Original Contribution

Vertebral Fractures Assessed by Dual-Energy X-Ray Absorptiometry and All-Cause Mortality: The Tromsø Study, 2007–2020

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Vertebral fractures have been associated with increased mortality, but findings are inconclusive, and many vertebral fractures avoid clinical attention. We investigated this association in a general population of 2,476 older adults aged ≥55 years from Tromsø, Norway, who were followed over 2007–2020, using dual-energy x-ray absorptiometry (DXA) at baseline to evaluate vertebral fractures (mild, moderate, or severe). We used multiple Cox regression models to estimate hazard ratios (HRs) for all-cause mortality, adjusted for age, sex, body mass index, education, smoking, alcohol intake, cardiovascular disease, and respiratory disease. Mean follow-up in the cohort was 11.2 (standard deviation, 2.7) years; 341 participants (13.8%) had ≥1 vertebral fracture at baseline, and 636 participants (25.7%) died between baseline and follow-up. Full-adjustment models showed a nonsignificant association between vertebral fracture status (yes/no) and mortality. Participants with ≥3 vertebral fractures (HR = 2.43, 95% confidence interval: 1.57, 3.78) or ≥1 severe vertebral fracture (HR = 1.65, 95% confidence interval: 1.26, 2.15) had increased mortality compared with those with no vertebral fractures. Dual-energy x-ray absorptiometry–based screening could be a potent and feasible tool in detecting vertebral fractures that are often clinically silent yet independently associated with premature death. Our data indicated that detailed vertebral assessment could be warranted for a more accurate survival estimation.

all-cause mortality; dual-energy x-ray absorptiometry; older adults; vertebral fractures

Vertebral fractures are common osteoporotic fractures among older adults, especially in Scandinavia (1), with prevalence ranging from 3%–7% in individuals younger than 60 years to 20% in those aged 70 years or older (2). However, vertebral fractures are often "clinically silent" and do not receive medical attention (3). With the global aging populations, the number of people with vertebral fractures will likely increase in the future, further accelerating their public health impact.

Vertebral fractures often result in height loss, back pain, impaired respiratory function, reduced quality of life, and increased risk of subsequent vertebral fractures (4–7). Several studies indicate that having a vertebral fracture is associated with increased mortality in the years after the fracture (8–12), although findings are inconsistent as not all studies confirm this association (13–16). Further, there are indica-

tions of sex differences, as studies in women consistently show increased mortality after 1 or more vertebral fractures (8–12), whereas studies in men are more equivocal (8, 10, 12, 17, 18). Collectively, these disparate findings may be partly due to methodological limitations such as small samples sizes, short follow-up times, and scarce investigation of confounding factors, such as bone mineral density (BMD). Additionally, some studies indicate that the presence of multiple vertebral fractures is related to higher mortality compared with having just 1 vertebral fracture (19, 20).

The vast majority of existing studies on vertebral fracture and mortality are based on vertebral morphometry performed on conventional spinal radiographs (i.e., morphometric x-ray radiography) (9, 11–23). Although spine radiography is considered the gold standard for diagnosing vertebral fractures (24, 25), vertebral fracture assessment (VFA) from

dual-energy x-ray absorptiometry (DXA) scans (i.e., morphometric x-ray absorptiometry) results in considerably less radiation exposure and may be more feasible in large population studies. DXA provides high-resolution scans (26–28), and the diagnostic sensitivity and specificity of VFA is comparable to spine radiography, at least for moderate and severe vertebral fractures (29, 30). Using VFA, the aim of the present prospective, population-based study was to examine the association between vertebral fractures and all-cause mortality in a general population of women and men aged 55 years or older, followed for 12 years from baseline examinations.

METHODS

Study subjects and ethical approval

This prospective cohort study included adults at least 55 years of age who participated in the sixth survey (2007–2008) of the Tromsø Study (Tromsø6, $n = 12,984$; attendance rate 65.7%). The Tromsø Study is a longitudinal, population-based, multipurpose health study with 7 repeated surveys performed to date in the municipality of Tromsø, Norway (31). Each survey is usually divided into 2 phases, with the second phase involving extended measurements in randomized subsamples. During phase 2 of Tromsø6, 3,854 women and men attended DXA measurement of the hip, based on the condition that they had participated in DXA measurements from the previous, fifth survey of the Tromsø Study in 2001 (2). Among these DXA attendees, lateral vertebral fracture assessment (VFA) was performed in a randomly selected group ($n = 2,894$). The potential for selection bias in this group has been previously evaluated; the VFA group was slightly older and shorter compared with the entire phase 2 sample, but slightly younger, taller, and heavier compared with DXA attendees who did not have VFA performed. Overall, the representativeness of the VFA sample is believed to be fair (2). Seven blurred VFA scans were excluded, leaving 2,887 persons with valid VFA measurements. Participants younger than 55 years were also excluded, to include primarily postmenopausal women, and thus 2,476 participants were included as the final study sample. The present study was approved by the Regional Committee for Medical and Health Research Ethics North, and all participants provided written informed consent.

Ascertainment of vertebral fractures and mortality

Vertebral fractures were ascertained by lateral spine DXA scans using the Lunar Prodigy Advance (GE Medical Systems, Madison, Wisconsin), including the enCORE software, version 12.20 (GE Medical Systems, Madison, Wisconsin), and according to standard operating procedures set by GE Medical Systems (32). These standards included using VFA and Genant's semiquantitative method to visually inspect and identify osteoporotic vertebral fractures based on vertebral height measurements, identifying the anterior, middle, and posterior heights of each vertebra (33). The software identifies 3 types of vertebral fractures: wedge, biconcave, and compression. The wedge fractures are characterized by

deformed structure of the anterior part of the vertebra, the biconcave of the middle part, and the compression of the total vertebra. Vertebral fractures are further categorized according to severity degrees, ranging from mild (grade 1, 20%–25% vertebral height loss) through moderate (grade 2, 26%–40% height loss) to severe (grade 3, >40% height loss) (26, 34). In our data set, only 0.1% of the vertebral fractures were identified as being mild; thus, persons with mild vertebral fracture were moved to the moderate category.

Trained technicians performed DXA scanning according to a standardized protocol. Further data processing included one sole experienced technician performing visual quality assessment and inspection of the whole sample, to determine whether the software hade positioned each region of interest for each identified vertebra correctly. Previous studies have shown that such visual evaluation has an overall agreement with vertebral fracture detection by conventional spine radiographs of 96.3%, and that VFA has a high sensitivity and specificity (0.81 and 0.98, respectively) for correctly identifying vertebral fractures of at least grade 2 (28, 35). For precision analysis of the VFA, data from a random sample of 50 participants were reanalyzed and inspected again. The mean intraclass correlation coefficients were 0.82, 0.79, 0.82, and 0.84 for anterior, middle, posterior, and average height, respectively, all vertebrae considered (2).

Outcome

Date of death was obtained from the Norwegian Cause of Death Registry. The participants were observed from the date of examination in 2007–2008 until the date of death, or date of censoring due to migration, or end of follow-up on October 17, 2020, whichever came first.

Baseline measurements

Baseline covariates were collected using self-administered questionnaires and physical examinations. Participants reported smoking status (current/previous/never), cardiovascular disease (angina/stroke/myocardial infarction), respiratory disease (bronchitis/emphysema/chronic obstructive pulmonary disease), educational level (college or university ≥4 years/college or university <4 years/high school diploma/technical or vocational school/primary or secondary school) and alcohol intake (frequency per week × units). Areal BMD (aBMD) of the total hip was measured in g/cm² using the Lunar Prodigy Advance DXA (GE Medical Systems). Height and weight were measured to the nearest centimeter and half-kilogram, respectively. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Leisure-time physical activity level (inactive/light/moderate/vigorous) was reported using the validated Saltin-Grimby Physical Activity Level Scale (36).

Statistical analyses

Descriptive data are presented as means and standard deviations (SDs) or as numbers of participants and percentages. Multiple Cox proportional hazards regression models

were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality according to presence, number, and severity of vertebral fractures. For regression models, we dichotomized smoking status into current smoker versus nonsmoker or previous smoker, and education into low education (vocational school/primary or secondary school) versus all higher categories. Regression models were inspected for multicollinearity (variance inflation factor), interaction (vertebral fracture variable × age, × sex, or × education), and additionally checked for proportional hazards assumption using a log-log plot of survival and tested with Schoenfeld's residuals. There was no evidence of significant interaction between the investigated variables; thus, they were added as confounders in the main regression models. Sex-stratified analyses and interaction results are further detailed in Web Table 1. Age was the only confounder that violated the proportional hazards assumption in all models ($P < 0.05$ for all). Thus, age was controlled for by stratification (using regression option "strata") into 5-year age groups instead of being included as a continuous variable in the model.

Model 1 adjusted for sex and age only, while model 2 (full adjustment) additionally included body mass index, education, smoking, alcohol intake, cardiovascular disease, and respiratory disease. Physical activity and total hip aBMD were separately included in a subsample analysis due to the amount of missing data (5%–13%) for those covariates. We also performed 2 sensitivity analyses: 1) restricting the sample to participants having ≥2 years of follow-up time, and 2) restricting the follow-up time to the first 5 years. All analyses were performed using STATA, version 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

The mean follow-up time in the study sample was 11.2 (SD, 2.7) years. Between baseline and end of follow-up, 636 participants (25.7%) died and the average time to death was 7.7 (SD, 3.3) years. In total, 341 participants (13.8%) had at least 1 vertebral fracture at baseline, of whom 175 (7.1%) had moderate vertebral fractures and 166 (6.7%) had severe vertebral fractures. In all, 226 participants had 1 vertebral fracture (9.1%), 76 participants had 2 vertebral fractures (3.1%), and 39 participants had 3 or more vertebral fractures (1.6%).

The baseline characteristics of the study sample are described in Table 1. The mean age was 67.9 (SD, 7.5) years, mean body mass index was 27.2 (SD, 4.1), and 58.4% of participants were women. Current smoking was reported by 399 participants (16.4%), and the average alcohol use was 1.9 (SD, 2.9) units per week. Prevalent cardiovascular disease and respiratory disease were reported by 397 (16.4%) and 149 (6.2%) participants, respectively. A large proportion of the participants ($n = 1,039$, 42.9%) reported having completed primary/secondary or modern secondary school, the lowest of the 5 educational levels. With respect to leisure-time physical activity, 428 participants (19.9%) considered themselves to be physically inactive, while 1,385 participants (64.4%) reported light physical activity, and 338 (15.8%) were moderately/vigorously active (Table 1).

The survival estimates based on vertebral fracture occurrence, number and severity are visualized with Kaplan-Meier plots in Figure 1A–1C, and the results of the multivariate Cox regressions are presented in Table 2. The full model showed an increase in mortality among participants with at least 1 vertebral fracture compared with those without, although this was not statistically significant (HR = 1.21, 95% CI: 0.97, 1.51). Additionally, participants with 2 vertebral fractures showed no increased mortality (HR = 0.95, 95% CI: 0.59, 1.53), while the mortality was more than twice as high among those having 3 or more vertebral fractures (HR = 2.43, 95% CI: 1.57, 3.78), compared with those without. Considering vertebral fracture severity, having a moderate vertebral fracture (grade 2) did not lead to increased mortality compared with having no vertebral fractures (HR = 0.83, 95% CI: 0.59, 1.16), while having a severe vertebral fracture (grade 3) led to a 65% higher mortality (HR = 1.65, 95% CI: 1.26, 2.15) (Table 2). These results were not significantly altered in subsample analyses with additional adjustment for physical activity or aBMD, or in a sensitivity analysis restricting the sample to participants with ≥2 years of follow-up time (Web Tables 2–3). Restricting the sample to the first 5 years of follow-up (Web Table 4) led to increased mortality only for participants with severe vertebral fractures, in the full model (HR = 1.89, 95% CI: 1.13, 3.14).

DISCUSSION

In the present study of 2,476 community-dwelling women and men aged 55 or older, we found increased all-cause mortality for participants with ≥3 vertebral fractures or severe vertebral fracture, as ascertained by VFA. These findings were robust in sensitivity analyses with additional adjustments for total hip aBMD and leisure-time physical activity. In contrast, we did not observe any significantly increased mortality after these adjustments when comparing crude categories of having a vertebral fracture (ignoring quantity or severity) versus not having a vertebral fracture, indicating that detailed assessment could be warranted for a more accurate survival estimation. Vertebral fracture severity seems particularly important to determine, as severe vertebral fractures were significantly associated with increased mortality even when follow-up time was restricted to the first 5 years.

Our findings are partly consistent with previous studies (8–12, 17–23), although nuances in methodology and study characteristics need clarifying. Some of these studies investigated women only (9, 11), included adjustment only for age and/or sex (12, 17, 18, 21), or involved smaller study samples, thus increasing the risk of type 2 error (17, 21–23). Two large studies ($n > 100,000$) reported increased mortality (HRs of approximately 1.30–1.80) in multiply adjusted analyses for participants with a prevalent vertebral fracture compared with matched controls without, although no details on fracture characteristics were reported, and unmeasured confounding was raised as a potential problem because important lifestyle parameters, such as smoking and body mass index, were not assessed (8, 10). Mortality was reportedly increased by cumulative numbers of vertebral fractures

Table 1. Baseline Characteristics of the Study Sample ($n = 2,476$), the Tromsø Study, Norway, 2007–2020

Characteristic	No.	%	No. Missing	%
Age, years[a]	67.91 (7.49)		0	0
Sex			0	0
Female	1,445	58.4		
Male	1,031	41.6		
BMI[a,b]	27.17 (4.14)		1	0
Smoking status			48	1.9
Current smoker	399	16.4		
Previous smoker	1,187	48.9		
Nonsmoker	842	34.7		
Education			53	2.1
Primary/secondary, modern secondary school	1,039	42.9		
Technical/vocational school, 1–2 years senior high school	655	27.0		
High-school diploma	120	5.0		
College/university <4 years	317	13.1		
College/university ≥4 years	292	12.1		
Alcohol use, units per week[a]	1.90 (2.89)		105	4.2
CVD			58	2.3
Yes	397	16.4		
No	2,021	83.6		
Respiratory disease			71	2.9
Yes	149	6.2		
No	2,256	93.8		
Total hip aBMD, g/cm^2			140	5.7
Women[a]	0.89 (0.13)			
Men[a]	1.02 (0.15)			
Leisure-time physical activity categories			325	13.1
Inactive	428	19.9		
Light physical activity	1,385	64.4		
Moderate physical activity	328	15.3		
Vigorous physical activity	10	0.5		

Abbreviations: aBMD, areal bone mineral density; BMI, body mass index; CVD, cardiovascular disease.
[a] Values are expressed as mean (standard deviation).
[b] Calculated as weight (kg)/height (m)^2.

in the study by Ensrud et al. (9), and similar to the present study, some studies detected significantly higher mortality only when multiple vertebral fractures were present (19, 20), in fully adjusting models. Additionally, very few studies evaluated the impact of vertebral fracture severity; van der Jagt-Willems et al. (19) reported that a grade 3 vertebral fracture had no independent association with mortality, which is in contrast to our own findings and possibly explained by them following roughly 400 geriatric patients over 3 years, compared with the 2,500 community-dwelling participants followed over 12 years in the present study. Of note, our sex-stratified data suggested a stronger association with mortality for women compared with men, which has been reported by some (18). However, this could not be

statistically confirmed in the present study because there was no evidence of an interaction between sex and fracture status, and because each 95% CI overlapped the point estimate in the other stratum. Larger studies, likely more adequately powered for sex-stratified analyses, have to this end reported no significant differences between men and women (8, 10).

In contrast, several studies did not observe any associations between vertebral fracture and premature death, or they reported that the association became nonsignificant in full-adjustment models (13–16). The discrepancies in the results are not easily explained but could be influenced by methodological differences such as shorter follow-up times (15, 16), fracture assessment only in the thoracic
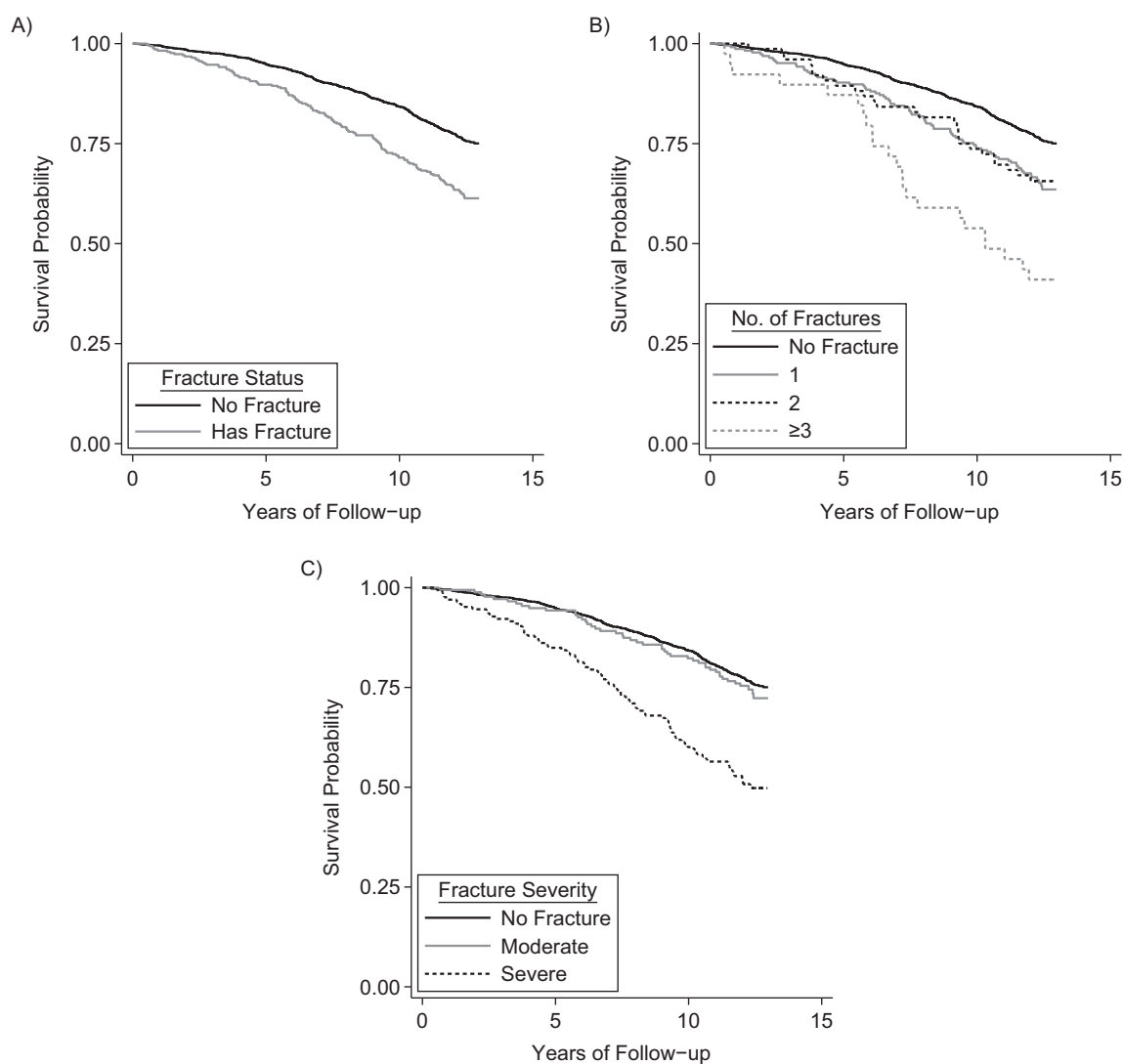
Figure 1.   Kaplan-Meier survival estimation plots, the Tromsø Study, Norway, 2007–2020. A) Fracture occurrence; B) fracture number; C) fracture severity.

region (13), or unmeasured confounding (14). None of the aforementioned studies investigated the impact of multiple vertebral fractures or fracture severity, which were the main parameters associated with increased mortality in our study. Kado et al. (14) reported that the association between prevalent vertebral fractures and mortality disappeared when adjusting for frailty markers, such as weight loss or inability to rise from a chair. However, they also stated that they could not discern whether these frailty markers were caused by or resulted from the vertebral fractures. The present study did not include such data, and while it would have been interesting to mirror the analyses by Kado et al., we showed that adjustment for other potentially important confounders, such as aBMD and physical activity, did not significantly influence our results. Nonetheless, a vertebral fracture may not be the direct cause of death but can rather act as an indicator of frailty and a complex pathogenesis (14). This

is supported by Kanis et al. (37), who reported that only 28% of deaths were attributed to the vertebral fracture itself, and that it was difficult to assume a causal link between vertebral fracture prevention and increased survival. Likewise, Puisto et al. (13) showed that vertebral fractures were mainly associated with death from injury in women, and with respiratory death in men, although similar to our study, they detected no associations between vertebral fractures and respiratory disease at baseline. They further speculate that prominent thoracic kyphosis from vertebral fractures could explain the association with respiratory death in men, and that acute trauma would be more fatal because of frailty and poor health status in women with vertebral fractures. It is clear that more studies including longitudinal data on disease and trauma incidence during the follow-up period would be needed to improve our understanding of the chain of events from vertebral fractures leading up to death.

Table 2. Cox Proportional Hazards Regression for All-Cause Mortality, the Tromsø Study, Norway, 2007–2020

Exposure	Model 1[a]					Model 2[b]				
	HR	95% CI	No.	Deaths	%	HR	95% CI	No.[c]	Deaths	%
Fracture status										
No fracture	1.00	Referent	2,135	508	24	1.00	Referent	1,922	427	22
Has fracture	1.23	1.01, 1.49	341	128	38	1.21	0.97, 1.51	288	102	35
No. of fractures										
No fracture	1.00	Referent	2,135	508	24	1.00	Referent	1,922	427	22
1	1.15	0.91, 1.46	226	79	35	1.11	0.85, 1.45	192	62	32
2	1.05	0.71, 1.57	76	26	34	0.95	0.59, 1.53	61	18	30
$\geq$3	2.08	1.36, 3.17	39	23	59	2.43	1.57, 3.78	35	22	63
Fracture severity										
No fracture	1.00	Referent	2,135	508	24	1.00	Referent	1,922	427	22
Moderate	0.84	0.62, 1.13	175	46	26	0.83	0.59, 1.16	150	36	24
Severe	1.67	1.32, 2.12	166	82	49	1.65	1.26, 2.15	138	66	48

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age and sex.

[b] Adjusted for covariates in model 1 with the addition of low education, current smoker status, body mass index, alcohol use, cardiovascular disease, and respiratory disease.

[c] Numbers in model 2 do not sum to the total ($n = 2,476$) because of missing data on covariates, as presented in Table 1.

Interestingly, adjustment for total hip aBMD in our subsample analyses did not significantly change the associations between number of vertebral fractures, fracture severity, and all-cause mortality. Jalava et al. (15) suggested that adjustment for BMD may be important to increase understanding of the excess mortality that occurs due to vertebral fractures, and this argument was supported by a later study reporting increased mortality only for vertebral fractures that occurred in the presence of osteoporosis (38). The present study's use of the hip measurement site, rather than the spine, could perhaps explain why aBMD did not significantly influence the association between vertebral fractures and mortality. This assumption is partly supported by a study in women where total hip BMD did not add to the prediction of spine fractures when spine BMD was already considered (39). However, others have shown that in men, the total hip BMD measurements produced the highest HRs for vertebral fracture (40), thus indicating that the accuracy of different BMD measurement sites to predict vertebral fractures might be influenced by sex. Our subsample analyses also indicate a more pronounced attenuation by leisure-time physical activity on the association between vertebral fracture characteristics and mortality, although the HRs remained statistically significant. Participants reporting higher physical activity could in this regard be engaging in weight-bearing activities or resistance exercise that has been reported to both improve spine BMD and reduce mortality (41, 42). Similarly, individuals who have sustained moderate or severe vertebral fractures also experience reduced physical activity after the event, potentially explaining part of the attenuated association in the present study (43).

We are unaware of any previous study that has investigated DXA-derived vertebral fractures and all-cause mortality. Compared with conventional spinal radiographs, DXA exposes the patient to considerably less radiation and is a less costly alternative (35), thus increasing its clinical utility. Moreover, VFA was recently added as an acknowledged measurement technique in the European osteoporosis guidelines (3). Our data suggest that DXA provides a valid and feasible low-radiation screening method of older adults for detecting hazardous vertebral fracture phenotypes, which seldom receive clinical attention (1). The clinical implications convey that individuals sustaining subsequent vertebral fractures, or vertebral fractures of higher severity, require extra care and targeting of potentially underlying frailty processes and comorbidities to increase survival.

The present study has some limitations that need addressing. As we had access only to prevalent vertebral fractures at baseline, we could not perform a proper time-to-event analysis between fracture incidence and mortality, thus limiting our inferences. Restricted to baseline exposure data only, we were unable to determine potential competing risks or disease events during the follow-up period that could lead to premature death. Similarly, as we did not investigate cause of death, we lacked detailed information on the relationship between vertebral fractures and specific fatal disease events, which could have informed potential treatment targets. The Tromsø Study was performed primarily in an urban setting, and the findings may not be entirely generalizable to more rural settings, as fracture mortality has been shown to differ between these independently of socioeconomic status (44). This study was also conducted in the Arctic region, and

results could therefore differ compared with investigations in more southern or warmer regions. Additionally, some caution is warranted when interpreting our findings on number of vertebral fractures and all-cause mortality, as the group with ≥3 vertebral fractures included only 39 participants. That multiple vertebral fractures are more hazardous is supported by some previous studies, but it is difficult to conclude that mortality increases exactly at a given number of vertebral fractures (9, 19, 20). This was also indicated by the lack of significant association between ≥3 vertebral fractures and mortality when analyzing only the first 5 years of follow-up. Last, our results are potentially subject to residual confounding because we lacked information on relevant covariates such as kidney disease, rheumatologic disease, and use of corticosteroids, antiepileptic medication, and vitamin D supplementation. Neither did we have access to information on femoral neck aBMD and could thus not investigate any potential impact on our associations from other clinical bone sites.

The study also has several strengths. First, we were able to investigate a relatively large, population-based sample over a long follow-up period and report associations for both women and men. Second, we included a rich set of covariates, thus increasing the robustness of our results. Third, we provide potentially novel and clinically important information regarding the association between vertebral fractures and all-cause mortality, by analyzing detailed vertebral fracture characteristics such as fracture number and severity, in comparison with reporting only whether a vertebral fracture was present.

In conclusion, this prospective cohort study showed that individuals aged at least 55 years who have sustained 3 or more vertebral fractures, or have sustained at least 1 severe vertebral fracture, have significantly increased all-cause mortality compared with individuals without vertebral fractures. DXA-based screening should be recommended in vulnerable populations to detect vertebral fractures that are usually underdiagnosed, yet still hazardous, and detailed vertebral fracture assessment may be required for a more accurate survival estimation. Further research is required to elucidate the relationship between vertebral fracture characteristics, subsequent disease events and death causes to support treatment alternatives.

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