± 18.1	71.6 ± 18.1
21 – <28 ng/mL	219	2.58 ± 0.33	70.8 ± 17.6	70.7 ± 17.6
≥28 ng/mL (reference)	231	2.62 ± 0.29	73.5 ± 17.5	73.0 ± 17.5
Vertebral fracture				
Yes	92	2.56 ± 0.33	67.2 ± 16.9^{b}	67.7 ± 16.6^{b}
No (reference)	798	2.56 ± 0.29	71.7 ± 17.6	71.8 ± 17.5
Vertebral fracture severity				
Grade 2 and 3	76	2.56 ± 0.33	66.6 ± 17.2^{b}	67.1 ± 16.8^{a}
Grade 1	16	2.59 ± 0.21	70.7 ± 13.7	70.3 ± 14.2
No (reference)	798	2.56 ± 0.30	71.7 ± 17.6	71.8 ± 17.5
Non-vertebral fractures				
Yes	100	2.56 ± 0.28	68.4 ± 16.9^{a}	69.2 ± 16.5
No (reference)	790	0.52 ± 0.33	71.5 ± 17.8	71.8 ± 17.9
All fractures (vertebral and non-vertebral jointly)				
>1 fracture	61	2.56 ± 0.31	67.2 ± 17.2^{a}	67.7 ± 16.5^{a}
1 fracture	106	2.53 ± 0.27	68.9 ± 15.9	69.5 ± 15.8
No (reference)	723	2.56 ± 0.33	71.9 ± 17.8	72.0 ± 17.7

The analyses were performed using the analysis of covariance. The covariables in the models include age, body mass index (both continuous), smoking, alcohol intake, occupational and leisure physical activity, hypertension, diabetes mellitus, Parkinson's disease, prior stroke, prior myocardial infarction, AFTC, 25OHD, and CRP. Unless otherwise stated, the variables were introduced in the models as described in the Table.

[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.005$; [d]$p < 0.001$—vs. the reference group using the post hoc Dunnett–Hsu test.

difference in grip strength lost significance after adjustment for upper limb RASM ($p = 0.26$). Men in the lowest AFTC quartile had lower upper limb RASM (3.5%, 0.28SD, $p < 0.001$), but not grip strength, vs. men in the highest quartile. However, men with low AFTC (<192 pmol/L) had 4.5% lower grip strength (0.18SD, $p < 0.01$) vs. men with AFTC ≥ 192 pmol/L, also after adjustment for upper limb RASM (3.8%, 0.16SD, $p < 0.05$). Men with increased CRP levels had 3.5% lower grip strength (0.23SD, $p < 0.05$) vs. men with normal CRP (<1 ng/mL). The difference in grip strength lost significance after adjustment for upper limb RASM.

In the models including the above confounders, Grade 2 and 3 vertebral fractures and multiple fractures were associated with lower grip strength (7.1%, 0.29SD, $p < 0.01$ and 6.5%, 0.27SD, $p < 0.05$, respectively, vs. men without these characteristics). The differences persisted after adjustment for upper limb RASM (6.5%, 0.28SD, $p < 0.05$ and 6.0%, 0.25SD, $p < 0.05$).

Poor physical function

We defined poor physical function as the score < 9 (lowest quintile). This threshold was more discriminating vs. others based on the preliminary analyses. Previously, the same threshold was strongly associated with mortality in another cohort of men.[46] Prevalence of poor physical function increased with age from 2% before the age 60 to 47% after the age of 80 (p for trend $p < 0.001$) (*Figure 1A*). After adjustment for age, men with poor physical function had 2.0% lower RASM of the lower limbs (0.20SD, $p < 0.05$).

In the multivariable logistic regression model, age, lower RASM of the lower limbs, low alcohol intake, low leisure physical activity, very high occupational physical activity, diabetes mellitus, history of stroke, low AFTC and 25OHD, high CRP, and vertebral fractures were all associated with higher odds of poor physical function (*Table 3*).

In the final model, variables showing thresholds were dichotomized: occupational physical activity as very high vs. others, 25OHD as <15 vs ≥15 ng/mL, CRP as ≥5 vs <5 ng/mL. Other variables were introduced as above. Presence of vertebral fracture was associated with higher odds of poor physical function (*Table 4*). Odds of poor physical function increased with vertebral fracture severity (trend $p < 0.005$). Non-vertebral and all fractures were associated with higher odds of poor physical function. Odds of poor physical function increased with the number of non-vertebral fractures (trend $p < 0.005$) and with the number of all fractures (trend $p < 0.001$). Trends did not change after additional adjustment for lower limb RASM.

Incident falls

The 12 men lost to follow-up were 5 years older and more often had ischemic heart disease ($p < 0.05$). Over 5 years, 144 men (of 813 who were followed up) sustained at least two falls. Men who sustained multiple falls were older. After adjustment for age, they had lower RASM of the lower limbs and lower calcium intake, spent less time outdoors, and self-reported more often Parkinson's disease and prior falls ($p < 0.05$ to <0.001).

Incidence of multiple falls increased with age (trend $p < 0.005$) (*Figure 1*B). In multivariable models, history of falls was associated with more than twofold higher risk of multiple falls. Grade 2 and 3 and multiple vertebral fractures were each associated with higher risk of multiple falls after adjustment for confounders (*Table 5*). For multiple non-vertebral fractures, point estimate was similar, but not significant, probably because only 15 men had multiple non-vertebral fractures. Men having multiple fractures (vertebral or non-vertebral) had a twofold higher risk of multiple falls after

Figure 1 A) Prevalence of poor physical function (defined as the lowest quintile of the score of physical function) according to the age. B) Incidence of multiple falls according to the age (the incidence was calculated using time to the first fall in men with multiple falls).

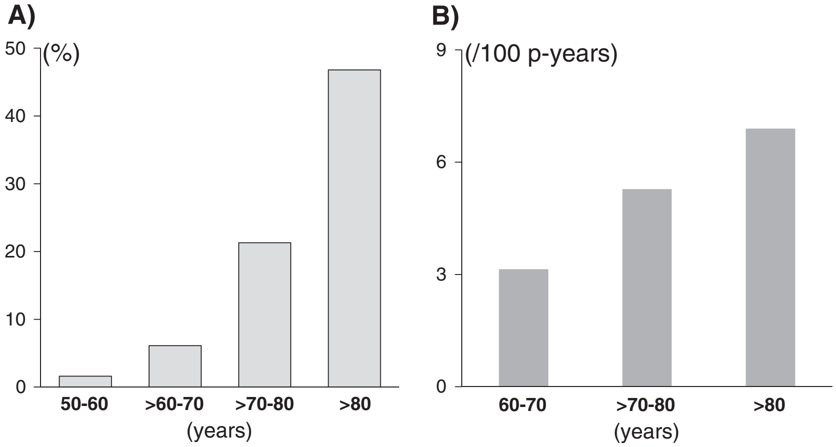

Table 3 Association of poor physical function (defined as score <9) with potential determinants in the multivariable model—all the variables were introduced simultaneously in the model

Variable	OR (95%CI)—without adjustment for lower limb RASM	OR (95%CI)—with adjustment for lower limb RASM
Lower limb RASM <5.28 kg/m^2	—	2.05 (1.03 – 4.04)[a]
5.28 – <5.66 kg/m^2	—	1.78 (0.90 – 3.51)
5.66 – <6.11 kg/m^2	—	2.04 (1.02 – 4.08)[a]
≥6.11 kg/m^2	—	1.00
Age (year)	1.13 (1.10 – 1.17)[d]	1.12 (1.09 – 1.16)[d]
Current smoking—yes vs. no	2.21 (0.94 – 5.19)	2.22 (0.94 – 5.26)
Alcohol drinking—≤1 unit/wk	2.21 (1.14 – 4.26)[a]	2.22 (1.14 – 4.30)[a]
>1 – 7 units/wk	2.26 (1.14 – 4.45)[a]	2.15 (1.07 – 4.29)[a]
>7 – 14 units/wk	1.00	1.00
>14 units/wk	1.50 (0.76 – 2.97)	1.42 (0.71 – 2.84)
Leisure physical activity—<1 vs ≥1 h/wk	3.56 (2.28 – 5.58)[d]	3.67 (2.33 – 5.77)[d]
Occupational physical activity—Light	1.00	1.00
Moderate	1.01 (0.51 – 2.01)	1.01 (0.51 – 2.02)
High	1.16 (0.59 – 2.26)	1.14 (0.58 – 2.24)
Very high	2.09 (1.06 – 4.14)[b]	2.06 (1.04 – 4.10)[b]
Diabetes mellitus—yes vs. no	2.68 (1.52 – 4.71)[d]	2.79 (1.57 – 4.96)[d]
History of stroke—yes vs. no	3.69 (1.42 – 9.61)[b]	3.52 (1.33 – 9.30)[d]
Apparent free testosterone—<192 pmol/L	2.48 (1.23 – 5.01)[b]	2.66 (1.31 – 5.41)[b]
192 – <243 pmol/L	1.45 (0.69 – 3.05)	1.46 (0.69 – 3.07)
243 – <297 pmol/L	2.66 (1.30 – 5.44)[b]	2.62 (1.28 – 5.39)[a]
≥297 pmol/L	1.00	1.00
25-Hydroxycholecalciferol—<15 ng/ml	2.18 (1.19 – 3.99)[d]	2.15 (1.15 – 4.27)[d]
15 – <21 ng/mL	1.12 (0.59 – 2.10)	1.12 (0.59 – 2.11)
21 – <28 ng/mL	0.70 (0.34 – 1.43)	0.74 (0.36 – 1.53)
≥28 ng/mL	1.00	1.00
C-reactive protein—<1 ng/mL	1.00	1.00
1 – <3 ng/mL	1.00 (0.57 – 1.74)	1.04 (0.60 – 1.82)
3 – <5 ng/mL	0.97 (0.44 – 2.16)	1.02 (0.46 – 2.27)
≥5 ng/mL	2.26 (1.18 – 4.33)[c]	2.22 (1.15 – 4.27)[b]
Abdominal aortic calcification (unit)	1.07 (0.93 – 1.16)	1.06 (0.92 – 1.13)
Vertebral fracture—yes vs. no	2.53 (1.19 – 2.02)[c]	2.59 (1.40 – 4.80)[c]

[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.005$; [d]$p < 0.001$.

adjustment for all confounders. In the fully adjusted models, risk of multiple falls increased with the number and severity of vertebral fractures and with the number of all fractures (trend p < 0.05 for all).

In these models, following variables were associated with higher risk of multiple falls: age (HR = 1.03/year, 95%CI: 1.00–1.06, p = 0.05), diabetes mellitus (HR = 1.59, 95%CI: 1.00–2.53, p = 0.05), Parkinson's disease (HR = 3.97, 95%CI: 1.78–8.89, p < 0.001), low AFTC (lowest vs. three upper quartiles combined: HR = 1.83, 95%CI: 1.19–2.83, p < 0.01), and less time spent outdoors (HR = 1.08 per h/wk, 95%CI: 1.04–1.11, p < 0.005).

Table 4 Association of poor physical function with the prior fractures in multivariable models adjusted for the confounders presented in *Table 3*

Variable	*N*	OR (95%CI)—without adjustment for lower limb RASM	OR (95%CI)—with adjustment for lower limb RASM
Vertebral fracture—yes vs. no		2.45 (1.34 – 4.48)[b]	2.59 (1.41 – 4.76)[c]
Vertebral fracture severity—none	798	1.00[#]	1.00[#]
Grade 1	17	1.98 (0.47 – 8.35)	2.17 (0.49 – 9.58)
Grade 2	56	2.12 (1.01 – 4.44)[a]	2.28 (1.08 – 4.82)[a]
Grade 3	19	4.24 (1.38 – 13.0)[c]	4.04 (1.31 – 12.5)[b]
Non-vertebral fractures—yes vs no		2.36 (1.27 – 4.38)[b]	2.28 (1.22 – 4.25)[b]
Non-vertebral fractures—0	790	1.00[#]	1.00[#]
1	84	1.81 (0.90 – 3.63)	1.76 (0.87 – 3.54)
>1	16	7.56 (2.13 – 26.9)[b]	7.05 (1.96 – 25.3)[a]
All fractures—yes vs. no		2.56 (1.55 – 4.24)[d]	2.57 (1.55 – 4.27)[d]
Number of all fractures—none	723	1.00[§]	1.00[§]
1	106	1.91 (1.03 – 3.54)[b]	1.92 (1.03 – 3.58)[a]
>1	61	3.99 (1.97 – 8.09)[c]	3.96 (1.95 – 8.05)[c]

Both models are adjusted for age, current smoking, alcohol drinking, leisure and occupational physical activity, diabetes mellitus, prior stroke, apparent free testosterone concentration, 25-hydroxycholecalciferol, C-reactive protein, and abdominal aortic calcification.
[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.005$; [d]$p < 0.001$; *p* for trend; [#]$p < 0.005$ [§]$p < 0.001$.

Table 5 Association with vertebral and non-vertebral fractures at baseline with the risk of multiple falls assessed prospectively over 5 years

	N	Multivariable model HR (95%CI)	+ as above and lower limb RASM HR (95%CI)
Vertebral fracture: 2 and 3 vs. 0 and 1		2.22 (1.37 – 3.60)^{c}	2.22 (1.37 – 3.61)^{c}
Vertebral fracture—none	723	1.00$^{\#}$	1.00$^{\#}$
1	54	1.59 (0.86 – 2.94)	1.59 (0.86 – 2.94)
>1	36	2.73 (1.39 – 5.35)^{c}	2.73 (1.39 – 5.36)^{c}
Vertebral fracture severity—none	723	1.00$^{\#}$	1.00$^{\#}$
Grade 1	16	0.52 (0.07 – 3.77)	0.53 (0.07 – 3.84)
Grade 2	57	2.16 (1.27 – 3.66)^{c}	2.16 (1.27 – 3.66)^{c}
Grade 3	17	2.39 (0.85 – 6.71)	2.39 (0.85 – 6.72)
Non-spine fractures: yes vs. no		1.36 (0.81 – 2.27)	1.36 (0.81 – 2.28)
Non-spine fractures: none	715	1.00	1.00
1	83	1.19 (0.67 – 2.12)	1.19 (0.67 – 2.13)
>1	15	2.62 (0.94 – 7.27)	2.67 (0.96 – 7.46)
All fractures: yes vs. no		1.74 (1.17 – 2.59)^{b}	1.74 (1.17 – 2.59)^{b}
All fractures: none	651	1.00$^{\#}$	1.00$^{\#}$
1	104	1.45 (0.89 – 2.36)	1.45 (0.89 – 2.37)
>1	58	2.61 (1.48 – 4.61)^{d}	2.61 (1.48 – 4.61)^{d}

$^{a}p < 0.05$; $^{b}p < 0.01$; $^{c}p < 0.005$; $^{d}p < 0.001$; p for trend; $^{*}p < 0.05$; $^{\#}p < 0.005$

Multivariable model—adjusted for age, height, current smoking, time spent outdoors, calcium intake, prior myocardial infarction, prior stroke, diabetes mellitus, Parkinson's disease, abdominal aortic calcification, AFTC, and C-reactive protein.

Discussion

In a large group of older men, we have shown that Grade 2 and 3 vertebral fractures and history of multiple fractures (vertebral and non-vertebral) are associated with low grip strength, poor physical function, and higher risk of incident multiple falls. These associations persisted after adjustment for muscle mass and other confounders.

We confirm that the association of muscle mass measured by DXA with muscle strength and physical function is weak. Muscle mass and strength do not change in parallel with age.[50] DXA overestimates skeletal mass because water and fibrous tissue are detected as 'lean'.[51] Muscle strength and physical function depend on muscle mass only partly.[52] Age-related factors contribute to the discrepancy in muscle mass and strength. Parkinson's disease and diabetes mellitus are associated with low muscle strength, but not mass. In these diseases the deficit in grip strength may be related to metabolic defect of muscle, defect of transmission at neuromuscular junction, and poor joint mobility.[53,54] CRP and 25OHD correlated with muscle mass and strength. After adjustment for upper limb RASM, their association with grip strength lost significance suggesting that they act on muscle strength via muscle mass.[55]

Upper limb RASM and grip strength were weakly associated with AFTC; however, they are lower mainly in hypogonadal men.[56] Lower grip strength and poor physical function were associated with very high occupational physical activity, also after adjusting for confounders. These men stem from lower social classes and have low incomes, poor education, and poor nutritional and health status. These factors are associated with low muscle strength.[57–59] In addition, heavy workload increases the risk of diseases of the upper limbs, e.g. carpal tunnel syndrome, which are associated with lower grip and pinch strength.[60,61]

Smoking and alcohol intake were not associated with muscle mass and strength. In our study, low alcohol drinking was associated with poor physical function. Moderate alcohol intake was associated with better physical performance and lower mortality in older men.[62,63] Several factors may contribute to these results: (i) heavy drinking may deteriorate muscle, (ii) men with poor health and low muscle strength intentionally limit alcohol intake, and (iii) moderate alcohol drinking is associated with better social participation and more active lifestyle.[64]

Men with Grade 2 and 3 vertebral fractures had lower grip strength, but not upper limb RASM. Patients with vertebral fracture were reported to have lower muscle mass in some,[65,66] not all studies.[28,29] Vertebral fractures were associated with low muscle strength in both sexes and lower functional reach of arms in women, not men.[15,16,67,68] In women, they were associated with abnormal electromyographic activity of trunk and paraspinal muscles.[69,70] However, grip strength and major fragility fractures are associated with high mortality.[71,72] Thus, the association between fractures and low grip strength may reflect residual confounding related to factors impairing health and bone strength and not accounted for in the model, e.g. severity and duration of co-morbidities, cancer, and heart failure.

Weak associations ($p < 0.05$) found in a large number of comparisons should be interpreted cautiously. Some may be because of a low number of men with a specific condition (Parkinson's disease and myocardial infarction). Others, e.g. with AFTC or CRP, reflect association of limited biological significance or simply a type I statistical error.

Age, low lower limb RASM, low leisure physical activity, very high occupational physical activity, diabetes mellitus, prior stroke, low AFTC, and 25OHD as well as high CRP levels were each associated with poor physical function. Several variables were associated with higher risk of fall, e.g. diabetes mellitus, Parkinson's disease, low AFTC, or prior stroke. These data confirm previous studies.[26,30,73–76]

Men with Grade 2 and 3 vertebral fractures had poor physical function and high risk of multiple falls. Data on this subject in men are limited. In 555 men, vertebral fractures were associated with longer up-to-go times and poor life quality.[15] In the Rotterdam study, severe vertebral fractures were associated with greater disability than moderate ones.[14] In 147 patients with vertebral fracture, greater fracture severity was associated with greater disability and pain.[17] Physical capacity was poorer in men with vertebral fracture vs. age-matched controls.[67,68] However, these analyses were poorly controlled for potential confounders.

Vertebral fractures may aggravate scoliosis or kyphosis leading to deviation from the correct position and displacement of the trunk centre of mass.[77] Thus, they may impair postural stability and gait (proportionally to the fracture number and severity) leading to the higher fall risk. Backache may compromise sleep leading to sleepiness and higher fall risk.[9,78] They may also change lordotic curve leading to difficulty in rising from a chair.[14,79]

Fractures, mainly severe or multiple, are associated with lower physical activity. The reduced physical activity may result in lower muscle strength, impaired neuromuscular coordination, and poor balance. This association has been studied in the elderly after a hip fracture.[18] In women aged 35–92 years, lower limb fractures were associated with poor mobility for several weeks.[80] By contrast, in our study, only few men self-reported hip fracture. Poor physical function is not limited to the period right after fracture occurrence. Hip, arm, and clinical vertebral fractures were associated with a long-term decline in physical performance.[81] In an Icelandic cohort, non-vertebral fractures were associated with poor physical function.[68] Again, most of the above analyses were only partly controlled for confounders. In our study, the odds of poor physical function were independent of confounders, including lower limb RASM, and showed significant trends across increasing fracture number and severity. Thus, the effect of fractures may accumulate and be mediated by other factors than loss of muscle mass, e.g. pain, deformation of lower limbs, and impaired coordination.

Poor physical function and fall risk in men with fractures may be because of reverse causation—poor physical function and propensity to fall may pre-exist and foster the fracture occurrence. However, vertebral fracture is rarely related to fall and median time elapse since the last non-vertebral fracture was 9 years. Moreover, higher muscle mass and strength are associated with wider bones and better bone microarchitecture, two factors which reduce risk of fracture.[35,43,82] Thus, lower muscle strength after a fracture may have a negative impact on bone.

Our study has limitations. The cross-sectional design limits inference on cause and effect. Older volunteers are a healthier subset of population. Individuals with severe disability do not accept invitation. Thus, our data may underestimate the strength of associations and cannot be extrapolated to the population of older men. Semiquantitative assessment of vertebral fracture is subjective. Prevalent non-vertebral fractures and co-morbidities were self-reported without adjudication. Some non-vertebral fractures could be forgotten and some non-fracture traumas be reported as fractures.[83,84] However, we could not scrutinize medical records. RASM may be overestimated, mainly in oldest men. Water and fibrous tissue increase with age and are considered 'lean'. Grip strength was measured only at the dominant arm. We did not measure strength of lower limbs. However, results of the Short Physical Performance Battery, which is similar to our score, are significantly correlated with the knee extensor strength.[85] Questionnaires were sent once yearly, and men might forget some falls.[86] However, recall bias increases with cognitive impairment.[87] We studied home-dwelling men without severe cognitive impairment at baseline. Then, during filling in follow-up questionnaires, they could receive help from a proxy or from a medical professional if they were institutionalized.

Thus, we show that, in older men, Grade 2 and 3 vertebral fractures and multiple vertebral and non-vertebral fractures are associated with lower grip strength, poor physical function, and higher risk of multiple falls after adjustment for multiple confounders. This suggests a real direct association rather than residual confounding. This finding indicates a robust association of prevalent fractures with dynapenia and functional impairment in the elderly. The higher risk of fracture in men with prior fractures may be partly mediated by higher risk of fall and poor physical function, which impair protective reflexes.[88] Thus, one fracture can initiate a vicious circle starting with reduced physical activity and leading, through dynapenia, poor balance, and higher risk of fall, to another fracture. Therefore, patients with fractures may need physical therapy regardless of their general health status.

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Conflict of interest

The authors declare that they have no conflict of interest as concerns this manuscript.

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