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Can bone mineral density loss in the non-weight bearing distal forearm predict mortality?☆

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ABSTRACT

Purpose: Low bone mineral density (BMD) is associated with increased risk of fractures and mortality. We investigated if rate of BMD loss in the distal forearm over seven years predicted mortality.
Methods: 1725 postmenopausal women and 1879 men aged 50–74 who participated in the longitudinal Tromsø Study waves 4 (1994–95) and 5 (2001 − 2002) were included. Cox regression models adjusted for lifestyle- and health related variables were used to assess associations between BMD change over seven years and subsequent mortality during up to 17 years of follow-up in participants with normal and low BMD at baseline.
Results: Baseline BMD decreased and seven-year bone loss increased with increasing age. Overall, mortality rates were higher among those with low versus normal BMD (38 vs 19 per 1000 py in women, 56 vs 34 in men) and at higher bone loss rates (rate ratio high:low = 1.2 in women, 1.7 in men). BMD change was associated with increased mortality only in men with normal baseline BMD. In this group, men with a BMD loss of > 4% had significantly higher mortality (HR 1.50, 95% CI 1.21, 1.87) than men with increased or unchanged BMD. BMD change was not significantly associated with increased mortality in women or in men with low BMD at baseline.
Conclusions: BMD loss in the distal forearm was associated with increased mortality in men with normal BMD at baseline, but not in women. We found no clear association between BMD loss and mortality in those with low BMD at baseline.

1. Introduction

Declining bone mineral density (BMD g/cm^2) is a part of the ageing process in both women and men. Peak bone mass is the point at which bone density is highest during the life span and is usually reached during the end of the second or beginning of the third decade [1–3]. The point of peak bone mass and the rate of decline can vary greatly from person to person, depending on both genetics and numerous health- and lifestyle-related variables such as level of physical activity, BMI, smoking habits, presence of various diseases and use of medication [4–8], resulting in some people developing osteoporosis while others do not. Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration causing increased bone fragility and susceptibility to fracture [9]. The condition is widespread in older populations globally, with an estimated prevalence of 22.1% in women and 6.6% in men aged 50+ and 47.2% in women and 16.6% in men aged 80+ [10]. Osteoporosis poses a huge public health burden through fragility fractures [11,12] and subsequent pain, disability, medical expenses, reduced quality of life and increased mortality [13–15], especially following hip fractures [16–21]. In a recent study, we found that low BMD in the distal forearm categorized as *osteopenia* and *osteoporosis* were both associated with increased mortality, and the association was only slightly attenuated by taking osteoporotic fractures into account [22]. This may suggest that vulnerability in people with low BMD comprises more than an increased fracture risk.

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In women, most of the bone loss occurs in the late perimenopause and beginning of the postmenopausal period [23,24]. In men, however, BMD loss varies less in older age and BMD levels in the distal forearm have been found to decrease consistently from around the age of 50 years [24–26].

Repeated measurements give information, not only about the updated BMD status, but also about the rate of BMD change which might help identification of individuals with a higher risk of developing osteoporosis and a higher mortality. While several recent prospective studies continue to confirm the association between BMD and mortality in general populations and within disease categories [15,22,27–32], it is uncertain whether rate of bone loss per se also contributes to predicting mortality. Some studies have indicated that the rate of bone loss in weight bearing sites such as hip, spine and calcaneus is positively associated with mortality [33–35], but these studies included relatively old populations with a mean age of > 70 years at baseline. One study [33] only included women and had a short mean follow-up of only 3.2 years and the most recent study found the association between rate of BMD loss and mortality to be most pronounced in men [35]. To the best of our knowledge, no studies have investigated the association between the rate of bone loss in non-weight bearing sites, such as the forearm, and mortality in a general population. While BMD loss at weight bearing sites can be a result of declining physical function and limited ability to stay active [36], BMD in non-weight bearing sites might be less sensitive to such changes in everyday load and therefore yield additional insight to any association between rate of BMD loss and mortality. BMD loss might also be more critical in regards of mortality for persons with already established osteoporosis due to marginal bone reserve and inherent structural integrity. If so, this is important to consider when discussing treatment strategies for patients with low BMD. The population-based Tromsø Study in Northern Norway performed bone densitometry in the distal forearm in men and women in 1994–95 and retested the same participants seven years later in 2001–02 [25]. We investigated whether the seven-year rate of bone loss in the distal forearm predicted mortality and whether the association between BMD loss and mortality varied between those with normal BMD, osteopenia or osteoporosis at baseline.

2. Method

2.1. Study population

The Tromsø Study, initiated in 1974, is a longitudinal, population based, multi-purpose study focusing on lifestyle-related diseases and their risk factors [37]. The current study population comprised individuals who participated in both the fourth (Tromsø 4) and fifth (Tromsø 5) wave, conducted in 1994–95 and 2001–02, respectively. Tromsø 4 included distal forearm bone densitometry in a subgroup as part of additional testing offered to all women aged 50–74 years, all men aged 55–74 year and random subsamples (10–15%) of younger (24–55 years) and older participants (74–85 years). All participants in Tromsø 4 who were still alive and residing in the area were invited to participate in Tromsø 5. The current analyses are restricted to participants aged 50–74 years at the time of Tromsø 4 and women who had undergone menopause more than five years prior to Tromsø 4, hence aged 57–81 years at Tromsø 5. The attendance rate in Tromsø 4 was 76% among men and 79% among women in this age group. Of the Tromsø 4 participants who were re-invited to Tromsø 5, 4936 (86% of those in the pertinent age range who were still alive and residing in Tromsø county) attended the additional testing in Tromsø 5 [38]. After exclusion of participants with missing values for potential health- and lifestyle related confounders (see covariate section), the final study population for analysis consisted of 3604 participants, 1725 women with a mean age of 62.4 years (SD = 6.2) and 1879 men with a mean age of 61.7 years (SD = 6.0) per 31st December 1994. See Fig. 1 for flow chart of inclusion and exclusion of participants.

2.2. Assessment of bone mineral density (BMD)

BMD was measured using single X-ray absorptiometry (SXA) on the non-dominant forearm at the distal and ultra-distal sites with two SXA devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California). The same devices were used in both Tromsø 4 and Tromsø 5. The dominant arm was used for measurement in 1% of the participants when the non-dominant arm was ineligible due to wounds, plaster casts etc. The testing procedure and quality assessment is described in detail by Berntsen et al. and Emaus et al. [38,39]. An individual BMD change should be > 2% (distal) or 3% (ultra-distal) before it can be reliably detected by two separate measurements [40]. We have previously used the distal measurements, including both radius and ulna, from 1994 in analyses on BMD and mortality [22] and continued to do so in this study for the sake of comparability. Least significant change (LSC) was therefore defined as > 2% in our analyses.

2.3. Reference values for low BMD (osteopenia and osteoporosis)

Gender specific internal BMD reference values were created for osteopenia and osteoporosis. These were based on BMD values corresponding to 1 and 2.5 SDs below the mean BMD of healthy men and women aged 24–39 years in the Tromsø 4 densitometry data [22]. The mean BMD-value of the reference groups were 0.471 g/cm^2 (SD = 0.043) in women and 0.575 g/cm^2 (SD = 0.045) in men, yielding threshold values for osteopenia and osteoporosis of 0.428 g/cm^2 and 0.364 g/cm^2 in women and 0.531 g/cm^2 and 0.464 g/cm^2 in men. Participants with osteopenia or osteoporosis were placed in the category “Low BMD” in the analyses. Any BMD value above the threshold for osteopenia was categorized as “Normal”.

2.4. Ascertainment of deaths

Data on each participant was linked to the Norwegian Cause of Death Registry and to the National Registry for assessment of death and emigration by the means of the unique personal identification number. Participants were followed from the Tromsø 5 study wave in 2001 until emigration, death or October 6th 2018, whichever occurred first.

2.5. Covariates

The following lifestyle and health related variables from Tromsø 4 were considered to be potential confounders: BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Both height and weight were objectively measured by trained personnel. Self-reported smoking habits were categorized as “current”, “previous” or “never-smoker”. Education level based on years of completed education was grouped into five levels: “7-10 years primary/secondary school”, “Technical school, middle school, vocational school, 1-2 years senior high school”, “High school diploma (3-4 years)”, “College/university, less than 4 years” and “college/university 4 or more years”. Self-reported level of activity, reported as number of hours spent on light physical activity (not sweating or out of breath) and hard physical activity (sweating and/or out of breath) during a typical week, was categorized in four groups for each variable: “none”, “less than one”, “one to two”, “three or more”. Self-reported chronic diseases were registered by answering “yes” or “no” following questions about whether they have had or currently have the following diseases: stroke, myocardial infarction, angina, diabetes or asthma. Self-perceived health was described in the categories: “poor”, “not so good”, “good” and “very good”. The following variables from Tromsø 5 were also included: BMI-change between Tromsø 4 and Tromsø 5 and use of anti-osteoporosis drugs (AOD) within ATC-category “M05B” (drugs affecting bone structure and mineralization). In women, we also adjusted for hormone replacement therapy (HRT), reported as “current”,” previous” or “never” in Tromsø 5, cessation of HRT between Tromsø 4 and

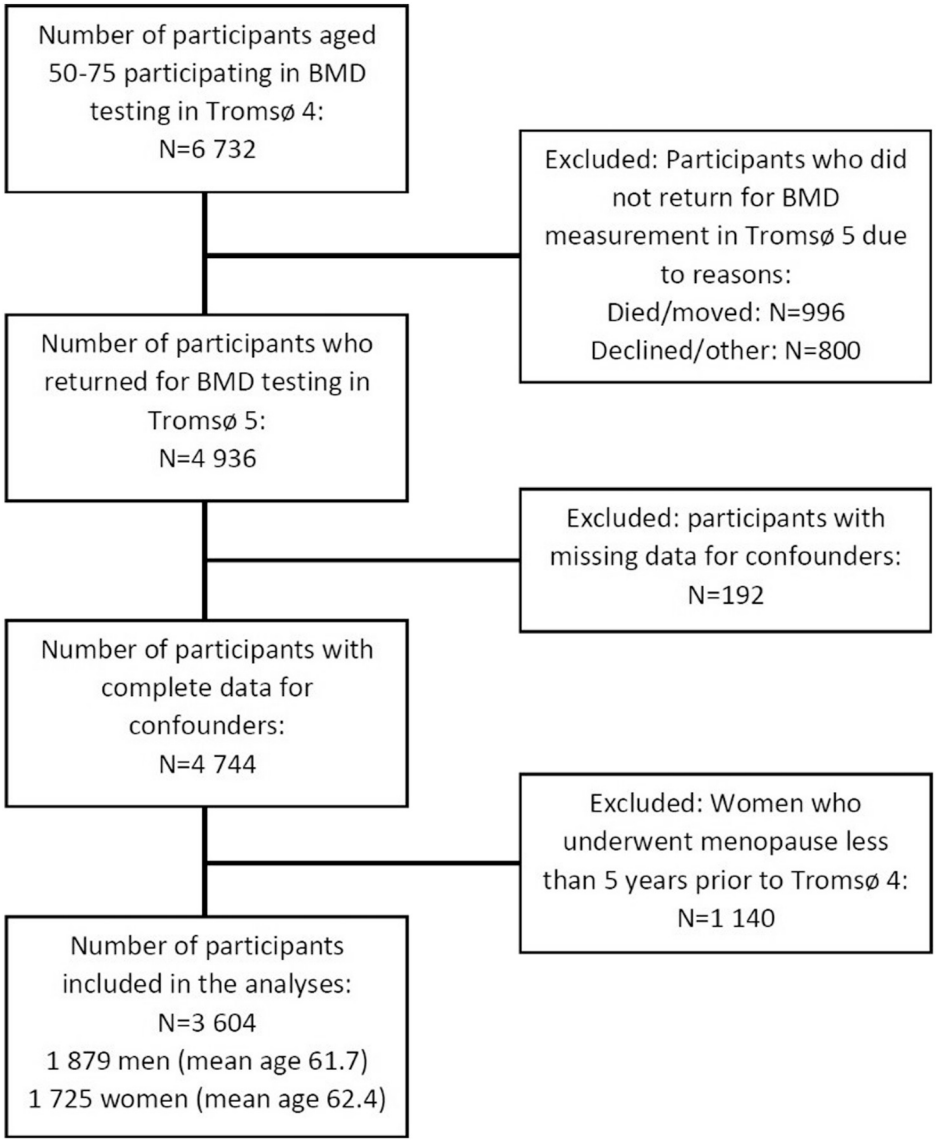

Fig. 1. Flow chart describing inclusion and exclusion of participants.

Tromsø 5 and years since menopause. The onset of menopause was self-reported as age when menstruation ceased, given amenorrhea for at least 12 months.

2.6. Statistical analysis

Separate analyses were conducted for women and men with gender-specific cut-off values for "Normal BMD" and "Low BMD" based on T-scores above or below −1 and adjustment for menopause and HRT only in women. Participants were divided into two groups: "Normal BMD" or "Low BMD" based on their distal forearm BMD at baseline. These groups were further divided into three groups of BMD change over the period: 1: positive or unchanged (≥ −2%), 2: 1× LSC to 2× LSC bone loss (−2% to −4%), or 3: > 2× LSC bone loss (< −4%), in order to allow for comparison between the upper and lower extremes of the distribution of BMD change. A set of Cox regression models were used to estimate the association between seven-year BMD change and mortality with a maximum follow-up time of 17 years. First, within each of the two baseline BMD groups, BMD change over the seven-year period categorized by LSC were regressed against mortality, using group 1 (positive or unchanged) as reference category. Attained age defined the time scale in the Cox models, thereby effectively adjusting for age, and we successively adjusted for potential confounders assessed at baseline: BMD, BMI, level of physical activity, smoking habits, category of completed education, self-rated health, self-reports of chronic diseases and follow-up information on use of AODs and BMI change between Tromsø 4 and Tromsø 5. In women, we also adjusted for years since menopause and use/cessation of HRT at follow-up. Secondly, within the two baseline BMD groups, mortality across the distribution of percentage BMD change was assessed by modelling continuous BMD change as restricted cubic splines with three knots, using default knot location. In the analysis with splines, outliers defined as BMD change exceeding +5% or −15% were removed to avoid a large influence by a few extreme values, excluding 211 participants in total. Outliers were not excluded in the Cox models on LSC of BMD change because they were not expected to influence the models as much. Statistical significance was defined by an alpha level of 0.05 and statistical analyses were carried out with Stata/SE 15.

3. Results

Mean age at baseline was 62.4 (SD 6.2) in women and 61.7 (SD 6.0) in men and BMD change during follow-up was −4.8% (SD 6.7) and −3.2% (SD 3.9) respectively. Complete demographics for our study

Table 1
Descriptive baseline characteristics (first visit, Tromsø 4) presented as mean values with standard deviations (SD) for continuous variables and number of participants (N) with rates (%) for categorical variables. Use of anti-osteoporotic drugs (AODs) and hormone replacement therapy (HRT) is described at second visit (Tromsø 5). Characteristics described for women and men separately in our study sample, in those who only participated in Tromsø 4 and in those who participated in both Tromsø 4 and 5 (including those who did not meet our inclusion criteria).

Variables included in analyses	Women			Men		
	Our study	Only Tromsø 4	Tromsø 4 + Tromsø 5	Our study	Only Tromsø 4	Tromsø 4 + Tromsø 5
	(*n* = 1725)	(*n* = 941)	(*n* = 2973)	(*n* = 1879)	(*n* = 855)	(*n* = 1963)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (T4)	62.4 (6.2)	62.7 (7.6)	59.9 (7.0)	61.7 (6.0)	64.3 (6.5)	61.8 (6.1)
BMI (T4)	26.1 (4.2)	26.3 (4.9)	26.0 (4.2)	26.1 (3.2)	26.0 (3.7)	26.1 (3.2)
BMI change (T4 ➔ T5)	0.9 (2.2)	–	0.9 (2.2)	0.6 (1.6)	–	0.6 (1.7)
BMD, g/cm^2 (T4)	0.392 (0.065)	0.390 (0.072)	0.408 (0.067)	0.541 (0.063)	0.519 (0.070)	0.540 (0.063)
BMD change, % (T4 ➔ T5)	−4.8 (6.7)	–	−5.8 (6.6)	−3.2 (3.9)	–	−3.2 (4.0)
Years since menopause (T4)	21.9 (6.7)	19.4 (8.8)	17.9 (8.8)	–	–	–
Menopause age	47.7 (4.9)	48.3 (4.8)	48.4 (4.7)	–	–	–
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Use AODs (T5)	68 (3.9)	–	96 (3.2)	5 (0.3)	–	5 (0.3)
Use HRT (T5)						
Never	1369 (79.4)	912 (96.9)	2325 (78.2)	–	–	–
Previous	207 (12.0)	15 (1.6)	350 (11.8)	–	–	–
Current	149 (8.6)	14 (1.5)	298 (10.0)	–	–	–
Smoking (T4)						
Never	775 (44.9)	357 (38.0)	1332 (44.8)	390 (20.8)	127 (14.9)	401 (20.4)
Previous	483 (28.0)	238 (25.3)	803 (27.0)	970 (51.6)	398 (46.5)	1016 (51.8)
Current	467 (27.1)	344 (36.6)	836 (28.1)	519 (27.6)	330 (38.6)	545 (27.8)
Education (T4)						
7–10 years prim./sec. School	1083 (62.8)	602 (64.7)	1773 (60.0)	865 (46.0)	426 (50.1)	903 (4.6)
[…]/ 1–2 years senior high school	388 (22.5)	195 (21.0)	673 (22.8)	553 (29.4)	244 (28.7)	576 (29.4)
High school diploma (3–4 years)	47 (2.7)	21 (2.3)	86 (2.9)	74 (3.9)	37 (4.4)	78 (4.0)
College/University < 4 years	114 (6.6)	68 (7.3)	222 (7.5)	238 (12.7)	83 (9.8)	247 (12.6)
College/University 4 years or more	93 (5.4)	44 (4.7)	200 (6.8)	149 (7.9)	60 (7.1)	152 (7.8)
Diseases (T4)						
Stroke	25 (1.4)	32 (3.4)	40 (1.3)	44 (2.3)	47 (5.5)	48 (2.5)
Angina	108 (6.3)	97 (10.3)	162 (5.5)	199 (10.6)	139 (16.3)	211 (10.8)
Myocardial infarction	28 (1.6)	60 (6.4)	50 (1.7)	162 (8.6)	120 (14.0)	171 (8.7)
Diabetes	39 (2.3)	46 (4.9)	65 (2.2)	44 (2.3)	52 (6.1)	49 (2.5)
Asthma	156 (9.0)	99 (10.5)	234 (7.9)	123 (6.5)	70 (8.2)	132 (6.8)
Light physical activity (T4)						
None	203 (11.8)	187 (19.9)	354 (11.9)	200 (10.6)	144 (17.0)	212 (10.9)
< 1 time per week	196 (11.4)	129 (13.7)	368 (12.4)	230 (12.2)	116 (13.7)	238 (12.2)
1–2 times per week	584 (33.9)	295 (31.4)	1013 (34.1)	554 (29.5)	236 (27.8)	582 (29.8)
3 times per week or more	742 (43.0)	328 (34.9)	1233 (41.5)	895 (47.6)	352 (41.5)	921 (47.2)
Hard physical activity (T4)						
None	1258 (72.9)	748 (80.6)	2066 (70.2)	999 (53.2)	550 (65.4)	1032 (53.0)
< 1 time per week	212 (12.3)	83 (8.9)	416 (14.1)	331 (17.6)	101 (12.0)	346 (17.8)
1–2 times per week	179 (10.4)	67 (7.2)	332 (11.3)	341 (18.1)	119 (14.1)	353 (18.1)
3 times per week or more	76 (4.4)	30 (3.2)	131 (4.4)	208 (11.1)	71 (8.4)	215 (11.0)
Self-reported health (T4)						
Poor	37 (2.1)	65 (6.9)	65 (2.2)	46 (2.4)	45 (5.3)	50 (2.5)
Not so good	815 (47.2)	484 (51.5)	1333 (44.9)	688 (36.6)	395 (46.3)	722 (36.8)
Good	791 (45.9)	342 (36.4)	1396 (47.0)	1027 (54.7)	378 (44.3)	1068 (54.5)
Very good	82 (4.8)	48 (5.1)	175 (5.9)	118 (6.3)	35 (4.1)	121 (6.2)
BMD group (T4)						
Normal BMD	531 (30.8)	307 (32.6)	1230 (41.4)	1101 (58.6)	395 (46.2)	1148 (58.5)
Osteopenia	624 (36.2)	284 (30.2)	986 (33.2)	571 (30.4)	282 (33.0)	593 (30.2)
Osteoporosis	570 (33.0)	350 (37.2)	757 (25.5)	207 (11.0)	178 (20.8)	222 (11.3)
Deaths	756 (43.8)	621 (66.0)	1094 (36.8)	1001 (53.3)	696 (81.4)	1058 (53.9)

T4 = Tromsø 4. T5 = Tromsø 5. BMI = Bone mineral density of distal forearm. AOD = Anti-osteoporotic drug. HRT = Hormone replacement therapy.

population, those who only attended Tromsø 4 and the complete population who attended both Tromsø 4 and Tromsø 5, (including those excluded from our study sample) is presented in Table 1. Table 2 shows mean BMD at baseline and follow-up, as well as BMD changes and number of deaths in 5-year age groups in women and men. Out of 3604 participants, 1363 had unchanged or increased BMD values at the follow-up measurement based on the LSC definition of 2% (548 women and 815 men). A higher proportion of these women reported use of HRT (15.3%) or AODs (5.7%) at the second measurement than those with a decrease in BMD (5.5% and 3.1%). Only 5 men (0.3%) in total reported currently using AODs in 2001, of whom two men had unchanged/increased BMD. BMD was strongly inversely correlated with age (Table 2). Mean BMD loss over seven years was similar across age groups in women, while it increased with advancing age in men. Percent BMD loss increased with age in both women and men (Table 2).

Those with low BMD at baseline were oldest and had the highest mortality rates (Table 3). Overall, mortality rates were highest in the groups with the largest bone loss in both women and men, but mortality rates in women varied less between groups of BMD change than in men. The absolute differences in mortality between the upper and lower groups of BMD change were similar in both baseline BMD groups (3–4 per 1000 person years) but larger within the group with normal

Table 2
Mean BMD at baseline (Tromsø 4, 1994/95) and follow-up (Tromsø 5, 2001/02), changes in BMD between baseline and follow-up and number of deaths in 5-year age groups for women and men separately.

Age baseline	N	Mean BMD baseline g/cm^2 (SD)	Mean BMD follow-up g/cm^2 (SD)	Mean BMD change g/cm^2 (%)	Deaths N (%)
Women: 62.4 (6.2)	1725	0.392 (0.065)	0.373 (0.067)	−0.019 (−4.8)	756 (43.8)
50–54	195	0.438 (0.053)	0.418 (0.059)	−0.020 (−4.5)	32 (16.4)
55–59	411	0.418 (0.054)	0.399 (0.057)	−0.018 (−4.4)	88 (21.4)
60–64	443	0.396 (0.059)	0.378 (0.062)	−0.018 (−4.6)	162 (36.6)
65–69	412	0.368 (0.061)	0.347 (0.063)	−0.021 (−5.6)	252 (61.2)
70–74	264	0.350 (0.065)	0.332 (0.063)	−0.018 (−4.9)	222 (84.1)
Men: 61.7 (6.0)	1879	0.541 (0.063)	0.524 (0.068)	−0.017 (−3.2)	1001 (53.3)
50–54	175	0.566 (0.048)	0.556 (0.050)	−0.010 (−1.8)	31 (17.7)
55–59	582	0.556 (0.054)	0.543 (0.057)	−0.012 (−2.3)	180 (30.9)
60–64	500	0.543 (0.060)	0.526 (0.066)	−0.017 (−3.3)	270 (54.0)
65–69	372	0.524 (0.068)	0.503 (0.072)	−0.021 (−4.1)	287 (77.2)
70–74	250	0.509 (0.070)	0.485 (0.075)	−0.024 (−4.9)	233 (93.2)

baseline BMD in men compared to those with low baseline BMD (23 vs 13). However, the mortality rate ratio in group 3 to group 1 of BMD change was clearly higher in the group with normal BMD at baseline in both genders, although most pronounced in men, (1.25 in women and 1.85 in men) compared to the group with low BMD at baseline (1.10 in women and 1.28 in men). Both women and men with a large BMD loss (group 3) in the distal forearm between Tromsø 4 and Tromsø 5 had the lowest BMD total hip values at Tromsø 5. The men with unchanged or increased BMD in the forearm (group 1) had the highest total hip BMD in both baseline BMD groups while in women, those with a low baseline BMD who experienced a BMD loss in the distal forearm between −2 and −4% (group 2) had the highest hip BMD.

HRs with 95% CI in successively adjusted Cox regression models in women and men with normal and low BMD at baseline are shown in Table 4. No associations were found between BMD loss and mortality in the fully adjusted models for women, regardless of baseline BMD group. Among men with normal BMD at baseline, those with a large bone loss had significantly higher mortality compared with those with unchanged or increased BMD (group 3 vs group 1: HR = 1.50, 95% CI 1.21, 1.87). Differences in mortality between BMD change groups were not statistically significant among men with low BMD levels at baseline (Table 4).

Mortality HRs with 95% confidence intervals across the range of continuous percent BMD change, based on cubic splines, are shown in Fig. 2. In women, no statistically significant associations were observed between BMD change and mortality in either category of baseline BMD. In men, CIs exceeded HR = 1.00 in the group with normal BMD at baseline, indicating a statistically significant increase in mortality with increasing bone loss for this group.

Table 3
Mean age, percentage distal forearm BMD change over seven years, number of deaths and mortality rates in men and women and within groups of BMD change based on least significant change (LSC) = 2%. 1: BMD gain or BMD loss of < 1× LSC, 2: BMD loss between 1× and 2× LSC, 3: BMD loss of > 2× LSC. Crude mortality rates (MR) are given as number of deaths per 1000 person years (py). BMD values for total hip by DEXA in Tromsø 5 presented as g/cm^2 is given for comparison.

Women	N	Mean age (SD)	Mean BMD change % (SD)	Deaths N	MR per 1000 py	Mean BMD total hip Tromsø 5 (SD)
All	**1725**	**62.4 (6.2)**	**−4.8 (6.7)**	**756**	**31.8**	**0.875 (0.135)**
1 Positive or unchanged	548	61.9 (6.3)	1.9 (5.0)	224	29.4	0.902 (0.144)
2 1× LSC to 2× LSC BMD loss	261	62.2 (6.2)	−3.0 (0.6)	99	26.8	0.918 (0.132)
3 > 2× LSC BMD loss	916	62.8 (6.1)	−9.4 (4.5)	433	34.9	0.846 (0.123)
Normal BMD	**531**	**59.2 (5.7)**	**−4.2 (4.8)**	**151**	**19.0**	**0.968 (0.128)**
1 Positive or unchanged	187	58.9 (5.7)	0.4 (2.0)	50	17.6	1.003 (0.129)
2 1× LSC to 2× LSC BMD loss	106	59.6 (6.0)	−3.0 (0.6)	24	15.0	0.988 (0.125)
3 > 2× LSC BMD loss	238	59.2 (5.7)	−8.3 (3.8)	77	22.0	0.931 (0.120)
Low BMD	**1194**	**63.8 (5.9)**	**−5.1 (7.3)**	**605**	**38.3**	**0.831 (0.115)**
1 Positive or unchanged	361	63.4 (6.1)	2.7 (5.8)	174	36.3	0.847 (0.120)
2 1× LSC to 2× LSC BMD loss	155	64.0 (5.7)	−3.0 (0.6)	75	35.8	0.868 (0.114)
3 > 2× LSC BMD loss	678	64.0 (5.8)	−9.7 (4.6)	356	39.9	0.815 (0.109)
Men	**N**	**Mean age (SD)**	**Mean BMD change % (SD)**	**Deaths N**	**MR per 1000 py**	**Mean BMD total hip Tromsø 5 (SD)**
All	**1879**	**61.7 (6.0)**	**−3.2 (3.9)**	**1001**	**42.3**	**1.010 (0.140)**
1 Positive or unchanged	815	60.2 (5.8)	−0.2 (1.8)	362	33.1	1.050 (0.134)
2 1× LSC to 2× LSC BMD loss	431	61.8 (5.9)	−2.9 (0.6)	230	41.9	1.018 (0.127)
3 > 2× LSC BMD loss	633	63.7 (5.9)	−7.3 (3.4)	409	56.5	0.950 (0.135)
Normal BMD	**1101**	**60.4 (5.8)**	**−2.5 (3.2)**	**496**	**34.0**	**1.058 (0.127)**
1 Positive or unchanged	561	59.3 (5.5)	−0.3 (1.4)	213	27.2	1.082 (0.125)
2 1× LSC to 2× LSC BMD loss	280	60.9 (6.0)	−2.8 (0.6)	128	34.8	1.055 (0.115)
3 > 2× LSC BMD loss	260	62.2 (5.6)	−6.9 (3.2)	155	50.4	1.012 (0.129)
Low BMD	**778**	**63.6 (5.9)**	**−4.2 (4.5)**	**505**	**55.6**	**0.936 (0.126)**
1 Positive or unchanged	254	62.1 (5.9)	0.1 (2.5)	149	47.8	0.976 (0.126)
2 1× LSC to 2× LSC BMD loss	151	63.4 (5.4)	−3.0 (0.6)	102	56.5	0.949 (0.120)
3 > 2× LSC BMD loss	373	64.7 (5.9)	−7.6 (3.6)	254	61.1	0.903 (0.119)

LSC = Least significant change, defined as 2% negative change between measurements. MR = Mortality rate. Py = Person years.

Table 4
Hazard ratios (HR) with 95% confidence intervals (CI) of mortality for 7-year BMD change in persons with normal and low BMD during 17 years mortality follow-up. Models 1–3 progressively adjusted for age and lifestyle- and health-related covariates. Women and men analyzed separately with BMD change group 1 (positive or no change) as reference.*

Women model adjusted for	BMD change	All women N = 1725			Normal *N* = 531			Low *N* = 1194		
	Group 1–3	HR	95% CI		HR	95% CI		HR	95% CI	
1: Attained age, baseline BMD	1	1.00	–	–	1.00	–	–	1.00	–	–
	2	0.89	0.70	1.12	0.75	0.46	1.23	0.95	0.72	1.25
	3	1.12	0.95	1.31	1.34	0.95	1.95	1.08	0.90	1.29
2: 1 + Use of AODs, BMI change, HRT, years since menopause	1	1.00	–	–	1.00	–	–	1.00	–	–
	2	0.94	0.74	1.19	0.81	0.49	1.34	1.00	0.76	1.32
	3	1.10	0.93	1.29	1.34	0.93	1.95	1.05	0.88	1.27
3: 2 + Physical activity level, BMI, smoking status, level of education, self-reported health, chronic diseases	1	1.00	–	–	1.00	–	–	1.00	–	–
	2	0.96	0.75	1.23	0.84	0.50	1.42	1.00	0.76	1.33
	3	1.10	0.93	1.31	1.41	0.94	2.12	1.04	0.86	1.25

Men model adjusted for	BMD change	All men N = 1879			Normal *N* = 1101			Low *N* = 778		
	Group 1–3	HR	95% CI		HR	95% CI		HR	95% CI	
1: Attained age, baseline BMD		1.00	–	–	1.00	–	–	1.00	–	–
	2	1.08	0.92	1.28	1.14	0.91	1.41	0.98	0.76	1.27
	3	*1.23	1.07	1.28	*1.57	1.28	1.94	0.97	0.79	1.20
2: 1 + Use of AODs, BMI change	1	1.00	–	–	1.00	–	–	1.00	–	–
	2	1.07	0.91	1.27	1.14	0.92	1.42	0.96	0.74	1.24
	3	*1.20	1.03	1.39	*1.53	1.24	1.88	0.95	0.78	1.17
3: 2 + Physical activity level, BMI, smoking status, level of education, self-reported health, chronic diseases	1	1.00	–	–	1.00	–	–	1.00	–	–
	2	1.06	0.90	1.25	1.13	0.90	1.42	0.97	0.74	1.26
	3	1.13	0.97	1.31	*1.50	1.21	1.87	0.91	0.74	1.13

Abbreviations: AOD = anti-osteoporosis drug, BMD = bone mineral density, BMI = body mass index, HRT = hormone replacement therapy.
* Statistically significant values ($p < 0.05$).

3.1. Potential non-response bias

The group of participants in Tromsø 4 who *did not* attend BMD-testing in Tromsø 5 (and were therefore not eligible for this study) were older, had a higher prevalence of osteoporosis, a higher percentage of chronic diseases and poorer self-rated health compared to those who participated in both Tromsø 4 and Tromsø 5 and the subgroup of these which was our study sample (Table 1). Furthermore, a higher percentage of non-participants died across all baseline BMD ranges, also when excluding those who died before Tromsø 5.

4. Discussion

In this study, we examined the association between BMD loss in the distal forearm and mortality in the general population of Tromsø, Norway. We found no association between BMD loss and mortality in women, regardless of baseline BMD. In men with normal BMD at baseline, a large reduction in BMD of > 4% over seven years was associated with significantly increased mortality compared to men with an unchanged or increased BMD. No associations between BMD loss and mortality were found in those with low BMD at baseline.

This is somewhat in contrast with the results of previous studies from the US and Australia that found a statistically significant association between bone loss and mortality in women as well as in men [33,34]. Also, in the US Study of Osteoporotic Fractures, the association between bone loss and mortality did not depend on baseline BMD [33] as we found in our study. Results from a Korean study found similar results to ours, namely that the association between bone loss and mortality was most pronounced in men [35].

Although we observed the highest mortality rates among those with the largest bone loss, differences between groups of BMD change were not statistically significant in those with low baseline BMD and there was no linear relationship between rate of bone loss and mortality. There are some methodological differences between our study and the abovementioned studies to be discussed. While the intervals between baseline- and follow-up measurements were comparable (~5–6 years vs

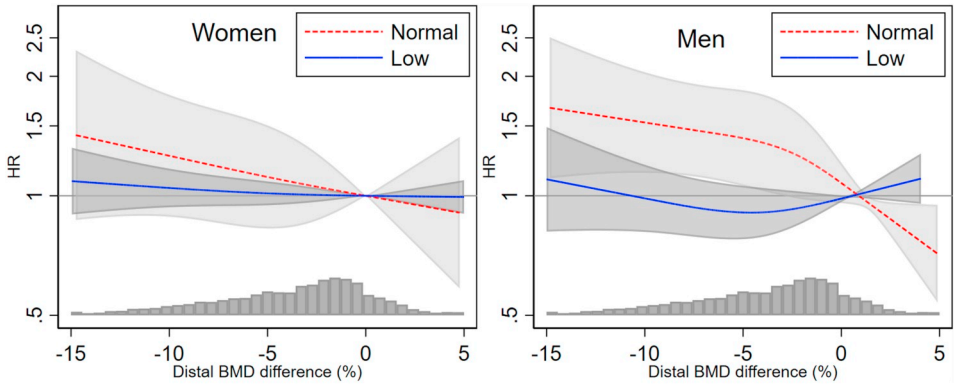

Fig. 2. Mortality hazard ratios (HR) with 95% confidence intervals across the range of percent seven-year change in distal forearm BMD in women and men with normal BMD (short-dashed line) and low BMD (solid line) at baseline. No BMD change is the reference level. Histogram illustrates the population distribution.

7 years in our study), their study populations were older than ours with mean ages of > 70 years compared to 62 years in our study. However, we only found BMD loss to be associated with mortality among participants with normal BMD at baseline and that group had the lowest mean age. The previous studies also used measurements from weight-bearing skeletal sites such as the spine, hip and calcaneus while we used measurements from the non-weight-bearing distal forearm in our analyses. The rates of bone loss are therefore not comparable and the results indicate a difference in how rate of bone loss relates to mortality in weight-bearing and non-weight-bearing bones.

The reason why we only found an association between BMD loss and mortality in those with normal baseline BMD could be the relatively low background mortality in this group compared to those with low BMD. Overall, people with low BMD have a higher mortality [13–15,22] and that could be masking any additional increase in mortality from additional BMD loss. In women, the absolute differences in mortality between the upper and lower groups of BMD change were similar in those with normal and low baseline BMD while the relative differences in mortality across groups of BMD change were higher in the group with normal BMD at baseline in both genders and especially in men (not adjusted for age). Although the women with normal baseline BMD and the largest BMD loss had the highest HR (1.41 in the fully adjusted model) that were comparable to that of the men (HR = 1.50), the association between BMD loss and mortality did not reach statistical significance due to wide CIs, indicating a very heterogeneous group. The corresponding male group had twice the sample size of the women which could explain why the association between BMD loss and mortality reached statistical significance only in men with normal BMD at baseline.

A possible explanation for why we only found an association between BMD loss and mortality in those with normal baseline BMD is that it is not actually the change in BMD which explains mortality, but rather the latest BMD measurement. Based on our results, the rate of bone loss appears less predictive of mortality when BMD is already in the osteopenic or osteoporotic range. A large reduction in BMD from a point of “normal” values would cause a faster approach to an osteopenic and osteoporotic BMD range and an associated increase in mortality. However, it is also possible that our population of participants with low BMD from Tromsø 4, who chose to return for testing in Tromsø 5, is a particularly healthy or resilient selection, as Emaus et al. have pointed out earlier [25]. Participants who only attended Tromsø 4 reported more chronic diseases, poorer health and had a higher death rate than those who returned for Tromsø 5, suggesting that our population represent a somewhat healthier selection that might not be representative for the average person with osteopenia or osteoporosis.

In women with normal baseline BMD, those with a moderate BMD loss of 2–4% (group 2) had the lowest mortality. Women experience a larger reduction in BMD during- and up to 10 years following menopause due to the natural change in estrogen production [23,41,42]. The fact that a higher rate of bone loss is part of the normal ageing process in women, could explain why the group of women who experienced a moderate reduction in BMD had the lowest mortality risk and not the group who experienced no change or an increase in BMD as we found in men. Mean BMD loss in women over seven years was −4.8% and varied little across age groups, meaning that group 2 had a smaller BMD loss than the average woman in our population, unlike the men who had a mean BMD loss of −3. 2%. The men's average BMD loss was also much smaller in the younger men than in the older. The women in our study who had unchanged or increased BMD used AODs and HRT more frequently than those with a BMD reduction, also in the group with normal baseline BMD. It indicates that these women might be of poorer health since treatment had been initiated. AODs and HRT is also not without side effects [43]. The fully adjusted models included use of AODs and HRT as current, previous and never, and cessation between Tromsø 4 and Tromsø 5, but this information might not be sufficient to account for the entire effect they have on BMD change and mortality. These variables were also self-reported and can be subject to recall bias, particularly the time of start or cessation [44].

Individuals who are eligible for BMD screening are often identified due to a previous fragility fracture or the presence of established risk factors [45]. Most people with normal BMD are not in the target group for BMD screening, hence repeated measurements to monitor BMD change is not likely achievable, nor advisable for this group. According to our results, the overall impression is that BMD change in the distal forearm does not have a strong predictive value in assessing mortality.

This study included men and postmenopausal women and is therefore not generalizable to changes in BMD that occur before, during or directly after menopause. We excluded women up to 5 years post menopause to remove the main effect of menopause on bone loss and adjusted the statistical models for years since menopause. A study on BMD changes at different measurement sites found that accelerated bone loss at the distal forearm persisted at the same rate throughout life after menopause while BMD at the hip and lumbar spine show more variation [24]. Thus, we do not suspect menopause to represent a substantial source of bias in our results.

Strengths of this study include the population-based design with a large sample size, standardized objective measures of BMD using the same devices at both measurements, information on a large number of potential confounders including measured weight and height and self-reported lifestyle and use of medication, and a long follow-up period of 17 years with updated time of death until October 2018. The population in the present study consists of people living in both urban and rural areas and the study had a high attendance rate (78% in Tromsø 4 and 86% in Tromsø 5).

The study also has some limitations. BMD was measured using a technique (SXA) that is no longer the standard method for measuring BMD. However, comparing the precision of BMD measurements of the forearm using SXA, and the now more commonly used DXA (dual x-ray absorptiometry) in a population based health survey in northern Trøndelag in Norway (HUNT), precision was found to be better for SXA measurements than DXA [46]. It should therefore be considered a valid and solid measurement in this type of research were the aim was to assess BMD changes in the distal forearm specifically.

BMD is most commonly measured in the lumbar spine and proximal femur, and sometimes in distal forearm [47]. It has been suggested that natural bone loss might occur earlier in distal, non-weight bearing areas like the distal forearm, than in central areas like the proximal femur or spine [48] and the rate of bone loss appears to be site-specific [24]. Our results therefore represent BMD changes in the distal forearm only, not BMD changes in general since bone loss can occur later in the hip or spine region and changes here could have a stronger or weaker association with mortality due to the fact that these are weight bearing sites.

5. Conclusion

In this population-based study, we found that BMD loss in the distal forearm was associated with increased mortality in men with normal BMD at baseline, but not in women. While the highest mortality rates were found in those with the largest BMD loss, there was no clear association between BMD loss and mortality in those with low BMD in the form of osteopenia or osteoporosis at baseline. Our findings contribute to a further understanding of distribution of bone loss in the distal forearm and its potential association with mortality.

CRediT authorship contribution statement

Annette V. Hauger:Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Project administration.**Astrid Bergland**:Writing - review & editing, Funding acquisition.**Kristin Holvik**:Writing - review & editing.**Nina Emaus**:Conceptualization, Data curation, Writing - review & editing.**Bjørn Heine Strand**:Methodology, Formal analysis, Data

curation, Writing - review & editing, Visualization, Supervision.

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