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# Musculoskeletal decline and mortality: prospective data from the Geelong Osteoporosis Study

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## Abstract

**Background** We aimed to examine the relationship between musculoskeletal deterioration and all-cause mortality in a cohort of women studied prospectively over a decade.

**Methods** A cohort of 750 women aged 50–94 years was followed for a decade after femoral neck bone mineral density (BMD) and appendicular lean mass (ALM) were measured using dual energy X-ray absorptiometry, in conjunction with comorbidities, health behaviour data, and other clinical measures. The outcome was all-cause mortality identified from the Australian National Deaths Index. Using Cox proportional hazards models and age as the time variable, mortality risks were estimated according to BMD groups (ideal-BMD, osteopenia, and osteoporosis) and ALM groups (*T*-scores > –1.0 high, –2.0 to –1.0 medium, < –2.0 low).

**Results** During 6712 person years of follow-up, there were 190 deaths, the proportions increasing with diminishing BMD: 10.7% (23/215) ideal-BMD, 23.5% (89/378) osteopenia, 49.7% (78/157) osteoporosis; and with diminishing ALM: 17.0% (59/345) high, 26.2% (79/301) medium, 50.0% (52/104) low. In multivariable models adjusted for smoking, polypharmacy, and mobility, compared with those with ideal BMD, mortality risk was greater for those with osteopenia [hazard ratio (HR) 1.77, 95% confidence interval (CI) 1.11–2.81] and osteoporosis (HR 2.61, 95%CI 1.60–4.24). Similarly, compared with those with high ALM, adjusted mortality risk was greater for medium ALM (HR 1.36, 95%CI 0.97–1.91) and low ALM (HR 1.65, 95%CI 1.11–2.45). When BMD and ALM groups were tested together in the model, BMD remained a predictor of mortality (HR 1.74, 95%CI 1.09–2.78; HR 2.82, 95%CI 1.70–4.70; respectively), and low ALM had borderline significance (HR 1.52, 95%CI 1.00–2.31), which was further attenuated after adjusting for smoking, polypharmacy, and mobility.

**Conclusions** Poor musculoskeletal health increased the risk for mortality independent of age. This appears to be driven mainly by a decline in bone mass. Low lean mass independently exacerbated mortality risk, and this appeared to operate through poor health exposures.

**Keywords** Dual energy X-ray absorptiometry; Lean mass; Mortality risk; Musculoskeletal health; Osteoporosis; Osteosarcopenia; Sarcopenia

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## Introduction

As the population ages, more attention is being focussed on delaying morbidity. The cumulative effect of multiple morbidities over a lifetime manifests as frailty, loss of independence,

and diminished quality of life. Musculoskeletal decline is an important feature of frailty.<sup>1</sup> An age-related decline in musculoskeletal health is well documented, particularly for bone,<sup>2,3</sup> with more recent attention directed towards the decline in skeletal muscle mass and function.<sup>4–7</sup> Associations

between decreased bone mineral density (BMD),<sup>8–10</sup> accelerated bone loss,<sup>11</sup> fracture,<sup>12</sup> and mortality have been described. Measures of skeletal muscle mass including mid-arm muscle circumference,<sup>13,14</sup> lean mass by bioelectrical impedance analysis (BIA),<sup>15–18</sup> and appendicular lean muscle mass by dual energy X-ray absorptiometry (DXA)<sup>17</sup> report an inverse relationship with premature mortality. However, some studies that have assessed lean mass by BIA<sup>14</sup> and calf muscle density and muscle area by peripheral quantitative computed tomography<sup>19</sup> have not observed such a relationship.

While the evidence supports an association between skeletal deterioration and mortality risk, the association is uncertain for low skeletal muscle mass. Whether skeletal deterioration and low skeletal muscle mass act alone or in combination to determine mortality risk is unclear. The rationale for investigating mortality risk in association with components of musculoskeletal deterioration rests with the notion of a bone-muscle coupling<sup>20,21</sup> that is underpinned by cross-talk between bone and muscle involving mechanical and hormonal stimuli;<sup>22–24</sup> this notion is supported by observed associations between bone mass and muscle mass.<sup>25,26</sup> Therefore, we aimed to examine the relationship between the components of musculoskeletal deterioration and all-cause mortality in a cohort of women studied prospectively over a decade.

## Methods

### Subjects

An age-stratified sample of 1494 women was selected at random from electoral rolls for the Barwon Statistical Division, a geographically distinct area surrounding the regional city of Geelong in south-eastern Australia, for participation in the Geelong Osteoporosis Study.<sup>27</sup> Registration on Australian electoral rolls is compulsory, providing a complete listing of the adult population. Women aged 20 years and over were enrolled 1993–1997, with a participation of 77.1%. Details of non-participation have been described elsewhere.<sup>28</sup> For this study, we included only women aged 50 years and over. Of the potential 837 women, 87 were excluded because measures of lean mass were unavailable for analysis including 15 with bilateral prostheses. Thus, 750 women with a median age of 70.5 years (range 50–92) were eligible for the analysis. Written, informed consent was obtained from all participants. This study was approved by the Barwon Health Human Research Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Measurements

The outcome was all-cause mortality, determined by data linkage of our database with the Australian National Deaths Index. All exposure data were recorded at baseline. Height and weight were measured to the nearest 0.001 m and 0.1 kg, respectively, and body mass index calculated in kg/m<sup>2</sup>. Body composition was assessed by DXA using a Lunar densitometer (Lunar DPX-L, Madison, WI, USA) thereby providing measures of lean tissue mass and BMD. Lean tissue assessed by whole body DXA technology comprises non-fat and non-bone tissue and compares well with skeletal muscle mass measured using magnetic resonance imaging.<sup>29</sup> Appendicular lean mass (ALM) (kg) was determined by summing lean mass measures for the arms and legs. Low ALM was recognized for *T*-scores < -2.0 (low, equivalent to the cut-point used to identify sarcopenia) and -2.0 to -1.0 (medium, equivalent to pre-sarcopenia); ideal lean mass (high) was equivalent to ALM *T*-score > -1.0.<sup>4</sup> For individuals who had incomplete scans (*n*=100) or were affected by prostheses one side of the body (*n*=14), ALM measures were derived by doubling values for the unaffected side of the body. BMD measures of the femoral neck were used to identify osteoporosis (*T*-score < -2.5) and osteopenia (*T*-score -2.5 to -1.0) and ideal BMD (*T*-score > -1.0).<sup>2</sup>

Self-reported details of medication use and health behaviours were documented by questionnaire. Mobility was categorized as very active, active, sedentary, limited, inactive, or chair/bed ridden (descriptors were included in the questionnaire<sup>27</sup> but are not shown here), and for this analysis, these categories were collapsed into three groups of active (includes very active), sedentary, and inactive (includes the other categories). Tobacco smoking was identified as current, past, or never. Alcohol use was recorded as either never, less than once a week, once or twice a week, several times a week, or every day. Polypharmacy referred to the number of prescription medications used regularly; they were categorized into groups of three or more for descriptive purposes. Exposures to disease states were self-reported and grouped into cardiovascular disease, neurological disorders, endocrine disorders, lung diseases, gastrointestinal disorders, malignancies, and 'other' disorders that were not classified elsewhere (including kidney stones, pernicious anaemia, cirrhosis of the liver, liver failure, kidney failure, and nephrotic syndrome). Socio-economic status was ascertained using Socio-Economic Index for Areas index scores based on census data from the Australian Bureau of Statistics (1996). These data were used to derive an Index of Relative Socio-Economic Disadvantage that was categorized into five groups, according to quintiles of Index of Relative Socio-Economic Disadvantage for the study region.

## Statistics

Collection of BMD, ALM, and other clinical measures, together with questionnaire data, was performed concurrently at baseline. To test for differences in subject characteristics according to categories of BMD or ALM, we used one-way analysis of variance for continuous data that were normally distributed, a Kruskal–Wallis test for continuous non-parametric data and a Chi-squared test for categorical data.

Subjects were followed longitudinally from baseline for 10 years or until the date of death, whichever occurred first. Overall survival was compared between the three BMD groups (or the three ALM groups) with the use of a two-sided log-rank test. Hazard ratios (HRs) for the BMD groups  $-2.5 < T\text{-score} < -1.0$  and  $T\text{-score} < -2.5$  (or ALM groups,  $-2.0 < T\text{-score} < -1.0$  and  $T\text{-score} < -2.0$ ) as compared with the ideal BMD (or ALM) group ( $T\text{-score} > -1.0$ ), and corresponding 95% confidence intervals (95% CI) were estimated with the use of Cox proportional hazards models. Survival curves were estimated using Kaplan–Meier product-limit method. We assessed a pre-specified set of baseline characteristics for their relevance as prognostic factors for overall survival that included factors related to anthropometry, mobility, smoking practices, alcohol use, medication use, disease states, and socio-economic status, as described previously and listed in *Table 1*. Using Cox proportional hazards modelling with age as the time variable and BMD or ALM status as the exposure of interest, we performed bivariate analysis of overall survival. Mobility and polypharmacy were considered as ordinal variables in the models. Baseline characteristics significant at a 0.1 level were used to construct the multivariable models. A backward elimination process with a 0.05 type I error was implemented to identify the final models. Estimated HR and two-sided 95% CI and *P* values were calculated for relevant prognostic factors. Finally, the three BMD groups and the three ALM groups were tested in the models simultaneously as exposures. The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

## Sensitivity analysis

Hazard ratios were re-analysed after excluding women whose ALM values were derived by doubling measurements for one side of their body. Thus, 114 were excluded because of unilateral prosthesis or a body size that was too large to be fully accommodated in the DXA scan field.

## Results

### Characteristics

Subject characteristics are shown in *Table 1*, for the whole group and by categories of BMD and ALM. During 6712

person-years of follow-up, 190 women died. When considering BMD, mortality was greatest in the osteoporosis category and for ALM, mortality was greatest in the low category. There was a pattern of increasing age, and decreasing weight, height and body mass index (BMI) across categories of diminishing BMD and ALM. Women with osteoporosis were less likely to be active and more likely to avoid alcohol, whereas those with normal BMD were less likely to have cardiovascular disease, malignancies, and ‘other’ disorders. Those with low ALM were more likely to be inactive, use three or more medications, and have endocrine, gastrointestinal, or ‘other’ disorders.

### Bone mineral density as the exposure of interest

Bivariate analysis identified the following as statistically significant factors: height (HR 0.97, 95%CI 0.95, 0.99), currently smoke (HR 1.61, 95%CI 0.99, 2.56), ever smoke (HR 1.49, 95%CI 1.10, 2.04), poor mobility (HR 1.76, 95% CI 1.40, 2.07), neurological disorders (HR 1.92, 95%CI 1.15, 3.19), polypharmacy (HR 1.15, 95%CI 1.09, 1.21), cardiovascular disease (HR 1.42, 95%CI 1.05, 1.92), endocrine disorders (HR 1.67, 95%CI 1.17, 2.37), and gastrointestinal disorders (HR 1.70, 95%CI 1.25, 2.30). No associations were observed for the other variables tested, including weight and BMI.

Compared with women with ideal BMD, mortality risk was 1.90-fold greater for those with osteopenia (HR 1.90, 95%CI 1.20, 3.01; *P*=0.006) and 3.43-fold greater for those with osteoporosis (HR 3.43, 95%CI 2.14, 5.48; *P*<0.001) (*Figure 1*). The multivariable model showed that mortality risks were 1.77-fold and 2.61-fold greater for those with osteopenia and osteoporosis, respectively, and the relationships were independent of smoking, polypharmacy, and mobility, which were also identified as significant predictors in the model (*Table 2*). Height, neurological disorders, cardiovascular disease, and endocrine and gastrointestinal disorders did not contribute to the final multivariable model.

### Appendicular lean mass as the exposure of interest

Bivariate analysis identified the following as statistically significant factors: height (HR 0.96, 95%CI 0.94, 0.99), currently smoke (HR 1.67, 95%CI 1.03, 2.70), ever smoke (HR 1.43, 95%CI 1.05, 1.96), poor mobility (HR 1.28, 95% CI 1.02, 1.59), polypharmacy (HR 1.14, 95%CI 1.08, 1.20), cardiovascular disease (HR 1.51, 95%CI 1.12, 2.04), endocrine disorder (HR 1.68, 95%CI 1.18, 2.38), gastrointestinal disorders (HR 1.68, 95%CI 1.23, 2.29), and malignancy (HR 1.53, 95%CI 1.06, 2.22). No associations were observed for the other variables tested, including weight and BMI.

Compared with women with high ALM, mortality risk was 1.51-fold greater for those with medium ALM (HR 1.51,

**Table 1** Subject characteristics at baseline for all and according to categories of bone mineral density at the femoral neck (osteoporosis  $T$ -score  $< -2.5$ , osteopenia  $T$ -score  $-2.5$  to  $-1.0$ , and ideal BMD  $T$ -score  $> -1.0$ ) and appendicular lean mass (low  $T$ -score  $< -2.0$ , medium  $T$ -score  $-1.0$  to  $-2.0$ , and high  $T$ -score  $> -1.0$ )

	Bone mineral density					Appendicular lean mass			P
	All n = 750	Osteoporosis n = 157	Osteopenia n = 378	Ideal n = 215	P	Low n = 104	Medium n = 301	High n = 345	
Deaths	190 (43.9%)	78 (49.7%)	89 (23.5%)	23 (10.7%)	<0.001	52 (50.0%)	79 (26.2%)	59 (17.0%)	<0.001
Age (year)	69.7 (59.9–79.3)	80.6 (72.4–83.3)	70.5 (61.4–79.0)	60.6 (54.5–68.9)	<0.001	81.1 (72.8–83.6)	71.4 (62.5–80.6)	64.2 (57.2–72.6)	<0.001
Weight (kg)	66.2 ( $\pm$ 12.0)	56.9 ( $\pm$ 9.1)	65.4 ( $\pm$ 10.1)	74.3 ( $\pm$ 11.7)	<0.001	53.1 ( $\pm$ 7.6)	61.4 ( $\pm$ 7.9)	74.2 ( $\pm$ 10.3)	<0.001
Height (m)	1.58 ( $\pm$ 0.07)	1.54 ( $\pm$ 0.05)	1.58 ( $\pm$ 0.06)	1.60 ( $\pm$ 0.06)	<0.001	1.51 ( $\pm$ 0.06)	1.57 ( $\pm$ 0.05)	1.61 ( $\pm$ 0.06)	<0.001
BMI (kg/m <sup>2</sup> )	26.5 ( $\pm$ 4.4)	23.9 ( $\pm$ 3.5)	26.1 ( $\pm$ 3.9)	29.0 ( $\pm$ 4.5)	<0.001	23.4 ( $\pm$ 3.5)	25.1 ( $\pm$ 3.5)	28.6 ( $\pm$ 4.2)	<0.001
Mobility					<0.001				<0.001
Active	387 (51.6%)	46 (29.3%)	205 (54.2%)	136 (63.3%)	—	28 (26.9%)	160 (53.2%)	199 (57.7%)	—
Sedentary	259 (34.5%)	66 (42.0%)	123 (32.5%)	70 (32.6%)	—	40 (38.5%)	104 (34.6%)	115 (33.3%)	—
Inactive	104 (13.9%)	45 (28.7%)	50 (13.2%)	9 (4.2%)	—	36 (34.6%)	37 (12.3%)	31 (9.0%)	—
Smokers					0.659				0.505
Never	502 (66.9%)	106 (67.5%)	260 (68.8%)	136 (63.3%)	—	74 (71.2%)	207 (68.8%)	221 (64.1%)	—
Current	74 (9.9%)	16 (10.2%)	36 (9.5%)	21 (9.8%)	—	7 (6.7%)	30 (10.0%)	36 (10.4%)	—
Past	174 (23.2%)	35 (22.3%)	82 (21.7%)	58 (27.0%)	—	23 (22.1%)	64 (21.3%)	88 (25.5%)	—
Alcohol use <sup>a</sup>					<0.001				0.581
Never	242 (32.3%)	63 (40.4%)	119 (31.5%)	60 (27.9%)	—	41 (39.8%)	98 (32.6%)	103 (29.9%)	—
<Once/week	262 (35.0%)	54 (34.6%)	128 (33.9%)	80 (37.2%)	—	35 (34.0%)	103 (34.2%)	124 (35.9%)	—
1–2/week	88 (11.8%)	7 (4.5%)	42 (11.1%)	39 (18.1%)	—	8 (7.8%)	34 (11.3%)	46 (13.3%)	—
Several/week	60 (8.0%)	6 (3.9%)	37 (9.8%)	17 (7.9%)	—	6 (5.8%)	23 (7.6%)	31 (9.0%)	—
Every day	97 (13.0%)	26 (16.7%)	52 (13.8%)	19 (8.8%)	—	13 (12.6%)	43 (14.3%)	41 (11.9%)	—
Polyparmacy					—				—
Three or more	329 (43.9%)	78 (49.7%)	159 (42.1%)	92 (42.8%)	0.252	59 (56.7%)	118 (39.2%)	152 (44.1%)	0.008
Diseases					—				—
Cardiovascular	351 (46.8%)	79 (50.3%)	190 (50.3%)	82 (38.1%)	0.011	53 (51.0%)	146 (48.5%)	152 (44.1%)	0.347
Neurological	28 (3.7%)	9 (5.7%)	12 (3.2%)	7 (3.3%)	0.331	5 (4.8%)	8 (2.7%)	15 (4.4%)	—
Endocrine	116 (15.5%)	23 (14.7%)	54 (14.3%)	39 (18.1%)	0.436	24 (23.1%)	35 (11.6%)	57 (16.5%)	0.016
Lung	114 (15.2%)	24 (15.3%)	54 (14.3%)	36 (16.7%)	0.725	17 (16.4%)	38 (12.6%)	59 (17.1%)	0.269
Gastrointestinal	172 (22.9%)	42 (26.8%)	85 (22.5%)	45 (20.9%)	0.401	34 (32.7%)	64 (21.3%)	74 (21.5%)	0.039
Malignancy	81 (10.8%)	22 (14.0%)	46 (12.2%)	13 (6.1%)	0.024	12 (11.5%)	35 (11.6%)	34 (9.9%)	0.743
Other	480 (64.0%)	111 (70.7%)	246 (65.1%)	123 (57.2%)	0.023	78 (75.0%)	195 (64.8%)	207 (60.0%)	0.016
SES <sup>b</sup>					0.209				0.457
Quintile 1	137 (18.3%)	33 (21.0%)	60 (15.9%)	44 (20.5%)	—	21 (20.2%)	62 (20.6%)	54 (15.7%)	—
Quintile 2	171 (22.8%)	44 (28.0%)	83 (22.0%)	44 (20.5%)	—	28 (26.9%)	62 (20.6%)	81 (23.5%)	—
Quintile 3	173 (23.1%)	35 (22.3%)	89 (23.5%)	49 (22.8%)	—	24 (23.1%)	71 (23.6%)	78 (22.6%)	—
Quintile 4	124 (16.5%)	20 (12.7%)	62 (16.4%)	42 (19.5%)	—	16 (15.4%)	43 (14.3%)	65 (18.8%)	—
Quintile 5	145 (19.3%)	25 (15.9%)	84 (22.2%)	36 (16.7%)	—	15 (14.4%)	63 (20.9%)	67 (19.4%)	—

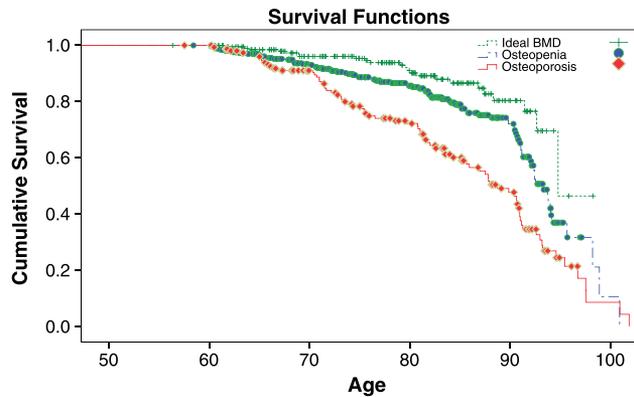
SES, Socio-economic status.

<sup>a</sup>n = 1 missing data

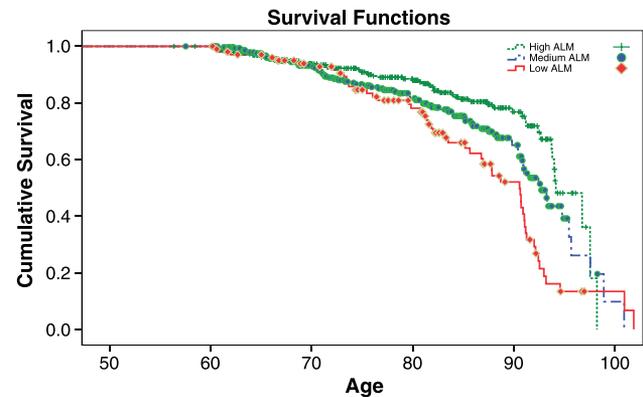
<sup>b</sup>Socio-economic status where Quintile 1 is the most disadvantaged and Quintile 5 is the least disadvantaged.

Data are expressed as mean ( $\pm$ SD), median (interquartile range), or n (%).

**Figure 1** Observed cumulative survival functions for bone mineral density status. Ideal bone mineral density (BMD) ( $T$ -score  $> -1.0$ ); osteopenia ( $T$ -score  $-2.5$  to  $-1.0$ ); and osteoporosis ( $T$ -score  $< -2.5$ ).



**Figure 2** Observed cumulative survival functions for appendicular lean mass (ALM) status. High ALM ( $T$ -score  $> -1.0$ ; medium ( $T$ -score  $-2.0$  to  $-1.0$ ); and low ALM ( $T$ -score  $< -2.0$ ).



95%CI 1.08, 2.11;  $p=0.017$ ) and 2.28-fold greater for those with low ALM (HR 2.28, 95%CI 1.56, 3.33;  $p < 0.001$ ) (Figure 2). In the multivariable model, mortality risks were 1.36-fold and 1.65-fold greater for those with medium and low ALM, respectively, and the relationships were

independent of smoking, polypharmacy, and mobility, which were also identified as significant predictors in the model (Table 2). Height, smoking, cardiovascular disease, endocrine and gastrointestinal disorders, and malignancy did not contribute to the final multivariable model.

**Table 2** Multivariable models for evaluating mortality risk according to bone mineral density status (Models 1 and 2), appendicular lean mass status (Models 3 and 4), and both bone mineral density and appendicular lean mass (Models 5 and 6)

Model	Factor	HR	Lower 95%CI	Upper 95%CI
Model 1	Ideal BMD	1.00	—	—
	Osteopenia	1.90	1.20	3.01
	Osteoporosis	3.43	2.14	5.48
Model 2	Ideal BMD	1.00	—	—
	Osteopenia	1.77	1.11	2.81
	Osteoporosis	2.61	1.60	4.24
	Smoking (yes)	1.96	1.20	3.18
	Polypharmacy (yes)	1.11	1.05	1.17
	Poor mobility (yes)	1.59	1.30	1.96
	ALM $T$ -score $> -1.0$	1.00	—	—
Model 3	ALM $T$ -score $< -2.0$ to $-1.0$	1.51	1.08	2.11
	ALM $T$ -score $< -2.0$	2.28	1.56	3.33
	ALM $T$ -score $> -1.0$	1.00	—	—
Model 4	ALM $T$ -score $< -2.0$ to $-1.0$	1.36	0.97	1.91
	ALM $T$ -score $< -2.0$	1.65	1.11	2.45
	Smoking (yes)	1.98	1.22	3.22
	Polypharmacy (yes)	1.10	1.04	1.16
	Poor mobility (yes)	1.70	1.39	2.08
	Ideal BMD	1.00	—	—
	Osteopenia	1.74	1.09	2.78
Model 5	Osteoporosis	2.82	1.70	4.70
	ALM $T$ -score $> -1.0$	1.00	—	—
	ALM $T$ -score $< -2.0$ to $-1.0$	1.25	0.89	1.78
	ALM $T$ -score $< -2.0$	1.52	1.00	2.31
	Ideal BMD	1.00	—	—
	Osteopenia	1.68	1.05	2.69
Model 6	Osteoporosis	2.37	1.41	3.98
	ALM $T$ -score $> -1.0$	1.00	—	—
	ALM $T$ -score $< -2.0$ to $-1.0$	1.19	0.84	1.68
	ALM $T$ -score $< -2.0$	1.25	0.82	1.90
	Smoking (yes)	1.97	1.21	3.20
	Polypharmacy (yes)	1.11	1.05	1.17
	Poor mobility (yes)	1.57	1.28	1.93

ALM, appendicular lean mass; BMD, bone mineral density; CI, confidence interval; HR, hazard ratio.

### *Bone mineral density and appendicular lean mass as the simultaneous exposures of interest*

Bone mineral density and ALM were positively correlated ( $r=0.49$ ,  $P<0.001$ ), and this association persisted after adjusting for age. When BMD and ALM were tested together in the models, BMD remained a predictor of mortality, and low ALM had borderline significance ( $P=0.051$ ), which was further attenuated after adjusting the model for smoking, polypharmacy, and mobility (Table 2). The data did not support a bone-muscle interaction in predicting mortality as the BMD–ALM interaction term was not significant in this multivariable model ( $P=0.263$ ).

### *Sensitivity analysis*

The sensitivity analysis, that involved 704 women for whom there were no exclusions for ALM, also identified ALM as a predictor of mortality. In this group, compared with women with high ALM, mortality risk was 1.42-fold greater for those with medium ALM (HR 1.42, 95%CI 1.00, 2.02;  $P=0.052$ ) and 2.38-fold greater for those with low ALM (HR 2.38, 95%CI 1.59, 3.56;  $P<0.001$ ).

## Discussion

We report that measures of both diminished bone mass and lean mass were markers for increased mortality risk. When considered in conjunction, mortality risk was associated with declining BMD and this was exacerbated by low ALM. The confounding effects of age were accounted for by using age as the time variable.

In the early 1990s, data from the Study of Osteoporotic Fractures in the USA revealed that women with low BMD at the proximal radius had higher mortality.<sup>8</sup> Subsequent studies confirmed this finding using BMD at the calcaneus for men and women from Sweden<sup>9</sup> and BMD at the hip for men from the UK.<sup>10</sup> A later prospective study from the Study of Osteoporotic Fractures reported that the rate of bone loss at the hip for women was prognostic for increased mortality, and that the relationship was independent of baseline BMD.<sup>11</sup> Higher rates of bone loss may be a marker for frailty associated with systemic disease, drug exposures, or immobility, which could also impact on skeletal muscle.

While muscle weakness is recognized as a risk factor for mortality,<sup>5–7</sup> less is known about the risk associated with diminished muscle mass. In a study of healthy older Chilean people, those in the lowest quartile of DXA-derived ALM had higher mortality during follow-up; this association was not evident for total lean mass.<sup>17</sup> Using muscle mass estimated by BIA, data from the US National Health and

Nutrition Examination Survey III revealed that low muscle mass (normalized by height) in women aged  $>60$  years was associated with increased mortality risk over a median period of 14.3 years, such that the adjusted HR for mortality was 1.32 (95%CI 1.04, 1.69); the adjusted HR for mortality among men was not significant.<sup>16</sup> In another analysis using data from the same phase of the National Health and Nutrition Examination Survey (National Health and Nutrition Examination Survey III), but this time involving well-nourished individuals (men aged  $>55$  years and women aged  $>65$  years) followed for a median period of 13.2 years, the adjusted HR for mortality was 0.80 (95%CI 0.66, 0.97) for the highest versus the lowest quartile of BIA-derived muscle mass normalized by height.<sup>15</sup> Deficits in skeletal muscle mass contribute to sarcopenia, a condition that also involves loss of muscle quality and performance.<sup>30</sup> In the Health, Ageing, and Body Composition study of older participants from the USA, the strong inverse association between muscle strength and mortality was not attenuated by ALM, suggesting that muscle strength is better than muscle mass as a marker of muscle quality in predicting mortality.<sup>7</sup> Nonetheless, the functional relevance of ALM in determining limb strength and mobility would contribute to sarcopenia being a risk factor for excess mortality.<sup>31,32</sup> Muscle strength and performance were not measured in this phase of our study, which limited our ability to further explore sarcopenia and mortality risk. However, our observations suggest that deficits in bone mass and muscle mass are additive rather than multiplicative in predicting mortality, and it seems likely that the co-occurrence of osteopenia/osteoporosis and sarcopenia, in a state described as osteosarcopenia,<sup>33</sup> would increase the risk for early mortality.

In conclusion, we report that musculoskeletal decline is associated with excess mortality in a relationship that appeared to be driven mainly by a decline in bone mass, but with an independent contribution from low ALM. In osteoporosis, interventions have been shown to reduce mortality,<sup>34</sup> and this initial observation was confirmed in a meta-analysis of randomized controlled trials<sup>35</sup> suggesting either a causal link between low bone mass and mortality and/or unrecognized off-target effects of osteoporosis therapies on mortality. The reports of sarcopenia as a predictor of mortality are consistent with our observations, but current evidence showing a benefit of intervention on mortality is lacking.<sup>36</sup> Low bone mass and low muscle mass may be markers of other processes that are driving excess mortality, such as the cumulative effect of co-morbidities that could eventually lead to organ failure, and this could incorporate musculoskeletal decline resulting from increased allostatic load related to systemic inflammation.<sup>37,38</sup>

Major strengths of this study include, a long period of follow-up, clinical assessments using DXA to obtain measures of both BMD and ALM, and data linkage to the national register that ensured complete ascertainment of deaths. We also

acknowledge several potential weaknesses. Changes in body composition during follow-up have not been considered, and participants who emigrated from Australia have not been identified. Exclusion of women with bilateral prostheses or who were unable to provide a complete whole body DXA scan may have introduced bias into the analyses, and the findings may not be generalizable, as the cohort comprised mainly (99%) White participants.<sup>27</sup> Finally, as in all observational studies, unrecognized confounding is likely.

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## Conflict of interest

J.A.P., M.M., K.L.H., S.L.B.-O., N.K.H., and M.A.K. declare that they have no conflict of interest.

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