Table 1 Comparison of baseline characteristics of subjects without and with mild cognitive impairment (MCI)

	Total (n=1676)			Men (n=591)			Women (n=1085)		
	Without MCI (N=1601)	With MCI (N=75)	p Value (Without vs with MCI)	Without MCI (N=561)	With MCI (N=30)	p Value (Without vs with MCI)	Without MCI (N=1040)	With MCI (N=45)	p Value (Without vs with MCI)
Number of subjects (prevalence, %) classified by age-strata									
≤39 (year)	45	0 (0.0)		14	0 (0.0)		31	0 (0.0)	
40–49	148	1 (0.7)		43	1 (2.3)		105	0 (0.0)	
50–59	314	2 (0.6)	<0.001***	106	1 (0.9)	<0.001***	208	1 (0.5)	<0.001***
60–69	467	10 (2.1)		151	5 (3.2)		316	5 (1.6)	
70–79	496	35 (6.6)		202	14 (6.5)		294	21 (6.7)	
≥80	131	27 (17.1)		45	9 (16.7)		86	18 (17.3)	
Total	1601	75 (4.5)		561	30 (5.1)		1040	45 (4.2)	
Mean values (SDs) of MMSE summary score	28.5 (1.7)	21.2 (3.2)	<0.0001***	28.4 (1.8)	20.7 (4.4)	<0.0001***	28.6 (1.7)	21.5 (2.1)	<0.0001***
Mean values (SDs) of selected characteristics									
Age (year)	64.7 (11.9)	75.8 (8.1)	<0.0001***	65.8 (11.7)	74.0 (9.3)	0.0002***	64.1 (12.0)	77.0 (6.9)	<0.0001***
Height (cm)	155.5 (9.1)	148.7 (9.8)	<0.0001***	163.8 (7.1)	157.4 (5.8)	<0.0001***	151.1 (6.7)	142.9 (7.4)	<0.0001***
Weight (kg)	55.8 (10.7)	51.7 (11.7)	0.0011**	62.5 (10.8)	57.7 (12.1)	0.0181*	52.2 (8.8)	47.7 (9.6)	0.0007***
BMI (kg/m^2)	23.0 (3.4)	23.2 (3.7)	0.5845	23.2 (3.2)	23.2 (3.9)	0.9346	22.9 (3.5)	23.2	0.4877
Grip strength (better side) (kg)	27.8 (9.5)	20.8 (8.5)	<0.0001***	36.4 (8.8)	27.6 (8.2)	<0.0001***	23.3 (6.0)	16.5 (5.3)	<0.0001***
Grip strength (worse side) (kg)	24.6 (9.3)	16.8 (9.3)	<0.0001***	32.8 (9.1)	22.4 (10.6)	<0.0001***	20.1 (5.6)	13.1 (6.2)	<0.0001***
Percentage of selected characteristics (%)									
Residing in a coastal area	50.1	28.0	<0.001***	47.8	26.7	0.024*	51.4	28.9	0.003**
Current smoking habit (more than once a month)	13.3	10.0	0.428	30.4	21.4	0.312	3.9	2.4	0.624
Current alcohol consumption (more than once a month)	40.5	24.0	0.004**	67.6	46.7	0.018*	26.0	8.9	0.010*
Regular exercise after graduation from school	14.9	4.0	0.008**	34.4	6.7	0.002**	4.4	2.2	0.478
Prevalence of KOA at the baseline (%)	48.8	75.7	<0.001***	41.0	50.0	0.328	53.0	93.2	<0.001***

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; KOA, knee osteoarthritis; MMSE, mini-mental state examination; n, number of subjects.

significantly higher than the percentage in the without-MCI group (48.8%, p<0.001). This significant tendency was observed in women, while in men the association was not significant.

Occurrence of radiographic KOA in participants with and without MCI

The baseline prevalence of KOA in the 1384 individuals who attended follow-up was 46.8% (men 37.3%; women 51.6%). After the exclusion of participants with a baseline KL grade ≥2 at one or both knees, the cumulative incidence of OA during the 3-year follow-up period was estimated using an at-risk population of 728 individuals (290 men, 438 women) without OA in either knee at baseline. Among these, 71 participants (18 men, 53 women) were newly diagnosed with KOA, and the annual cumulative incidence was estimated as 3.3% (men 2.1%; women 4.0%). The incidence of KOA increased with age (table 2).

The MMSE score was significantly lower in participants with, compared to those without, incident radiographic KOA (p<0.0001), and the prevalence of MCI at baseline was significantly higher (p=0.003). Those with KOA tended to reside in a mountainous area, were significantly taller, had greater BMI and weaker grip strength in both hands and were less likely to smoke, drink alcohol or exercise regularly compared with those without OA. History of knee injury was more common among those without KOA (table 2).

On univariate regression analysis, a one-digit increase in the MMSE score was associated with a 24% decreased risk of incident radiographic KOA (p<0.001; table 3). This trend remained after adjustment for age, gender, regional differences and BMI in model 1 (OR 0.85 for +1 MMSE score; p=0.015) and after adjustment for age, gender, regional differences, BMI, grip strength (kg) on the worse side, smoking, alcohol consumption, regular exercise and history of knee injury in model 2 (OR 0.83; p=0.010). The presence of MCI was associated with a fivefold increased risk of incident KOA (p=0.008), with ORs of 4.59 (p=0.027) in model 1 and 4.90 (p=0.027) in model 2.

Progression of radiographic KOA with and without MCI

We excluded 88 participants (21 men, 67 women) with a baseline KL grade of 4 at one or both knees, before estimating the cumulative rate for the progression of KOA during a 3-year follow-up. We estimated the rate of progression rate in KL grades over the 3 years using the population at risk comprising 1296 individuals (445 men, 851 women). Among these, 311 individuals (86 men, 225 women) had a higher KL grade assigned to one or both knees at follow-up than at baseline. The annual rate of progression in KL grades for either knee over the 3-year period was 8.0% (men 6.4%, women 8.8%) in the overall population at risk, and the rate increased with age (table 4). The MMSE summary score was significantly lower (p<0.0001) and the baseline prevalence of MCI was significantly higher (p=0.008) in participants with, than in those without, progression of radiographic KOA. Participants with progression of radiographic KOA tended to reside in a mountainous area, were significantly older and taller, had greater BMI and weaker grip strength in both hands and were less likely to smoke, drink alcohol or take regular exercise compared to those who did not have progression of KOA (table 4).

A one-digit increase in the MMSE was associated with a 16% increased risk of progression of radiographic KOA (OR 0.84; p<0.001). This tendency was no longer significant after adjustment for age, gender, regional differences and BMI in model 1 (OR 0.95; p=0.131), and for age, gender, regional differences, BMI, grip strength (worst side), smoking, alcohol consumption, regular exercise and history of knee injuries in model 2 (OR 0.96; p=0.232; table 5). On univariate analysis, the presence of MCI was associated with a 2.5-fold increased risk of progression of KOA (OR 2.54; p=0.010), but this was not significant after adjustment for confounding factors in model 1 (OR 1.56; p=0.242) or model 2 (OR 1.38; p=0.416).

Association of inflammation and metabolic risk factors with both KOA and MCI

In addition to the factors adjusted in model 2, we assessed the following two factors as potential confounders influencing both KOA and MCI: subclinical inflammation and metabolic risk factors.

As an index of inflammation, baseline serum C reactive protein (CRP) level was added as an explanatory factor in a logistic regression analysis similar to that performed in model 2. The adjusted ORs for the occurrence of OA in relation to the MMSE summary score (OR 0.83; 95% CI, 0.72 to 0.96 for +1 MMSE score; p=0.010) or to the presence of MCI (OR 5.18; 95% CI, 1.24 to 21.6 for presence of MCI; p=0.024) remained unchanged, and the serum CRP level was not significantly associated with occurrence (OR 0.47; 95% CI, 0.09 to 2.40 for +1 CRP level; p=0.365) or progression of OA (OR 0.96; 95% CI, 0.67 to 1.37; p=0.818).

Then, we performed logistic regression analysis, similar to that performed in model 2, by using the metabolic risk factors overweight (1: BMI≥25 kg/m^2, 0: BMI<25 kg/m^2), hypertension (1: systolic blood pressure (BP) ≥130 mm Hg and/or diastolic BP ≥85 mm Hg, 0: systolic BP <130 mm Hg and diastolic BP <84 mm Hg), dyslipidaemia (1: serum high-density lipoprotein cholesterol (HDL-cho) level <40 mg/dl, 0: HDL-cho level ≥40 mg/dl) and impaired glucose tolerance (1: serum haemoglobin A1c (HbA1c) level ≥5.5%, 0: HbA1c level <5.5%). Furthermore, subjects receiving medication for hypertension, dyslipidaemia or diabetes mellitus were regarded as having hypertension, dyslipidaemia or impaired glucose tolerance, respectively. The adjusted ORs for the occurrence of KOA in relation to the MMSE summary score (OR 0.84; 95% CI, 0.73 to

Table 2 Mean values (SDs) of anthropometric factors, mini-mental state examination (MMSE) and prevalence of mild cognitive impairment (MCI) and selected characteristics vs the occurrence of knee osteoarthritis

Occurrence of KOA	Total			Men			Women		
	KOA (–) (n=657)	KOA (+) (n=71)	p Value	KOA (–) (n=272)	KOA (+) (n=18)	p Value	KOA (–) (n=385)	KOA (+) (n=53)	p Value
Number of subjects classified by age-strata (cumulative incidence, %/year)									
≤39 (year)	38	0 (0.0)		10	0 (0.0)		28	0 (0.0)	
40–49	118	1 (0.3)		36	0 (0.0)		82	1 (0.4)	
50–59	201	15 (2.3)	<0.001***	77	0 (0.0)	0.009**	124	(3.6)	<0.001***
60–69	177	27 (4.4)		76	11 (4.2)		101	(4.6)	
70–79	108	23 (5.9)		62	6 (2.9)		46	17 (9.0)	
≥80	15	5 (8.3)		11	1 (2.8)		4	4 (16.7)	
Mean values (SDs) for MMSE summary score and prevalence of MCI									
MMSE summary score	29.1 (1.6)	28.0 (2.3)	<0.0001***	28.8 (1.9)	27.3 (2.7)	0.0017**	29.3 (1.3)	28.2 (2.1)	<0.0001***
Prevalence of MCI (%)	7/654 (1.1)	4/71 (5.6)	0.003**	6/270 (2.2)	2/18 (11.1)	0.026*	1/384 (0.3)	2/53 (3.8)	0.004*
Mean values (SDs) for age, anthropometric factors and neuromuscular function									
Age (year)	58.2 (11.8)	67.3 (8.2)	<0.0001***	61.0 (11.8)	70.0 (6.1)	0.0021**	56.4 (11.4)	66.4 (8.7)	<0.0001***
Height (cm)	158.8 (8.6)	153.9 (7.6)	<0.0001***	165.6 (7.0)	162.0 (5.0)	0.0360*	154.0 (6.0)	151.2 (6.2)	0.0018**
Weight (kg)	56.8 (11.0)	56.0 (8.8)	0.5560	63.7 (11.0)	63.7 (9.2)	0.9859	51.9 (8.1)	53.4 (7.1)	0.2051
BMI (kg/m^2)	22.4 (3.2)	23.6 (2.9)	0.0035**	23.2 (3.2)	24.2 (3.1)	0.1709	21.9 (3.1)	23.4 (2.8)	0.0012**
Grip strength (better side) (kg)	31.3 (9.9)	26.7 (8.1)	0.0002***	39.4 (8.8)	35.9 (7.1)	0.0996	25.6 (6.0)	23.5 (5.6)	0.0171*
Grip strength (worse side) (kg)	28.0 (9.6)	23.0 (8.5)	<0.0001***	35.9 (9.0)	30.7 (11.0)	0.0188*	22.5 (5.1)	20.4 (5.5)	0.0065**
Percentage of selected characteristics, %									
Residing in a coastal area	70.8	56.3	0.012*	66.9	55.6	0.324	73.5	56.6	0.011*
Current smoking habit (more than once a month)	16.9	7.1	0.034*	34.2	27.8	0.577	4.7	0.0	0.110
Current alcohol consumption (more than once a month)	47.9	35.2	0.041*	70.0	61.1	0.428	32.5	26.4	0.375
Regular exercise after graduation from school	19.9	7.0	0.008**	37.5	27.8	0.408	7.5	0.0	0.039*
Past injury of either knee	1.8	5.6	0.038*	0.4	5.6	0.010*	2.9	5.7	0.277

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; KOA, knee osteoarthritis; KOA(–), non-occurrence of KOA; KOA(+), occurrence of KOA; n, number of subjects.

Table 3 ORs for occurrence of knee osteoarthritis during the 3-year follow-up period versus mild cognitive impairment (MCI)

MMSE summary score		Univariate analysis			Logistic regression model 1			Logistic regression model 2		
Explanatory variables	**Reference**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
MMSE summary score	+1 score	0.76	0.68 to 0.85	<0.001***	0.85	0.73 to 0.97	0.015*	0.83	0.72 to 0.96	0.010*
Other potential risk actors										
Age (year)	1 year				1.09	1.06 to 1.13	<0.001**	1.10	1.06 to 1.14	<0.001***
Gender	0: men, 1: women				4.36	2.33 to 8.16	<0.001**	4.02	1.50 to 10.74	0.006**
Region	0: mountainous area, 1: coastal area				0.78	0.45 to 1.35	0.380	0.76	0.43 to 1.35	0.354
BMI (kg/m^2)	+1 kg/m^2				1.23	1.12 to 1.34	<0.001**	1.22	1.11 to 1.34	<0.001***
Grip strength (worse side) (kg)	+1 kg							1.01	0.96 to 1.06	0.730
Smoking	0: exsmoker or never smoker, 1: current smoker							1.01	0.35 to 2.91	0.986
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							1.11	0.60 to 2.04	0.746
Regular exercise after graduation from school	0: no, 1: yes							0.57	0.20 to 1.65	0.302
History of knee injuries	0: no, 1: yes							4.76	1.26 to 17.97	0.021*
MCI		Univariate analysis			Logistic regression model 1			Logistic regression model 2		
Explanatory variables										
MCI	0: absence, 1 :presence	5.52	1.57 to 19.34	0.008**	4.59	1.18 to 17.7	0.027*	4.90	1.20 to 20.05	0.027*
Other potential risk actors										
Age (year)	1 year				1.10	1.07 to 1.14	<0.001**	1.10	1.07 to 1.15	<0.001***
Gender	0: men, 1: women				4.36	2.32 to 8.17	<0.001**	3.80	1.42 to 10.19	0.008**
Region	0: mountainous area, 1: coastal area				0.75	0.44 to 1.30	0.310	0.73	0.41 to 1.29	0.280
BMI (kg/m^2)	+1 kg/m^2				1.23	1.13 to 1.35	<0.001**	1.23	1.12 to 1.34	<0.001***
Grip strength (worse side) (kg)	+ 1 kg							1.00	0.96 to 1.05	0.870
Smoking	0: exsmoker or never smoker, 1: current smoker							1.08	0.38 to 3.12	0.885
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							1.10	0.59 to 2.02	0.770
Regular exercise after graduation from school	0: no, 1: yes							0.57	0.20 to 1.65	0.304
Past history of knee injuries	0: no, 1: yes							4.28	1.13 to 16.19	0.032*

*p<0.05, **p<0.01, ***p<0.001.
BMI, body mass index; n, number of subjects; MMSE, mini-mental state examination.

Table 4 Mean values (SDs) of anthropometric factors, mini-mental state examination (MMSE) and prevalence of mild cognitive impairment (MCI) and selected characteristics versus progression of knee osteoarthritis

Progression of KOA Women

	Total			Men			Women		
	Progression			Progression			Progression		
	(–)	(+)		(–)	(+)		(–)	(+)	
	(n=985)	(n=311)	p Value	(n=359)	(n=86)	p Value	(n=626)	(n=225)	p Value
Number of subjects classified by age-strata (Proportion of progression, %/year)									
≤39 (year)	37	2 (1.7)		9	1 (3.3)		28	1 (1.1)	
40–49	128	7 (1.7)		38	2 (1.7)		90	5 (1.8)	
50–59	248	44 (5.0)	<0.001***	89	8 (2.8)	<0.001***	159	36 (6.2)	<0.001***
60–69	292	105 (8.2)		101			191	79 (9.8)	
70–79	241	115 (10.8)		105	38 (8.9)		136	77 (12.1)	
≥80	39	38 (16.5)		17	11 (13.1)		22	27 (18.4)	
Mean values (SDs) for MMSE summary score and prevalence of MCI									
MMSE summary score	28.7 (1.8)	28.0 (2.2)	<0.0001***	28.5 (1.9)	27.9 (2.3)	0.0056**	28.8 (1.8)	28.1 (2.1)	<0.0001***
Prevalence of MCI (%)	18/980 (1.8)	14/295 (4.5)	0.008**	9/357 (2.5)	5/85 (5.9)	0.112	9/623 (1.4)	9/224 (4.0)	0.022*
Mean values (SDs) for age, anthropometric factors and neuromuscular function									
Age (year)	61.6 (11.9)	68.7 (9.3)	<0.0001***	63.3 (11.8)	70.0 (9.4)	<0.0001***	60.7 (11.9)	68.2 (9.3)	<0.0001***
Height (cm)	156.7 (8.9)	153.1 (8.6)	<0.0001***	164.6 (7.1)	161.8 (6.2)	0.0010**	152.2 (6.4)	149.7 (6.9)	<0.0001***
Weight (kg)	56.0 (10.9)	55.6 (9.9)	0.5496	63.1 (10.9)	62.8 (10.2)	0.8520	52.0 (8.6)	52.9 (8.4)	0.1883
BMI (kg/m^2)	22.7 (3.3)	23.6 (3.1)	<0.0001***	23.2 (3.2)	23.9 (3.1)	0.0643	22.4 (3.3)	23.5 (3.1)	<0.0001***
Grip strength (better side) (kg)	29.3 (9.7)	25.7 (8.0)	<0.0001***	38.1 (8.7)	34.4 (7.2)	0.0003***	24.3 (6.0)	22.4 (5.3)	<0.0001***
Grip strength (worse side) (kg)	26.0 (9.4)	22.5 (7.9)	<0.0001***	34.6 (8.8)	30.1 (8.7)	<0.0001***	21.1 (5.3)	19.6 (5.2)	0.0003***
Percentage of selected characteristics (%)									
Residing in a coastal area	57.9	42.1	<0.001***	53.8	44.2	0.110	60.4	41.3	<0.001***
Current smoking habit (more than once a month)	14.1	8.6	0.013*	31.2	24.4	0.220	4.1	2.3	0.222
Current alcohol consumption (more than once a month)	44.4	32.5	<0.001***	72.1	57.0	0.006**	28.6	23.1	0.114
Regular exercise after graduation from school	18.1	8.0	<0.001***	39.6	23.3	0.005**	5.8	2.2	0.034*
Past injury of either knee	2.0	3.2	0.226	1.1	3.5	0.112	2.6	3.1	0.660

*p<0.05, **p<0.01, ***p<0.001.
KOA, knee osteoarthritis; progression(–), no progression of the Kellgren-Lawrence grade; progression(+), progression of the Kellgren-Lawrence grade.
BMI, body mass index; n, number of subjects.

Table 5 OR for the progression of the Kellgren-Lawrence grade for either knee during the 3-year follow-up period versus mild cognitive impairment (MCI)

MMSE summary score			Univariate analysis		Logistic regression model 1			Logistic regression model 2		
Explanatory variables	Reference	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
MMSE summary score	+1 score	0.84	0.79 to 0.90	<0.001***	0.95	0.88 to 1.02	0.131	0.96	0.89 to 1.03	0.232
Other potential risk actors										
Age (year)	+1 year				1.06	1.05 to 1.08	<0.001***	1.06	1.04 to 1.07	<0.001***
Gender	0: men, 1: women				1.89	1.40 to 2.55	<0.001***	1.29	0.798 to 2.11	0.308
Region	0: mountainous area, coastal 1: area				0.75	0.57 to 1.00	0.048*	0.69	0.52 to 0.92	0.011*
BMI (kg/m^2)	+ 1 kg/m^2				1.12	1.07 to 1.17	<0.001***	1.13	1.08 to 1.18	<0.001***
Grip strength (worse side) (kg)	+1 kg							0.99	0.97 to 1.02	0.572
Smoking	0: exsmoker or never smoker, 1: current smoker							0.99	0.59 to 1.64	0.964
Alcohol consumption	0: exdrinker or never drinker, 1 current drinker							0.84	0.61 to 1.15	0.274
Regular exercise after graduation from school	0: no, 1: yes							0.55	0.33 to 0.91	0.021*
History of knee injuries	0: no, 1: yes							2.27	0.99 to 5.22	0.053
MCI			Univariate analysis		Logistic regression model 1			Logistic regression model 2		
Explanatory variables										
MCI	0: absence, 1: presence	2.54	1.25 to 5.16	0.010*	1.56	0.74 to 3.30	0.242	1.38	0.63 to 3.03	0.416
Other potential risk actors										
Age (year)	+1 year				1.07	1.05 to 1.08	<0.001***	1.06	1.04 to 1.08	<0.001***
Gender	0: men, 1: women				1.89	1.40 to 2.54	<0.001***	1.26	0.77 to 2.05	0.353
Region	0: mountainous area, coastal 1: area				0.75	0.56 to 0.99	0.041*	0.68	0.51 to 0.91	0.010*
BMI (kg/m^2)	+ 1 kg/m^2				1.13	1.08 to 1.17	<0.001***	1.13	1.08 to 1.18	<0.001***
Grip strength (worse side) (kg)	+1 kg							0.99	0.97 to 1.02	0.484
Smoking	0: exsmoker or never smoker, 1: current smoker							0.99	0.60 to 1.65	0.974
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							0.83	0.61 to 1.15	0.264
Regular exercise after graduation from school	0: no, 1: yes							0.55	0.33 to 0.91	0.021*
History of knee injuries	0: no, 1: yes							2.27	0.99 to 5.21	0.053

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; ; MMSE, mini mental state examination; n, number of subjects.

0.97 for +1 MMSE score; p=0.019) or to the presence of MCI (OR 4.78; 95% CI, 1.15 to 19.9 for the presence of MCI; p=0.032) remained significant, and hypertension was also significantly associated with the occurrence of KOA in relation to MMSE summary score (OR 2.23; 95% CI, 1.04 to 4.79 for the presence of hypertension; p=0.039) or to the presence of MCI (OR 2.26; 95% CI, 1.06 to 4.85; p=0.036). However, there was no significant association between the occurrence of KOA and overweight, dyslipidaemia and impaired glucose tolerance after adjustment for the factors used in model 2.

DISCUSSION

We studied a population-based cohort with a high participation rate (81.9%) over a period of 3 years, and observed a significant association between the baseline presence of MCI and incident radiographic KOA identified at 3-year follow-up. This association persisted after adjustment for potential confounding factors.

In contrast, we did not observe an association between MCI and further progression of radiographic KOA identified at baseline. We identified progression of KOA when the KL grade was higher at follow-up than at baseline; MCI might have had less influence in patients with an increase of at least one KL grade compared to baseline. We reanalysed the influence of the MMSE score or the presence of MCI on rapid progression of OA, which was defined as an increase of at least two KL grades at either knee at follow-up. The results were similar after adjustment for confounders as in model 2; that is, we identified a significant association between MMSE score and rapid progression of OA (OR 0.84; 95% CI, 0.73 to 0.98, for +1 MMSE score; p=0.026). The OR for rapid progression of OA was increased in the presence of MCI, but not significantly so (OR 2.73; 95% CI, 0.71 to 10.5; p=0.144). Then we concluded that the influence of cognitive decline in the future KOA was more pronounced in occurrence of radiographic KOA than in progression.

Links between musculoskeletal disease and dementia have been reported previously; osteoporosis at the femoral neck, for example, is more common in patients with Alzheimer's disease than in healthy volunteers,[19] but the relationship between KOA and dementia has not been examined. In the current analysis, we showed that the occurrence of KOA was influenced not only by the MMSE scores but also by the presence of MCI. We think that this may be the effect of subclinical inflammation in both MCI and KOA, as inflammatory mechanisms could be involved in the pathogenesis of MCI[19 20] as well as OA.[21] Therefore, we performed logistic regression analysis similar to that performed in model 2, with the addition of the CRP values. The adjusted ORs for the occurrence of OA in relation to the MMSE summary score or to the presence of MCI remained unchanged, and serum CRP level was not significantly associated with occurrence or progression of OA. However, we used a standard method to measure CRP levels, and further studies using a more sensitive measurement method are required to assess the effect of systemic inflammation on cognitive impairment and KOA.

Another hypothesis is that there are hidden confounding factors that might affect both MCI and the onset of KOA. We considered risk factors for metabolic syndrome as potential confounders. Metabolic risk factors such as hypertension and diabetes have been suggested to play a role in the pathogenesis of Alzheimer's disease as well as in the development of vascular dementia.[22–24] We have also already reported the presence of hypertension and impaired glucose tolerance, and shown that accumulation of metabolic risk factors may cause the occurrence of KOA.[25] These findings may indicate that the MCI is a candidate surrogate index for metabolic risk factors as a predictor of KOA occurrence. Therefore, we performed logistic regression analysis similar to that performed for model 2, with the addition of metabolic risk factors. The adjusted ORs for the occurrence of KOA in relation to the MMSE summary score or to the presence of MCI remained significant. In addition, hypertension was also significantly associated with the occurrence of KOA in relation to the MMSE summary score and the occurrence of KOA in relation to MCI, but there was no significant association between the occurrence of KOA and overweight, dyslipidaemia and impaired glucose tolerance. This result shows that components of metabolic syndrome, such as hypertension and MCI, coexist as risk factors for onset of KOA, and MCI might not be a surrogate index for metabolic risk factors for indicating the occurrence of KOA. There might be a direct or an indirect pathway between cognitive impairment and onset of KOA, but based on the information currently available, a causal relationship between MCI and onset of KOA seems to be biologically improbable.

Besides inflammation and metabolic risk factors, there might be other hidden confounders, which could influence both MCI and OA, for example, nutritional factors. Further investigation would be needed to clarify whether the causal relationship still remains after careful consideration with analysis of other possible confounders.

There were several limitations to our study. First, although we used a standard measure of global cognitive function, we used only the MMSE to diagnose MCI, and were unable to perform additional examinations such as MRI to improve the accuracy of the diagnosis. Consequently, we may have underdiagnosed MCI. Second, we used KL grade ≥ 2 for diagnosis of KOA. However, the KL scale is a categorical index, and it is impossible to separately evaluate osteophytosis and the minimum joint space. A computer-assisted diagnostic system for the measurement of minimum joint space width and area of osteophytosis is currently under development;[26] this will help measure the severity of KOA using quantitative parameters, and allow us to establish a more accurate assessment of the association between MCI and the development of OA, and facilitate early

prevention of disability. Further, the small proportion of the population with MCI at risk for KOA onset detection might raise the bias in the results of the study.

On the contrary, the strengths of the present study include a population-based design of a cohort, large number of participants with KOA, and a 3-year follow-up with a high participation rate of 81.9%. Substantial amount of detailed information, including an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history, radiographic assessment and bone mineral density measurement, was collected at both the baseline and the second visit.

CONCLUSION

Our results indicated that MCI significantly influences the occurrence of radiographic KOA, and that KOA occurs more frequently with an decrease in the summary score of the MMSE and the presence of MCI. Prevention of MCI may be useful in preventing the occurrence of KOA and subsequent disability, while further investigation is needed to clarify whether such causalities were caused by direct or indirect associations.

Author affiliations
[1]Department of Joint Disease Research, 22nd Century Medical and Research Center, the University of Tokyo, Tokyo, Japan
[2]Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, the University of Tokyo, Tokyo, Japan
[3]Department of Orthopaedic Surgery, Sensory and Motor System Medicine, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
[4]National Rehabilitation Center for Persons with Disabilities, Saitama, Japan

Acknowledgements The authors wish to thank Dr Takako Nojiri and Mr Kazuhiro Hatanaka of the Gobo Public Health Centre; Dr Naoki Hirabayashi of the Kawakami Clinic, Hidakagawa Town; Mrs Tomoko Takijiri, Mrs Kumiko Shinou, Mrs Rie Takiguchi, Mrs Kyoko Maeda, Ms Ikuyo Ueyama, Mrs Michiko Mori, Mrs Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; Dr Shinji Matsuda of the Shingu Public Health Centre; and Mrs Tamako Tsutsumi, Mrs Kanami Maeda, Mr Shoichi Shimoichi, Mrs Megumi Takino, Mrs Shuko Okada, Mrs Kazuyo Setoh, Mrs Chise Ryouno, Mrs Miki Shimosaki, Mrs Chika Yamaguchi, Mrs Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examinations. We also thank Ms Kyoko Yoshimura, Mrs Toki Sakurai and Mrs Saeko Sahara for their assistance with data reduction and administration.

Contributors NY conceptualised the study, was primarily responsible for developing the protocol, and acts as the guarantor for this study. SM, HO and TA conducted data collection and x-ray assessment. All authors reviewed the protocol and contributed to interpretation of the results. All authors were involved in drafting the article and approved the final version submitted for publication. All authors had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analyses.

Funding This work was supported by Grants-in-Aid for Scientific Research B23390172 and B20390182 to NY, B23390357 and C20591737 to TA, B23390356 and C20591774 to SM, for Young Scientists A18689031 to HO, and Collaborating Research with NSF 08033011-00262 (Director, NY) from the Ministry of Education, Culture, Sports, Science, and Technology; and H17-Men-eki-009 (Director, KN), H18-Choujyu-037 (Director, Toshitaka Nakamura), H20-Choujyu-009 (Director, NY), and H23-Chojyu-002 (Director, TA) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (NY, SM, HO, and TA), and research aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1 & 2010-2, Director, HK).

Competing interests None.

Ethics approval Ethics approval was provided by the institutional review board at the University of Tokyo (approval number 1264).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. National Council of Aging. Fact Sheet: Chronic Disease Self-Management. http://www.ncoa.org/assets/files/pdf/NCOA-Chronic-Desease.pdf (accessed 12 Nov 2012).
2. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2010. (http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/l^tyousa10/4-2.html. (accessed 12 Nov 2012)
3. Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev* 2002;1:61–77.
4. Kalmijn S, Feskens EJ, Launer LJ, *et al.* Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096–102.
5. Gregg EW, Yaffe K, Cauley JA, *et al.* Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174–80.
6. Yaffe K, Barrett-Connor E, Lin F, *et al.* Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;59:378–84.
7. Yaffe K, Weston AL, Blackwell T, *et al.* The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 2009;66:324–8.
8. Helzner EP, Luchsinger JA, Scarmeas N, *et al.* Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol* 2009;66:343–8.
9. Ninomiya T, Ohara T, Hirakawa Y, *et al.* Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension* 2011;58:22–8.
10. Petersen RC, Smith GE, Waring SC, *et al.* Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
11. Yoshimura N, Muraki S, Oka H, *et al.* Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. *J Bone Miner Metab* 2009;27:620–8.
12. Yoshimura N, Muraki S, Oka H, *et al.* Cohort profile: research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study. *Int J Epidemiol* 2010;39:988–95.
13. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* 1975;12:189–98.
14. Anthony JC, LeResche L, Niaz U, *et al.* Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychological Med* 1982;12:397–408.
15. Foreman MD. Reliability and validity of mental status questionnaires in elderly hospitalized patients. *Nursing Res* 1987;36:216–20.
16. Mori E, Mitsuya Y, Yamadori A. Usefulness of the Japanese version mini-mental state examination for the neurological patients. *Jpn J Neuropsychol* 1985;33:228–35.
17. Kellgren JH, Lawrence JS eds. *The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis.* Oxford: Blackwell Scientific, 1963.
18. Muraki S, Akune T, Oka H, *et al.* Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. *Osteoarthritis Cartilage* 2010;18:1227–34.
19. McGeer EG, McGeer PL. Brain inflammation in Alzheimer disease and the therapeutic implications. *Curr Pharm Des* 1999;5:821–36.
20. Zandi PP, Anthony JC, Hayden KM, *et al.* Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. *Neurology* 2002;59:880–6.
21. Pottie P, Presle N, Terlain B, *et al.* Obesity and osteoarthritis: more complex than predicted! *Ann Rheum Dis* 2006;65:1403–5.
22. Kalmijn S, Feskens EJ, Launer LJ, *et al.* Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096–102.

23. Gregg EW, Yaffe K, Cauley JA, *et al.* Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160: 174–80.
24. Yaffe K, Barrett-Connor E, Lin F, *et al.* Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;59:378–84.
25. Yoshimura N, Muraki S, Oka H, *et al.* Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis Cartilage* 2012;20:1217–26.
26. Oka H, Muraki S, Akune T, *et al.* Fully automatic quantification of knee osteoarthritis severity on plain radiographs. *Osteoarthritis Cartilage* 2008;16:1300–6.

ORIGINAL ARTICLE

JBMR

Height Loss Starting in Middle Age Predicts Increased Mortality in the Elderly

Naomi Masunari,[1,2] Saeko Fujiwara,[1] Fumiyoshi Kasagi,[3] Ikuno Takahashi,[1] Michiko Yamada,[1] and Toshitaka Nakamura[4]

[1]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan
[2]Faculty of Pharmacy, Iwaki Meisei University, Fukushima, Japan
[3]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan
[4]Department of Orthopedics, University of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan

ABSTRACT

The purpose of this study was to determine the mortality risk among Japanese men and women with height loss starting in middle age, taking into account lifestyle and physical factors. A total of 2498 subjects (755 men and 1743 women) aged 47 to 91 years old underwent physical examinations during the period 1994 to 1995. Those individuals were followed for mortality status through 2003. Mortality risk was estimated using an age-stratified Cox proportional hazards model. In addition to sex, adjustment factors such as radiation dose, lifestyle, and physical factors measured at the baseline—including smoking status, alcohol intake, total cholesterol, blood pressure, and diagnosed diseases—were used for analysis of total mortality and mortality from each cause of death. There were a total of 302 all-cause deaths, 46 coronary heart disease and stroke deaths, 58 respiratory deaths including 45 pneumonia deaths, and 132 cancer deaths during the follow-up period. Participants were followed for 20,787 person-years after baseline. Prior history of vertebral deformity and hip fracture were not associated with mortality risk. However, more than 2 cm of height loss starting in middle age showed a significant association with all-cause mortality among the study participants (HR = 1.76, 95% CI 1.31 to 2.38, $p = 0.0002$), after adjustment was made for sex, attained age, atomic-bomb radiation exposure, and lifestyle and physical factors. Such height loss also was significantly associated with death due to coronary heart disease or stroke (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$), as well as respiratory-disease death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer death. Continuous HL also was associated with all-cause mortality and CHD- or stroke-caused mortality. Association between height loss and mortality was still significant, even after excluding persons with vertebral deformity. Height loss of more than 2 cm starting in middle age was an independent risk factor for cardiovascular and respiratory-disease mortality among the elderly, even after adjusting for potential risk factors. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: HEIGHT LOSS; MORTALITY; VERTEBRAL DEFORMITY; CORONARY HEART DISEASE; RESPIRATORY DISEASE

Introduction

Many studies have shown increased fracture risk[1–3] and mortality[4–8] after clinical vertebral fracture. Even subjects with no clinical fracture and little pain but with vertebral deformity detected by X-ray showed slightly increased mortality.[9] Other studies, however, showed no evidence of increased mortality among elderly with vertebral fracture.[10] Increased mortality after hip fracture was observed in several studies.[7,11,12]

Kyphosis and height loss are thought to result mainly from underlying vertebral fractures, but have not yet gained much clinical interest other than as markers for osteoporosis.[13–18] Height loss, however, not only could be caused by vertebral fracture, but also to some extent by intervertebral disk degeneration that decreases disk height; osteoarthritic conditions of the spine, hip, or knee, various inflammatory and structural/congenital spinal deformities; and weakness of the back muscles.[19,20] Our previous report showed that height loss and vertebral deformity significantly and independently affected quality of life (QOL) in the elderly, and height loss aggravated QOL more significantly than did vertebral deformity in all domains, even with different effect patterns between height loss and vertebral deformity.[21] The mechanism behind such decreased height loss–associated QOL remains uncertain. Recent reports have suggested that hyperkyphotic posture or marked height loss might predict future fracture risk[22] and mortality.[23–25]

Received in original form June 21, 2011; revised form August 8, 2011; accepted August 29, 2011. Published online September 19, 2011.
Address correspondence to: Saeko Fujiwara, MD, PhD, Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan. E-mail: fujiwara@rerf.or.jp

Journal of Bone and Mineral Research, Vol. 27, No. 1, January 2012, pp 138–145
DOI: 10.1002/jbmr.513

In the present study, we assessed whether height loss starting in middle age affects all-cause and specific-cause mortality, after taking into account vertebral deformity and hip fracture in Japanese men and women.

Materials and Methods

Data source

Study participants comprised cohort members of the Adult Health Study (AHS), which was established to investigate late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort was comprised of about 20,000 atomic-bomb survivors and their controls selected from residents of Hiroshima and Nagasaki, based on the 1950 national census. Since 1958, the AHS cohort members have been followed through biennial health examinations, including physical examinations; measurements of height, body weight, and blood pressure; and chest X-rays. The health study participants were interviewed by nurses to obtain disease histories and lifestyle information, such as smoking status and alcohol intake. Participation rates in the study were around 70% to 80% throughout the follow-up period. Further information about the cohort and details of the health examinations are available elsewhere.[26–28]

Subjects of this study numbered a total of 2498 individuals (755 men and 1743 women) aged 47 to 91 years old, undergoing physical examinations in Hiroshima during the health study's 1994 to 1995 examination cycle (Fig. 1). Measurements of height, using a stadiometer, were available for all subjects at each examination since 1962. Participants were measured without shoes, with their heels, buttocks, and back against an upright board. The participants with hyperkyphosis were instructed to stand straight and stretch the muscles in their backs as much as possible. We defined height loss starting in middle age (HL) as the difference between a participant's average height in their 40s and height measured in 1994 to 1995. We calculated average height based on from two to five measurements at ages in the 40s for each participant. If a participant did not have data on average height in the 40s, we then defined HL as the difference between his or her average height in the 50s and height measured in 1994 to 1995 (those for whom height in their 50s was used: 12.5%). We also defined marked HL as a difference of more than 2 cm based on results from receiver operating characteristic (ROC) analysis for mortality.

The subjects underwent bone mineral density (BMD) measurements at the spine (L1-4, anteroposterior direction) and the total hip using dual X-ray absorptiometry (DXA, QDR-2000 [Hologic Inc, Waltham, MA, USA]) at the time of the examinations in 1994 1995. Morphometric vertebral deformity was diagnosed by lateral and posterior-anterior chest and spinal X-ray examinations. An experienced radiologist diagnosed vertebral deformity using semi-quantitative procedures.[29,30] We defined "prevalent vertebral deformity" as vertebral deformity at thoracic and lumbar vertebrae diagnosed during the 1994 to 1995 examination cycle, that is, prevalent cases in 1994 to 1995. Diagnosis of hip fracture was based on history-taking by a physician. Pathologic fractures or fractures due to traffic accidents or falls from heights were excluded.

The study follow-up of all participants began in the 1994 to 1995 examination cycle. The accumulation of each participant's person-years of risk ended at the date of death, or the date of the last examination before December 2003. Mortality follow-up was conducted through checks of the vital status of cohort members using the Japanese family registration system. We were thus able to completely follow the mortality status of the cohort members.

Statistical Methods

The rates of many diseases increase as some power of age, so a simple linear adjustment factor would undercontrol for age effects. To avoid this bias, we used an age-stratified Cox proportional hazard analysis, whereby people are assigned to an age stratum reflecting their age at baseline according to five-year age intervals. After confirming the assumption that hazard ratios were proportional, we used an age-stratified Cox proportional

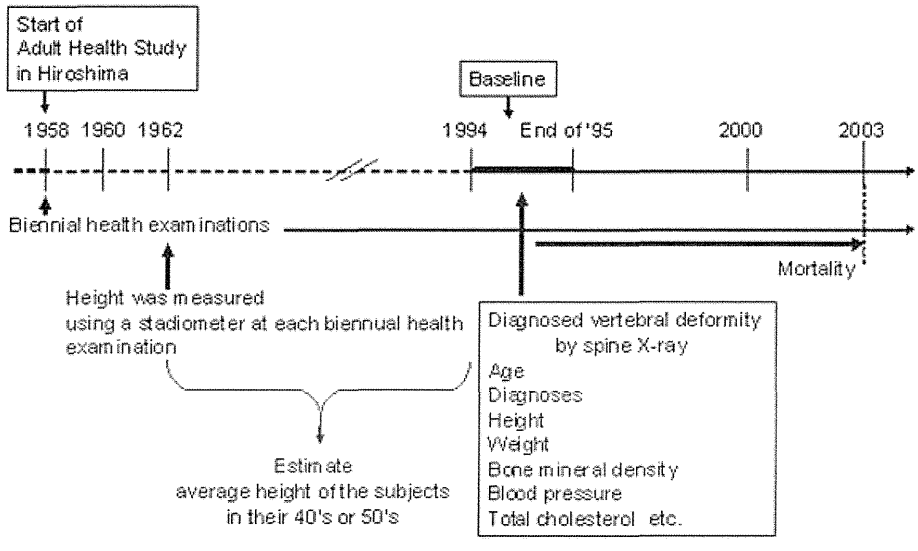

Fig. 1. Timeline of the study.

hazards model to assess the multivariate-adjusted hazard ratio (HR) for mortality. Fitted as categorical variables in the adjustment were assessments obtained at the 1994 to 1995 baseline: prevalent vertebral deformity (yes/no), prevalent hip fracture (yes/no), smoking status (never, current, former smoker, and unknown), alcohol intake (never, current occasional, current often, former drinker, and unknown), preexisting hypertension (yes/no), preexisting hyperlipidemia (yes/no), preexisting diabetes (yes/no), preexisting cardiovascular disease (yes/no), preexisting cancer (yes/no), marked HL (HL $\geq$ 2 cm/HL $<$ 2 cm). Weight, height, body mass index (BMI: calculated as weight in kilograms divided by height in meters squared), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, BMD at baseline, radiation dose, and HL were fitted as continuous variables. For each risk factor, we first evaluated all-cause mortality using an univariate model. We then conducted evaluation with multivariate model, including variables found to be significantly associated with all-cause mortality. We obtained a final model after removing non-significant terms. As a result, we included such variables as sex, preexisting cancer, preexisting cardiovascular disease (CVD), preexisting diabetes, radiation dose, marked HL, smoking status, and alcohol intake in the model. We also evaluated mortalities caused by coronary heart disease (CHD) or stroke, respiratory disease, pneumonia, and cancer. In the same procedure, we analyzed participants excluding 191 participants with prevalent vertebral deformities. We used individual radiation dose estimates on the Radiation Effects Research Foundation's Dosimetry System 2002 (DS02).[31]

For the mortality analysis, we used the PHREG procedure in SAS program (SAS version 9.1, SAS Institute Inc, Cary, NC, USA), with stratification by 5-year intervals of baseline age, for estimation of the parameters and testing. With consideration for parameter distributions, we tested differences between the alive group and the death group using Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. A value of $p < 0.05$ was used for determination of statistical significance.

Ethical considerations

The present study was carried out in accordance with such national regulations as the *Ethical Guidelines Concerning Epidemiological Studies* (Ministry of Education, Culture, Sports, Science and Technology [MEXT], and Ministry of Health, Labour and Welfare [MHLW]). The study was approved by the Research Protocol Committee and the Human Investigation Committee at the Radiation Effects Research Foundation. At the time of the health examinations, informed consent was obtained from the participants. All participants provided written consent for all aspects of the examinations.

Results

Characteristics of the participants taken at baseline are shown in Table 1. In men, mean ages $\pm$ 1 standard deviation (SD) in the 1994 to 1995 examination period for the alive group were 61.2 $\pm$ 8.9 years, and 70.3 $\pm$ 9.1 years for the death group, ranging from 47 to 91 years. In women, mean ages were 64.7 $\pm$ 9.1 years and 73.5 $\pm$ 8.9 years, respectively, ranging from 47 to 91 years. Mean age of the "death" group was significantly higher than that of the "alive" group. Mean height loss starting in middle age was 0.83 cm for men and 1.85 cm for women. Figure 2 shows HL distribution by sex. We used $\geq$ 2 cm as the cut-off value through the sensitivity analysis, and compared the death group with the alive group. Twenty-one men and 170 women had prevalent vertebral fracture, and 12 men and 44 women had prior history of hip fracture in the 1994 to 1995 examination period. Prevalence of diseases at baseline is presented in Table 1. The proportion of individuals with cancer and CVD appeared to be higher in the death group than in the alive group in both men and women. The proportion of individuals with hypertension appeared to be higher in the death group than in the alive group in women. Approximately 90% of women were postmenopausal with an average age at menopause of 47.7 years.

Through December 2003, there were 302 all-cause deaths, 46 CHD and stroke deaths, 58 respiratory-disease deaths including 45 pneumonia deaths, and 132 cancer deaths. Mean follow-up was 8.3 years (Table 2). Participants were followed for 20,787 person-years after baseline. The death rate was 14.5 per 1000 person-years.

Multivariate adjustments were made for variables including physical and lifestyle factors, as described in "Methods," which were further adjusted for estimation of mortality risk (Table 3). After these adjustments, mortality hazard ratio for the marked HL was 1.76 (95% CI, 1.31to 2.38), $p = 0.0002$.

Mortality risk also was analyzed for specific causes of death. Adjusted mortality risk results are presented in Table 4. When causes of death were classified, increased mortality risk for marked HL was observed in CHD- or stroke-caused death (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$) and respiratory disease-caused death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer-caused death ($p = 0.3143$). No significant increase in mortality from cancer was observed. With significance, continuous HL also was associated with all-cause mortality (HR = 1.08 per 1 cm HL increase, 95% CI 1.03 to 1.14, $p = 0.0034$) and CHD- or stroke-caused death (HR = 1.11, per 1 cm HL increase, 95% CI 1.00 to 1.23, $p = 0.0465$). Previous history of vertebral deformity and hip fracture were not associated with all-cause mortality risk (Table 4).

The hazard ratios for marked HL were reduced only slightly when the 191 prevalent cases of vertebral deformity were excluded (eg, HR of 1.65, rather than 1.76 for all-cause mortality) (analyses not shown).

Discussion

HL and mortality

This is the first study to show that HL of more than 2 cm increased the risk of all-cause death, CHD- or stroke- and respiratory disease-caused death, but not cancer death, with vertebral fracture assessed simultaneously. Furthermore, the present study showed that HL treated as a continuous variable was

Table 1. Baseline (1994–1995) Characteristics of Study Population by Sex and Vital Status

	Men		Women	
Variable	Alive	Dead	Alive	Dead
Number of subjects	627	128	1569	174
Age (years)	61.2 (8.9)	70.3 (9.1)**	64.7 (9.1)	73.5 (8.9)**
Height (cm)	163.9 (6.0)	161.5 (6.3)**	150.7 (5.7)	147.6 (6.4)**
Weight (kg)	61.4 (8.8)	58.2 (9.2)**	52.8 (8.7)	48.6 (9.3)**
BMI (kg/m^2)	22.8 (2.9)	22.3 (3.0)	23.2 (3.6)	22.3 (3.9)**
height at 40s or 50s (cm)[a]	164.5 (5.8)	162.9 (5.8)**	152.3 (5.2)	150.9 (5.4)**
HL (cm)	0.69 (1.01)	1.50 (1.46)**	1.69 (1.94)	3.34(2.76)**
marked HL (%)	67 (10.7)	42 (32.8)**	556 (35.4)	127 (73.0)**
BMD (g/cm2)				
Spine (L1-4)	0.960 (0.155)	0.972 (0.164)	0.796 (0.154)	0.739 (0.148)**
Total hip	0.739 (0.115)	0.709 (0.109)**	0.626 (0.107)	0.571 (0.093)**
Prevalent hip fracture	7 (1.1%)	5 (3.9%)*	34 (2.2%)	10 (5.8%)**
Prevalent vertebral deformity	15 (2.4%)	6 (4.7%)	138 (8.8%)	32 (18.4%)**
SBP	131.8 (20.3)	136.3 (22.1)*	130.7 (21.1)	136.4 (21.4)**
DBP	80.8 (11.4)	77.3 (15.2)**	77.3 (11.4)	76.4 (12.5)
Total cholesterol	203.2 (34.0)	202.0 (36.7)	221.3 (34.6)	211.1 (42.6)**
Diagnosed disease				
Hypertension	185 (32.9%)	37 (39.0%)	390 (27.7%)	50 (40.7%)**
Hyperlipidemia	44 (7.8%)	6 (6.3%)	194 (13.8%)	15 (12.2%)
Diabetes	96 (15.3%)	28 (21.9%)	162 (10.3%)	23 (13.2%)
CVD	288 (45.9%)	78 (60.9%)**	660 (42.1%)	113 (64.9%)**
Cancer	40 (6.4%)	18 (14.1%)*	153 (9.8%)	33 (19.0%)**
Alcohol intake				
Never	105 (16.7%)	27 (21.1%)	769 (49.0%)	102 (58.6%)*
Current occasional	107 (17.1%)	29 (22.7%)	256(16.3%)	31 (17.8%)
Current often	262 (41.8%)	31 (24.2%)**	113 (7.2%)	9 (5.2%)
Former	14 (2.2%)	8 (6.2%)*	13 (0.8%)	5 (2.9%)*
Unknown	139 (22.2%)	33 (25.8%)	418 (26.7%)	27 (15.5%)**
Smoking status				
Never	88 (15.6%)	9 (11.7%)	920 (64.5%)	67 (58.6%)
Current	210 (33.5%)	42 (32.8%)	104 (6.6%)	11 (6.3%)
Former	167 (26.6%)	35 (27.4%)	47 (3.0%)	6 (3.5%)
Unknown	152 (24.3%)	36 (28.1%)	406 (25.9%)	55 (31.6%)*
Radiation dose (Gy)	0.382 (0.634)	0.432 (0.608)	0.297 (0.514)	0.407 (0.568)

HL, historical height loss starting in middle age; BMI, body mass index; BMD, bone mineral density; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease.

Mean (SD).

With consideration for parameter distributions, we tested difference between death or alive using *t*-test for height, weight, BMI, height at 40s or 50s, marked HL, BMD, SBP, DBP, total cholesterol, radiation dose, using a Wilcoxon test for age, and using χ^2-test for prevalence of hip fracture, prevalence of vertebral deformity, alcohol intake, smoking status, and diagnosed diseases.

[a]Longitudinal data of height are available for all study participants of the cohort since 1962. We defined height loss starting in middle age (HL) as the difference between a participant's average height in his or her 40s and height measured in 1994 to 1995.

*$p < 0.05$.

**$p < 0.01$.

associated with significantly increased risk of all-cause mortality and CHD- or stroke-caused mortality.

Our previous report[21] showed that height loss and vertebral deformity affected QOL significantly and independently in the elderly. Even after excluding individuals with vertebral deformity, height loss was associated with decreased QOL. Furthermore, it is observed that factors other than vertebral deformity, such as intervertebral disk degeneration and osteoarthritic conditions, also caused height loss. In the present study, we observed association between mortality and height loss starting in middle age, but not prevalent vertebral deformity. The presence of certain adverse health conditions, for example poor muscle strength, possibly causing height loss may be implicated.

Wannamethee et al. followed 4213 men measured for height at ages 40 to 59 and again 20 years later, observing 760 deaths occurring after six more years. In the aforementioned study, Wannamethee et al. described how osteoporotic disease complicated by vertebral fractures was not likely to explain

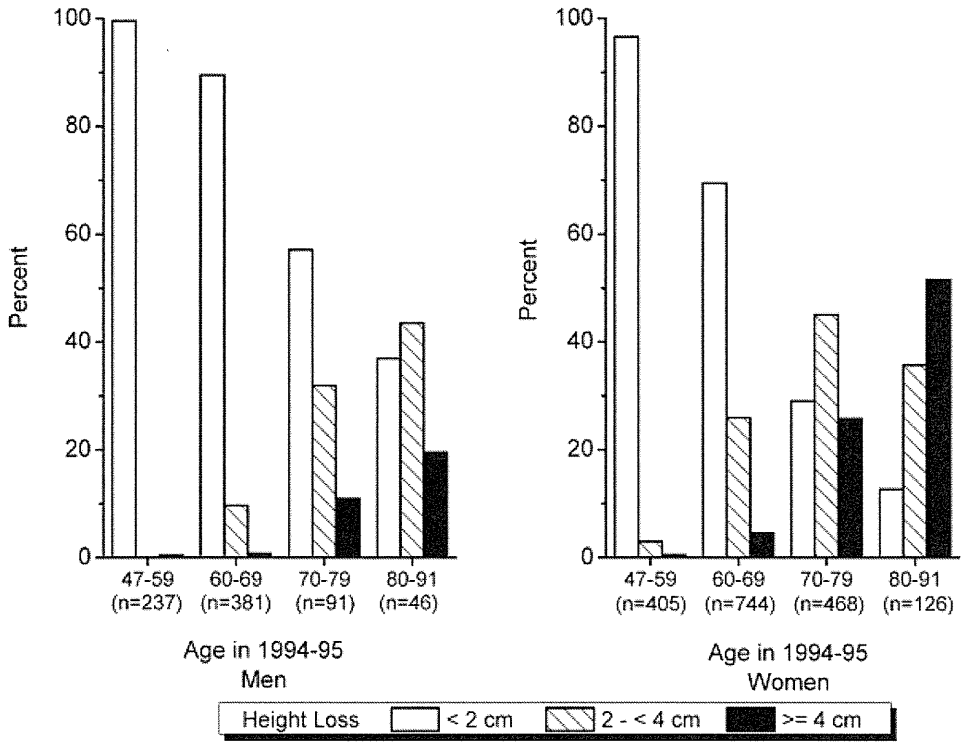

Fig. 2. Percentage of those with height loss starting in middle age, for men and women.

increased mortality risk associated with height loss. Poor muscular strength and low skeletal muscle mass have been linked to bone loss and poor bone structure in men, which could result in height loss.[32] The increased risk of CHD and all-cause mortality associated with height loss may thus reflect poor muscular strength and skeletal muscle mass loss from aging (sarcopenia), both of which have been shown to be predictors of mortality.[33–35] Wannamethee et al. also discussed the idea that height loss might serve as a marker for sarcopenia and frailty.[24] Hyperkyphosis, commonly used as a marker of aging, is frequently observed in the elderly. It is known that hyperkyphosis is associated with restrictive pulmonary disease[36] and poor physical function.[37–39] These findings suggest that hyperkyphosis also might be associated with occurrence of other states of poor health. Some studies have suggested association between kyphosis and mortality.[22,23,25] Recently, Kado et al.[25] conducted a prospective cohort study of 610 older white women who were diagnosed with kyphosis, and assessed mortality rates over an average follow-up of 13.5 years. They concluded that hyperkyphosis predicted increased risk of death independent of prevalent vertebral fractures. In addition, Kado et al.[23] followed 1353 men and women over a period of 4.2 years, with mortality and cause of death confirmed by review of death certificates. They observed that older men and women with hyperkyphotic posture had higher mortality rates.

Table 2. Deaths Observed Between Baseline Examinations in 1994 to 1995 and December 2003

	Men	Women	Total
Number of individuals	755	1743	2498
Number of all-cause deaths	128	174	302
Person-years	6188	14,599	20,787
Mean follow-up period (years)	8.2	8.4	8.3
Death rate (per 1000 person-years)	20.7	11.9	14.5
Number of deaths by cause			
Coronary heart disease and stroke	21	25	46
Respiratory disease	27	31	58
Pneumonia	19	26	45
Cancer	66	66	132

Table 3. Hazard Ratios (HRs) Using Age-Stratified Cox Regression Analysis for All-Cause Mortality[a]

Baseline factor in 1994–1995		Hazard ratio	95% CI
Sex	Women/Men	0.39	0.28–0.53**
Marked HL	Yes/No	1.76	1.31–2.38**
Preexisting cancer	Yes/No	1.55	1.12–2.15**
Preexisting CVD	Yes/No	1.32	1.03–1.71*
Preexisting DM	Yes/No	1.48	1.07–2.05*
Radiation dose	1 Gy increment	1.22	1.01–1.48*
Alcohol habit	Current occasional/Never	1.14	0.82–1.57
	Current often/Never	0.55	0.36–0.84**
	Former/Never	1.86	1.02–3.39*
	Unknown/Never	0.71	0.51–0.99*

CI, confidence interval; HL, height loss starting in middle age; CVD, cardio vascular disease.

[a]The analysis included all variables in the table simultaneously.

*$p < 0.05$; **$p < 0.01$.

Table 4. Hazard Ratios (HRs) Using Age-Stratified Cox Regression Analysis by Continuous HL, Marked HL, Vertebral Fracture, and Hip Fracture for Mortality

Death	Continuous HL	Marked HL	Prevalent Vertebral Deformity	Prevalent Hip Fracture
All-cause death				
HR	1.08	1.76	1.13	1.26
95% CI	1.03–1.14	1.31–2.38	0.78–1.64	0.72–2.18
p value	0.0034	0.0002	0.5267	0.4183
CHD- or Stroke-caused death				
HR	1.11	3.35	1.89	1.97
95% CI	1.00–1.23	1.63–6.86	0.86–4.16	0.67–5.82
p value	0.0465	0.0010	0.1123	0.2186
Respiratory disease–caused death				
HR	1.10	2.52	1.35	0.71
95% CI	0.99–1.23	1.25–5.22	0.63–2.89	0.17–2.95
p value	0.0684	0.0130	0.4378	0.6316
Cancer-caused death				
HR	1.05	1.26	0.92	1.17
95% CI	0.96–1.15	0.80–1.99	0.48–1.76	0.47–2.92
p value	0.2634	0.3143	0.7944	0.7367

HL, height loss starting in middle age; CHD, coronary heart disease.
Adjusted for sex, radiation dose, preexisting diabetes, preexisting cardiovascular disease, preexisting cancer, smoking status, and alcohol intake.

For CHD mortality, our results are consistent in principle with the results of the two previous studies. Additionally, we observed association between respiratory disease mortality and height loss starting in middle age in both men and women. Furthermore, height loss was associated with mortality even after individuals with vertebral deformity were excluded. The mechanism regarding how height loss might be associated with subsequent mortality is not currently well understood. Resulting height loss could affect normal functioning of the respiratory and gastrointestinal systems,[13] which in turn might lead to early satiety, poor nutritional status, and weight loss.[13] Height loss also appears to be related to sarcopenia,[32] which is defined as the loss of skeletal muscle mass and strength with aging and is associated with weight loss[40–43] and increased mortality.[33–35]

We found increased mortality associated with marked HL due to CHD or stroke and respiratory diseases, but no increased cancer mortality. Kado et al. reported that hyperkyphotic posture was specifically associated with increased rate of death due to atherosclerosis.[23] Browner et al. reported that low bone mass was significantly associated with death from CVD and specifically stroke.[44] Some evidence indicated similar pathophysiological mechanisms underlying both osteoporosis and cardiovascular disease.[45,46] Risk factors such as age, diabetes, hypertension, inflammation, dislipidemia, homocystienemia, and estrogen deficiency are prevalent in both disorders.[44,47]

Osteoporotic fracture and mortality

Bliuc et al.[48] reported that excess mortality was highest immediately after almost all fragility fracture events and then declined. The researchers observed that 30% of all post–hip-fracture deaths occurred in the first six months and 21% in the next 18 months. Other studies reported that increased mortality after hip and vertebral fractures was consistent over the initial five-year period.[4,6,8,11]

In the present study, prevalent morphometric vertebral deformity and prevalence of hip fracture were not associated with increased mortality. Inconsistency between our report and many previous studies can be explained by differences between incidence and prevalence of fracture, because prevalent vertebral deformity and hip fracture in our study included those cases that had developed many years in the past. In addition, in the follow-up period, such differences as whether or not to include morphometric vertebral fracture and adjustment of potential confounders might have resulted in the inconsistency.

Strengths and limitations

One strength of this study is that the investigation was based on measured height using consistent methods throughout biennial health examinations conducted since 1962, thus reducing measurement errors. Since mean height in most age groups has increased recently in many regions around the world, including Japan, height loss would be overestimated in cross-sectional studies, and bias would be significant if recalled height were used.[49] Our study was carried out using measured height at ages 40 to 49 and again some years later in a population-based study of men and women. Second, mortality follow-up has been carried out through checks of the vital status of cohort members using the Japanese family registration system. We were thus able to completely follow mortality of the cohort members.

There are some limitations to our findings. First, baseline data for physical activity and lung function were not available. Second, diagnosis of hip fracture was based on history taking by a physician, not X-ray examination. Furthermore, participants were atomic bomb survivors and thus not representative of the general Japanese population, although we adjusted for

radiation, and there are no indications from earlier studies of this cohort that radiation affected BMD and fracture frequency.[38,48,50]

Conclusion

In conclusion, height loss starting in middle age is considered to be a factor associated with CVD and respiratory-disease mortality, independent of vertebral deformity, in Japanese elderly men and women. Further studies will be needed to elucidate the mechanisms behind such findings. Although the mechanisms are unknown, height loss, regardless of its causes, is a clinically important finding.

Disclosures

All the authors state that they have no conflicts of interest.

Acknowledgments

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, nonprofit foundation funded by the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, the latter in part through the National Academy of Sciences. This publication was supported by RERF Research Protocol RP 3-89. This study also was supported by the research of "Effects of Vertebral Deformity and Body Height Loss on Activity of Daily Living and Its Prevention Among the Elderly" (16100201) by the Japanese Ministry of Health, Labour and Welfare.

Authors' roles: N Masuna and S Fujiwara made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. F Kasagi, I Takahashi, and M Yamada contributed to acquisition of data. T Nakamura made contributions to interpretation of data.

References

1. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15:721–39.
2. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35: 375–82.
3. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1999;14:821–8.
4. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353:878–82.
5. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int. 2003;14: 61–8.
6. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11: 556–61.
7. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359:1761–7.
8. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1999;159:1215–20.
9. Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, Delmas P, Falch JA, Felsch B, Hoszowski K, Johnell O, Diaz-Lopez JB, Lopez Vaz A, Marchand F, Raspe H, Reid DM, Todd C, Weber K, Woolf A, Reeve J, Silman AJ. Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int. 1998;8:291–7.
10. Trone DW, Kritz-Silverstein D, von Mühlen DG, Wingard DL, Barrett-Connor E. Is radiographic vertebral fracture a risk factor for mortality?. Am J Epidemiol. 2007;166:1191–7.
11. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone. 2003;32: 468–73.
12. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women: the study of osteoporotic fractures. Arch Intern Med. 1996;156:1521–5.
13. Ross PD. Clinical consequences of vertebral fractures. Am J Med. 1997;103 (suppl 2A): 30S–43S.
14. Papaioannou A, Watts NB, Kendler DL, Yuen CK, Adachi JD, Ferko N. Diagnosis and management of vertebral fractures in elderly adults. Am J Med. 2002;113:220–8.
15. Siminoski K, Jiang G, Adachi JD, Hanley DA, Cline G, Ioannidis G, Hodsman A, Josse RG, Kendler D, Olszynski WP, Ste Marie LG, Eastell R. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. Osteoporos Int. 2005;16:403–10.
16. Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone. 1993;14 (Suppl 1):S89–97.
17. Huang C, Ross PD, Lydick E, Davis JW, Wasnich RD. Contributions of vertebral fractures to stature loss among elderly Japanese-American women in Hawaii. J Bone Miner Res. 1996;11:408–11.
18. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause. 2006;13:340–67.
19. Samartzis D, Liu JC. Ankylosing spondylitis. In: Batjer HH, Loftus C, editors. Textbook of Neurological Surgery. Philadelphia, USA: Lippincott-Raven; 2002. 1713–23.
20. Sornay-Rendu E, Munoz F, Duboeuf F, Delmas PD. Disc space narrowing is associated with an increased vertebral fracture risk in postmenopausal women: the OFELY Study. J Bone Miner Res. 2004;19:1994–9.
21. Masunari N, Fujiwara S, Nakata Y, Nakashima E, Nakamura T. Historical height loss, vertebral deformity, and health-related quality of life in Hiroshima cohort study. Osteoporos Int. 2007;18:1493–9.
22. Huang MH, Barrett-Connor E, Greendale GA, Kado DM. Hyperkyphotic posture and risk of future osteoporotic fractures: the Rancho Bernardo study. J Bone Miner Res. 2006;21:419–3.
23. Kado DM, Huang MH, Karlamangla AS, Barrett-Connor E, Greendale GA. Hyperkyphotic posture predicts mortality in older community-dwelling men and women: a prospective study. J Am Geriatr Soc. 2004;52:1662–7.
24. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Height loss in older men: associations with total mortality and incidence of cardiovascular disease. Arch Intern Med. 2006;166:2546–52.

25. Kado DM, Lui LY, Ensrud KE, Fink HA, Karlamangla AS. Cummings SR; for the Study of Osteoporotic Fractures. Hyperkyphosis Predicts Mortality Independent of Vertebral Osteoporosis in Older Women. Ann Intern Med. 2009;150:681–7.
26. Beebe GW, Fujiwara H, Yamasaki M. Adult Health Study Reference Papers, A: Selection of the sample, and B: Characteristics of the sample. Hiroshima, Japan. Technical Report. 1960; 10–60.
27. Atomic Bomb Casualty Commission. Research plan for joint ABCC-NIH Adult Health Study in Hiroshima and Nagasaki. Hiroshima Japan. Technical Report. 1962; 11–62.
28. Fujiwara S, Kasagi F, Yamada M, Kodama K. Risk factors for hip fracture in Japanese cohort. J Bone Miner Res. 1997;12:998–1004.
29. National Osteoporosis Foundation Working Group on Vertebral Fractures. Assessing vertebral fractures. J Bone Miner Res. 1995;10: 518–23.
30. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137–48.
31. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res. 2004;162:377–89.
32. Szulc P, Beck TJ, Marchand F, Delmas PD. Low skeletal muscle mass is associated with poor structural parameters of bone and impaired balance in elderly men—the MINOS study. J Bone Miner Res. 2005;20:721–9.
33. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci. 2002;57:M772–7.
34. Hughes VA, Frontera WR, Roubenoff R, Evans WJ, Singh MAF. Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. Am J Clin Nutr. 2002;76:473–81.
35. Roubenoff R. Sarcopenia: effects on body composition and function. J Gerontol A Biol Sci Med Sci. 2003;58:1012–7.
36. Leech JA, Dulberg C, Kellie S, Pattee L, Gay J. Relationship of lung function to severity of osteoporosis in women. Am Rev Respir Dis. 1990;141:68–71.
37. Chow RK, Harrison JE. Relationship of kyphosis to physical fitness and bone mass on post-menopausal women. Am J Phys Med. 1987; 66:219–27.
38. Ryan SD, Fried LP. The impact of kyphosis on daily functioning. J Am Geriatr Soc. 1997;45:1479–86.
39. Kado DM, Huang MH, Barrett-Connor E, Greendale GA. Hyperkyphotic posture and poor physical functional ability in older community dwelling men and women: The Rancho Bernardo Study. J Gerontol A Biol Sci, Med Sci. 2005;60:633–7.
40. Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K, Guralnik JM. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. J Gerontol A Biol Sci Med Sci. 2000;55:M168–73.
41. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all cause mortality in healthy men. J Gerontol A Biol Sci Med Sci. 2002;57:B359–65.
42. Roubenoff R, Parise H, Payette HA, Abad LW, D'Agostino R, Jacques PF, Wilson PW, Dinarello CA, Harris TB. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. Am J Med. 2003; 115:429–35.
43. Castillo EM, Goodman-Gruen D, Kritz-Silverstein D, Morton DJ, Wingard DL, Barrett-Connor E. Sarcopenia in elderly men and women: the Rancho Bernardo Study. Am J Prev Med. 2003;25: 226–31.
44. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Lancet. 1991;338:355–8.
45. McFarlane SI, Muniyappa R, Shin JJ, Bahtiyar G, Sowers JR. Osteoporosis and cardiovascular disease: brittle bones and boned arteries, is there a link?. Endocrine. 2004;23:1–10.
46. Whitney C, Warburton DE, Frohlich J, Chan SY, McKay H, Khan K. Are cardiovascular disease and osteoporosis directly linked?. Sports Med. 2004;34:779–807.
47. von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. Am. J. Med. 1999;106:273–8.
48. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. 2009;301: 513–21.
49. Siminoski K, Warshawski RS, Jen H, Lee K. The accuracy of historical height loss for the detection of vertebral fractures in postmenopausal women. Osteoporos Int. 2006;17:290–6.
50. Cooper C, Alkinson HJ, Jacobsen SJ, O'Fallon WM, Mellon LJ III. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993;137:1001–5.

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2013; Early Online: 1–4

DOI: 10.3109/14397595.2013.866921

informa
healthcare

ORIGINAL ARTICLE

Osteoporosis, vertebral fractures and mortality in a Japanese rural community

Akinobu Nishimura[1,2], Koji Akeda[1], Ko Kato[2], Kunihiro Asanuma[1], Tomomi Yamada[3], Atsumasa Uchida[1], and Akihiro Sudo[1]

[1]*Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Mie, Japan,* [2]*Department of Orthopaedics and Sports Medicine, Mie University Graduate School of Medicine, Mie, Japan, and* [3]*Department of Translational Medical Science, Mie University Graduate School of Medicine, Mie, Japan*

Abstract

Objectives. The present study aims to determine the relationship between osteoporosis (OP), vertebral fracture (VF) and mortality.

Methods. We followed up 1024 residents of Miyagawa village every 2 years for a mean of 8.4 years between 1997 and 2009. The residents were assessed every 2 years. We defined OP as T scores for bone mineral density that were <2.5 standard deviations below peak bone mass. VF was assessed by lateral radiography of the thoracic and lumbar spine. The participants were allocated as follows depending on the presence or absence of OP and VF: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group). We determined survival/mortality rates until 2011 by reviewing medical histories and death certificates.

Results. By 2011, 304 participants had died. The respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. Mortality rates were significantly worse for the OP + VF group than the Control group (OP + VF Hazard Ratio: 1.89; 95% CI, 1.27–2.77).

Conclusion. Prevention of osteoporotic VF in elderly persons is very important from the viewpoint of increasing life expectancy.

Keywords

Elderly, Epidemiology, Mortality, Osteoporosis, Vertebral fractures

History

Received 21 August 2013
Accepted 15 November 2013
Published online 23 December 2013

Introduction

Osteoporosis (OP) is characterized by increased bone loss and enhanced bone fragility. Japanese society is rapidly aging. Yoshimura et al. [1] described that about 6.4 and 11 million individuals in Japan have L2–4 and femoral neck OP. Therefore, OP and osteoporotic fractures are major public health problems in this aging society.

Vertebral fractures (VF) are the most common type of osteoporotic fracture, with an estimated annual incidence of 700 000 in the US [2] and 1.4 million in Europe [3]. Elderly persons typically develop VF due to bone fragility caused by OP. However, VF are sometimes caused by high-velocity accidents, such as car crashes or falls from a considerable height. Morphological evaluation by radiography alone cannot easily differentiate whether or not VF result from high-velocity accidents involving osteoporotic bone. However, the possibility that a combination of OP and VF causes osteoporotic VF might be quite high.

Some investigators have reported that low bone mineral density (BMD) is a risk factor for death [4,5]. If OP is independently associated with mortality, increased mortality might be associated with other types of osteoporotic fractures. Many studies have shown that osteoporotic [6–9], particularly hip [10–13], fractures are associated with increased mortality. Several recent studies of VF have also found that mortality is higher in patients with OP than in the general population [6,14–16]. However, Cummings and Melton [17] noted that most VF are subclinical or remain unrecognized without radiographic examination. Haczynski and Jakimiuk [16] also noted only one third of all VF are diagnosed clinically. Many studies have evaluated clinical (symptomatic) VF, but few have described mortality rates based on prevalent, radiographically defined VF [18,19].

We tested the hypothesis that osteoporotic, radiographic VF is associated with an increased risk of death among Japanese community dwellers.

Materials and methods

This population-based study of the residents of Miyagawa, a rural mountain village located in the center of Mie Prefecture, Japan, began in 1997. The participants were self-recruited, community-dwelling volunteers aged ≥ 65 years, who were assessed every 2 years from 1997 to 2011 at Houtoku Hospital for a total of eight studies. The population of the village in 1997 and 2010 was 4196 and 3490, respectively, when 1463 and 1553 residents, respectively, met the age criterion. This study proceeded at a local hospital, so participants had to arrive by public transportation or by other means, and they also had to understand the purpose of the study. Thus, the participants were generally healthier than non-participants.

Of 1271 residents (806 women and 465 men) who participated in these studies at least once, 1024 (661 women and 363 men) who

Correspondence to: Akinobu Nishimura, MD, PhD, Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan. Tel: +81-59-231-5022. Fax: +81-59-231-5211. E-mail: meiten@clin.medic.mie-u.ac.jp

were followed up for a mean of 8.4 (1–14) years were included in the study.

The Committee for the Ethics of Human Research at Mie University approved the study protocol, and all participants provided written, informed consent before enrollment.

Baseline data obtained from standard questionnaires administered by orthopedic surgeons included information regarding age, gender and medical history. Body–mass index (BMI) was calculated from height and weight. Other medical examinations comprised radiography of the thoracic and lumbar spine and assessments of BMD at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). We defined OP as T scores of BMD < 2.5 standard deviations (SD) below peak bone mass according to the World Health Organization criteria [20]. Central DXA of the lumbar spine or femoral neck is generally used to diagnose OP. However, many elderly individuals have vertebral deformities. Thus, lumbar DXA tends to show high BMD. Positioning (degree of internal rotation) of the femoral neck for DXA is difficult and thus reproducibility is poor and femoral DXA is unsuitable for longitudinal studies. Therefore, we assessed the participants using radial DXA.

We assessed VF from lateral radiographs of the thoracic and lumbar spine in terms of a wedge, biconcave or crushed appearance according the Japanese Society of Bone and Mineral Research criteria [21].

Based on the baseline OP and VF criteria, the participants were allocated to the following groups: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group).

We assessed the survival/mortality rates of the participants until 2011 by reviewing their medical histories and death certificates with the help of local hospital staff. Causes of death were determined from death certificates.

Statistical analysis

Means ± SD were calculated for variables unless otherwise noted. Significant differences in baseline characteristics between the OP and Control groups, between the VF and Control groups, and between the OP + VF and Control groups were determined using t and χ^2 tests. Survival curves for the OP, VF, OP + VF and Control groups were constructed based on the Kaplan–Meier method. We also used Cox proportional hazards analyses to determine age–gender-adjusted mortality (as hazard ratios [HR] and 95% confidence intervals [CI]) among three groups (OP, VF and OP + VF groups) and the Control group. The Control group served as the reference for the Cox proportional hazards analyses. The period of the Cox model was measured in months. The significance level for entry into the model was 0.05. All data were statistically analyzed using PASW Statistics version 18 software (SPSS, Chicago, IL, USA).

Table 1. Baseline physical characteristics of all groups.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$
Gender (M/F)	9/116*	33/323*	40/19	281/201
Age (y)	77.1 ± 7.6*	72.2 ± 6.6*	72.1 ± 6.1	70.8 ± 5.6
Height (cm)	143.1 ± 7.6*	147.7 ± 7.0*	154.5 ± 7.4	154.8 ± 7.5
Weight (kg)	46.9 ± 10.0*	49.9 ± 8.4*	55.6 ± 10.1	56.6 ± 8.4
BMI (kg/m^2)	22.8 ± 3.9†	22.8 ± 3.3*	23.2 ± 3.6	23.6 ± 3.0

BMI, body–mass index; F, female; M, male; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.01$ and †$p < 0.05$ versus Control.

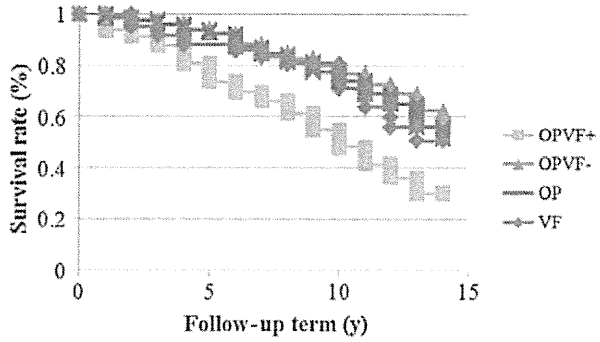

Figure 1. Survival rates for all groups. OP, osteoporosis; VF, vertebral fractures.

Results

The overall mean age of participants was 72.1 ± 6.5 years (average for men and women, 72.4 ± 6.3 and 72.0 ± 6.7, respectively). During a mean follow-up of 8.4 years, 304 participants (29.7%) had died. Table 1 compares the physical characteristics among the four groups. Height, weight and BMI were significantly lower, whereas the ratio of females and age were significantly higher for the OP + VF and OP groups than for the Control group.

Figure 1 shows the Kaplan–Meier survival curves for the four groups. The respective 5- and 10-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2% and 54.9%, 77.4%, 80.7% and 79.8%. Table 2 shows the results of the age and gender-adjusted Cox proportional hazards analyses. The mortality was significantly worse for the OP + VF group than for the Control group. The HR for the OP + VF group was 1.89 (95% CI, 1.27–2.77). The mortality rate tended to be worse for the OP group, but the difference did not reach significance.

Table 3 shows the causes of the 304 deaths. Malignant tumors, heart disease, old age, accidents, suicide, other and unknown causes accounted for 24.7%, 18.8%, 3.3%, 3.6%, 2.0%, 12.5% and 8.9%, respectively, of the deaths. These data were similar to the national data for Japan during 2009 [22]. The causes of death did not significantly differ among the four groups.

Discussion

We recognized the combination OP and VF (OP + VF group) as osteoporotic VF, and found that this combination was associated with high mortality rates among a Japanese village community.

Johnell et al. [15] and Cooper et al. [6] reported 5-year survival rates for individuals with VF of 28% in Sweden, and 61% in the USA, respectively. Our rates of all groups were higher than these findings, which might have been due to our study cohort being generally healthier.

Some authors [4,5] have reported that low BMD is a risk factor for death, and that it is probably related to comorbidity in affected patients. Of course, OP predisposes bones to easy breakage and

Table 2. Age and gender-adjusted Cox proportional hazards findings versus Control.

	Alive	Dead	HR	95% CI	DF	P
					3	0.01
Control	360	124	1			
OPVF+	64	61	1.88	1.27–2.77	1	<0.005*
OP	255	101	1.33	0.98–1.81	1	0.07
VF	41	18	0.91	0.55–1.49	1	0.70

95% CI, 95% confidence intervals; HR, hazard ratio; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.005$ versus Control.

Table 3. Causes of death.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$	Total $n = 1024$
Malignant tumor	11	21	3	40	75
Heart disease	10	18	3	26	57
Pneumonia	6	17	5	22	50
Brain disease	4	14	2	10	30
Old age	4	5	0	1	10
Accident	2	5	2	2	11
Suicide	2	2	1	1	6
Other	17	9	1	11	38
Unknown	5	10	1	11	27
Total	61	101	18	124	304

OP, osteoporosis; VF, vertebral fractures.

the relationship between OP and subsequent mortality might explain why survival decreases after sustaining osteoporotic fractures such as those of the hip [23]. In fact, a few studies have found that increased mortality is indeed associated with hip fractures [23–25]. Kanis et al. [26] reported that about 23% of deaths involving hip fractures might be causally related to the fracture itself. However, some [27–29] have shown that OP is associated with atherosclerosis, whereas others [30,31] have shown that OP does not increase the risk of mortality associated with fractures but is rather due to cardiovascular disease. The present study found that only OP without VF tended to associate with mortality, but a significant relationship was not identified ($p = 0.07$). Further study is needed to clarify this issue.

In term of causes of death, Kado et al. [14] reported that women with VF were 2- to 3-fold more likely to die of pulmonary causes than those without fractures. They also explained that severe kyphosis was highly predictive of pulmonary death, perhaps because those with underlying lung disease and decreased respiratory reserves might not be able to tolerate restrictive changes in thoracic anatomy resulting from VF. Indeed, Leech et al. [32] described a 9% decrease in predicted forced vital capacity per VF. Our preliminary report [19] associated the number of VF with mortality. Moreover, multiple VF might cause esophageal hiatal hernia and esophagitis [33,34], and restrict physical function, activities of daily living and quality of life [35,36]. Kado et al. [14] and Cooper et al. [6] also associated VF with increased cancer mortality. Thus, previous reports have associated VF with various causes of death. The present study associated the combination of VF and OP with increased mortality, but without relevance to a specific cause of death. Further investigation is needed to clarify the causes of death associated with osteoporotic VF.

Our study has several limitations. First, Miyagawa village is a rural mountain community, and many of the inhabitants are typically engaged in forestry. Thus, whether the present findings reflect the general population of Japan is doubtful. Second, participants who could attend the hospital were generally healthier than non-participants. Third, this investigation was based on a relatively small cohort. Therefore, the statistical significance of the risk factors might be relatively low. Fourth, since VF was evaluated only by radiographic morphometry and not clinically, we could not investigate differences between clinical and morphological VF.

In conclusion, the respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. The mortality rate was worse for elderly individuals with than without OP combined with VF (osteoporotic VF). Since osteoporotic VF increased the mortality rate 2-fold, efforts should be directed toward preventing such fractures in elderly populations to decrease mortality rates and increase life expectancy.

Acknowledgements

The authors thank the staff of Houtoku hospital for invaluable assistance.

Funding

This study was supported by Grants-in-Aid for H20-Choujyu-009 (Director, Noriko Yoshimura) from the Ministry of Health, Labor and Welfare in Japan.

Conflict of interest

None.

References

1. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab. 2009;27(5):620–8.
2. Riggs BL, Melton LJ III. The worldwide problem of osteoporosis: insights afforded by epidemiology. Bone. 1995;17(5 Suppl):505S–11S.
3. Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, Finn JD, et al. Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res. 2002;17(4):716–24.
4. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. Lancet. 1991;338(8763):355–8.
5. Johansson C, Black D, Johnell O, Odén A, Mellström D. Bone mineral density is a predictor of survival. Calcif Tissue Int. 1998; 63(3):190–6.
6. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ III. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993;137(9):1001–5.
7. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999;353(9156):878–82.
8. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7): 556–61.
9. Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, et al. Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int. 1998;8(3):291–7.
10. Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. Osteoporos Int. 1993;3(3):148–53.
11. Melton LJ III, Therneau TM, Larson DR. Long-term trends in hip fracture prevalence: the influence of hip fracture incidence and survival. Osteoporos Int. 1998;8(1):68–74.
12. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B. Survival after hip fracture: short- and long-term excess mortality according to age and gender. Osteoporos Int. 1999;10(1):73–8.
13. Muraki S, Yamamoto S, Ishibashi H, Nakamura K. Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab. 2006;24(2):100–4.
14. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1999;159(11):1215–20.
15. Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38–42.
16. Haczynski J, Jakimiuk A. Vertebral fractures: a hidden problem of osteoporosis. Med Sci Monit. 2001;7(5):1108–17.
17. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359(9319):1761–7.
18. Trone DW, Kritz-Silverstein D, von Mühlen DG, Wingard DL, Barrett-Connor E. Is radiographic vertebral fracture a risk factor for mortality? Am J Epidemiol. 2007;166(10):1191–7.
19. Ikeda Y, Sudo A, Yamada T, Uchida A. Mortality after vertebral fractures in a Japanese population. J Orthop Surg (Hong Kong). 2010;18(2):148–52.