

Osteoporosis and osteopenia in the distal forearm predict all-cause mortality independent of grip strength: 22 year follow-up in the population-based Tromsø Study

1 **Word count Mini-abstract: 49**

2 Low bone mineral density (BMD) gives an increased risk of fractures, which can lead to premature death. Can
3 BMD of the wrist predict mortality? BMD consistent with osteopenia and osteoporosis gave a significantly
4 increased risk of death for both men and women in a general population in Tromsø, Norway.

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6 **Word count abstract: 249**

7 **Purpose**

8 To investigate if bone mineral density (BMD) levels of the distal forearm, consistent with osteopenia and
9 osteoporosis, can predict mortality and if grip strength is an effect modifier.

10 **Methods**

11 The study population constituted 6 565 participants aged 50-79 years at baseline in the Tromsø study wave 4
12 conducted in 1994-5. Forearm BMD measured by SXA was categorized as “normal”, “osteopenia” or
13 “osteoporosis” following WHO’s definition. Cox regression with all-cause mortality as the outcome over 22
14 years of follow-up was performed for men and women separately, adjusting for health-related factors, as well as
15 BMD by grip strength interaction. A secondary analysis with 15 years follow-up also adjusted for hip fractures
16 and osteoporotic fractures.

17 **Results**

18 During follow-up, 3 176 of participants died (47%). Those categorized as osteoporotic had higher mortality
19 hazard ratio (HR) compared to those with normal BMD; Men HR=1.37 (95% confidence interval (CI) 1.19,
20 1.58) and women HR=1.32 (1.14, 1.53), adjusted for age, body mass index, physical activity, smoking habits,
21 education, health status, chronic diseases and grip strength. Corresponding HRs for osteopenia were; Men
22 HR=1.13 (1.00, 1.27) and women HR=1.17 (1.01, 1.35). Further adjustments for fractures did only marginally
23 attenuate the results, and HRs were still significant. There was no grip strength by BMD interaction.

24 **Conclusion**

25 Men and women with low distal forearm BMD-values, consistent with osteoporosis or osteopenia, had an
26 increased mortality compared to normal BMD participants. High grip strength did not modify this association,
27 and the association remained after adjustment for a range of health-related factors.

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Keywords:

Osteoporosis, osteopenia, bone mineral density, mortality, grip strength, hip fracture

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Introduction

Osteoporosis constitutes an important public health concern with its high incidence in Western populations, and progressive prevalence in Asia [1, 2]. Osteoporosis is known to vary by gender and age [3]. It is often defined as a disease of women because the prevalence and fracture rates are much higher among females, but once an osteoporotic hip fracture has occurred, excess mortality has been found to be higher in men [3, 4]. The incidence of osteoporosis is increasing with age, occurring mainly above the age of 50 years [5].

Osteopenia is the precursor of osteoporosis. The World Health Organization (WHO) Study Group on Osteoporosis has defined osteopenia and osteoporosis as bone mineral density (BMD) of more than 1 and 2.5 standard deviations (SDs), respectively, below the mean BMD of the young, white, female adult reference population [6]. Based on data from the United States, it has been estimated that 30 percent or more of all postmenopausal, white women have osteoporosis [7]. The lifetime risk of any fracture of the hip, spine, proximal- or distal forearm, all considered typical osteoporotic fractures, was estimated to be 46 percent in women and 22 percent in men from age 50 years onward in a Swedish population [8]. As life expectancy increases, the population burden of osteoporosis and related fragility fractures will increase [1, 9].

A systematic review and meta-analysis from 2013 [10] found an inverse relationship between BMD and all-cause mortality. The same result was found for women with type 2 diabetes [11]. An important pathway linking low BMD to mortality is via fractures, and hip fractures in particular. Furthermore, the association between BMD and mortality could be confounded by physical fitness, physical activity, body mass, smoking habits, level of education [4, 12-15] and by comorbidity such as stroke, angina, myocardial infarction, diabetes and asthma [16-18].

57 Grip strength measurements have been recommended in order to identify old people with sarcopenia [19] (low
58 muscle mass and low muscle function). Low grip strength has also been found to predict disability, impaired
59 quality of life, falls and mortality [20-22], while high grip strength may indicate resilience to aging [23].

60
61 Osteoporotic fractures of the proximal femur are particularly associated with excess mortality and studies have
62 consistently found that this association increases with age [4, 24]. For distal forearm fractures however, excess
63 mortality is found to be lower or non-significant [24], but a prior wrist fracture can increase the risk of any
64 osteoporotic fracture later in life [25, 26]. Recent studies have found that osteoporosis is more easily detected in
65 the peripheral regions (wrist) than in the central regions (spine and hip) [27] and wrist BMD has better accuracy
66 than lumbar BMD in diagnosing osteoporosis in postmenopausal women [28]. Measuring BMD in the distal
67 forearm might reveal a BMD deficiency at an earlier stage and give better prerequisites for treatment and
68 fracture prevention.

69
70 The main aim of this paper was to assess the predictive value of established definitions for osteopenia and
71 osteoporosis in evaluating risk of mortality. Identifying individuals at high risk is crucial in order to provide
72 interventions on amendable risk factors for osteopenia or osteoporosis. There have been previous studies on how
73 mortality is affected by different treatments of osteoporosis, fracture types [4, 24, 29] and BMD values in
74 various populations [10, 11, 30]. However, the association between osteoporosis and osteopenia of the distal
75 forearm and mortality, and the possible mediating effect of grip strength has to the very best of our knowledge
76 not been examined in a population-based study before. Thus an additional aim of this paper was to investigate if
77 a strong grip modified the potential association between low BMD and mortality and whether the association
78 was confounded by BMI, smoking, physical activity level, self-reported health status, level of education or
79 chronic diseases such as angina, stroke, myocardial infarction, diabetes and asthma. We hypothesized that those
80 with distal forearm BMD categorized as osteoporotic or osteopenic had a higher mortality risk compared to those
81 with normal BMD-values, but that this increased risk could be partly counteracted by a high grip strength.

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83 **Method**

84 **Study population**

85 The Tromsø Study was initiated in 1974 and is a longitudinal, population based, multi-purpose study focusing on
86 lifestyle-related diseases [31]. There have been seven study waves, and our study population is comprised of

87 participants from the fourth wave, conducted in 1994-95. This wave included a bone densitometry measurement
88 as a part of additional testing that was offered to all participants aged 55-74 years, all women aged 50-55 years
89 and a random selection of 10-15 percent of participants aged 24-55 years and 74-85 years. In the current
90 analyses, only participants aged 50-79 years were included. The attendance rate was 76 percent among men and
91 79 percent among women in this age group. Our study population consisted of 6 565 participants, 3 818 women
92 with a mean age of 60.7 years (SD=7.4) and 2 747 men with a mean age of 62.6 years (SD=6.4).

93

94 **Assessment of bone mineral density (BMD)**

95 Bone densitometry using SXA was performed on the non-dominant forearm at distal and ultra-distal sites with
96 two single x-ray absorptiometry devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California). Further
97 specification of the testing procedure can be found elsewhere [32]. No significant difference has been detected
98 regarding precision of the distal and ultra-distal measurement [33]. The distal measurement was chosen for our
99 analyses, including both radius and ulna. Osteopenia and osteoporosis were defined respectively as 1 and 2.5
100 SDs below the mean of young, healthy men and women (see below).

101

102 **Reference values**

103 Gender specific internal BMD reference values were created for osteopenia and osteoporosis, based on BMD
104 values corresponding to 1 and 2.5 standard deviations below the mean BMD of healthy men and women aged
105 24-39 years in the Tromsø 4 densitometry data. Besides gender and age range, the reference populations were
106 defined by a dichotomous variable, “healthy” (Yes/no), which was based on the following disease-related
107 questions: Do you have, or have you had a myocardial infarction? (Yes/no); Do you have, or have you had
108 angina pectoris? (Yes/no); Do you have, or have you had a cerebral stroke/brain hemorrhage? (Yes/no); Do you
109 have, or have you had asthma? (Yes/no); Do you have, or have you had diabetes? (Yes/no); What is your current
110 state of health? (Poor/not so good/good/very good). Those who reported “good” or “very good” self-rated health
111 combined with “no” on all the disease related questions were defined as “healthy”, and this group was used when
112 calculating reference values for categorization into “normal BMD”, “osteopenia” and “osteoporosis”. Only
113 including the “healthy” participants resulted in 252 women with a mean BMD-value of 0.471 g/cm² (SD=0.043)
114 and 147 men with a mean BMD-value of 0.575 g/cm² (SD=0.045). Thus, 2.5 SD below mean BMD
115 (osteoporosis) corresponded to 0.364 g/cm² in women and 0.464 g/cm² in men, and 1.0 SD below mean
116 (osteopenia) corresponded to 0.428 g/cm² in women and 0.531 g/cm² in men.

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118 **Ascertainment of deaths**

119 The outcome in this study was all-cause mortality. Data on each participant was linked, by the means of the
120 unique personal identification number, to the Norwegian Cause of Death Registry for assessment of death, and to
121 the National Registry for assessment of emigration. Participants were followed from baseline survey in 1994-95
122 until emigration, death or November 5th, 2016, whichever occurred first.

123

124 **Covariates**

125 Covariates known to be associated with lower BMD and mortality were selected a priori for inclusion as possible
126 confounders in addition to age and gender. Height and weight was measured by trained personnel in The Tromsø
127 Study and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared
128 (kg/m^2) and grouped as: low = $\text{BMI} \leq 20.00 \text{ kg/m}^2$, normal = 20.01 kg/m^2 to 25.00 , overweight = 25.01 to 30.00
129 kg/m^2 and obese $> 30.00 \text{ kg/m}^2$. Smoking was self-reported, and categorized in three groups as current, previous,
130 or never-smoker. Education level was based on years of completed education grouped into five levels ranging
131 from “7-10 years primary/secondary school” to “college/university 4 or more years”. Level of physical activity
132 was self-reported by counting hours of light physical activity (not sweating or out of breath) and hard physical
133 activity (sweating and/or out of breath) during a typical week in the previous year. The number of hours per
134 week for each variable was categorized in four groups: none, less than one, one to two, three or more. Chronic
135 diseases were self-reported in Tromsø 4 with alternatives “yes” or “no” following questions about stroke,
136 myocardial infarction, angina, diabetes or asthma in their medical history along with questions regarding self-
137 perceived health categorized as: very good, good, not so good, and poor. Grip strength of the non-dominant hand
138 was measured in bar using a Martin vigorimeter. Each participant was allowed two attempts, and the highest
139 score was recorded and used in analyses. Grip strength was grouped into gender specific quartiles. Records for
140 fractures were available for all participants until February 22th 2010. Fractures of the femur neck and –
141 trochanter were defined as “hip fractures”. These in addition to distal fractures of ulna and radius were defined as
142 “osteoporotic fractures”. Vertebral fractures were not reported in the material.

143

144 **Statistics**

145 Separate analyses were conducted for men and women. A Cox proportional hazards survival model was used to
146 assess the associations between T-score groups based on distal forearm BMD and mortality. We successively

147 adjusted for health- and lifestyle-related variables in three models; model 1: (attained) age, model 2: model 1 +
148 BMI, level of physical activity, smoking habits and category of completed education, model 3: model 2 + self-
149 reported health status and self-reports of chronic diseases including asthma, diabetes, angina pectoris, stroke and
150 myocardial infarction. In addition, grip strength by BMD interaction was tested in a fourth model. Fractures were
151 included in a secondary analysis since fracture data was only available until February 22th 2010, giving a shorter
152 follow-up period. Model 1 is minimally adjusted for age (attained), without fracture variables. Model 2 and 4
153 minimally adjusted for age (attained) and hip fractures or osteoporotic fractures. Model 3 and 5 fully adjusted in
154 addition to hip fractures or osteoporotic fractures. The fracture variables were modelled as time-dependent
155 covariates in order to avoid immortal time-bias. The proportional hazard (PH) assumption was inspected visually
156 and by formal tests based on scaled Schoenfeld residuals. Statistical significance was determined by an alpha
157 level of 0.05. The statistical analysis was carried out with Stata/SE 15.

158

159 **Results**

160 During follow up in the main analysis, 3 176 (46.8%) of the 6 790 participants died, 1 538 women and 1 638
161 men. Fifty-four participants were censored due to emigration. The mean BMD-value of the total study
162 population 50 to 79 years was 0.458 g/cm² (SD=0.094), 0.403 g/cm² (SD 0.069) in women and 0.533 g/cm² (SD
163 0.067) in men (Table 1). According to the definition, 1 512 (38%) female participants had normal BMD, 1 329
164 (34%) had osteopenia and 1 104 (28%) had osteoporosis. Corresponding numbers in men were 1 575 (55%), 870
165 (31%) and 400 (14%) (Table 1 and 2).

166

167 In our secondary analysis including fracture data, 1 242 women and 434 men experienced a fracture during 15
168 years follow-up from baseline to February 22th 2010. Among women, 265 experienced a hip fracture and 479
169 experienced a distal forearm fracture. Corresponding numbers among men were 132 and 194.

170

171 Participants categorized as having osteoporosis were significantly older, had a lower BMI, lower grip strength,
172 performed less hard physical activity, had inferior self-reported health and a higher percentage had experienced a
173 stroke compared to those with normal BMD-values (Table 2). Among women, the osteoporosis group also
174 performed less light physical activity, they were lower educated and had a higher lifetime prevalence of angina
175 pectoris or a myocardial infarction than participants with normal BMD. Significantly more men were smokers in
176 the osteoporosis group than in the normal BMD group.

177

178 Cox regression revealed a significantly higher mortality in both women and men with osteoporosis and
179 osteopenia compared to the normal BMD groups (Table 3). In the fully adjusted model, including adjustments
180 for age, BMI, level of education, physical activity, smoking, self-reported health, chronic diseases and grip
181 strength, the hazard ratio (HR) was 1.32 (95 % confidence interval (CI) 1.14 to 1.53) for women and 1.37 (95%
182 CI 1.19 to 1.58) for men with osteoporosis compared to those with normal BMD. Corresponding HRs for
183 mortality in participants with osteopenia were 1.17 (95% CI 1.01 to 1.35) in women and 1.13 (95% CI 1.00 to
184 1.27) in men. There was no grip strength by BMD interaction in women ($p=0.84$) or in men ($p=0.55$), see Figure
185 1 and 2 illustrating the effect of “low” (lowest quartile) and “high” (three highest quartiles) grip strength on the
186 association between BMD as a continuous variable and HR for mortality. Tests of the proportional hazards
187 assumption using scaled Schoenfeld residuals indicated some violation of proportionality of hazard. For
188 osteoporosis the HRs were comparable in the three time periods 1994-2000, 2001-2006, 2007-2016 in both
189 genders. For osteopenia, however, the HRs were slightly lower in the first time periods in men, while in women
190 they were comparable. Despite this slight violation of PH, results are presented as an average for the whole
191 period.

192 In the secondary analysis, adjusting for hip fractures or osteoporotic fractures did not explain the increased
193 mortality among participants with osteoporosis. The association between osteopenia and mortality was still
194 significant in women after adjusting for fractures, but not in men (Table 4).

195

196 **Discussion**

197 To the best of our knowledge, this is the first population-based study to examine the association between
198 osteoporosis and osteopenia of the distal forearm and mortality, and the possible mediating effect of grip
199 strength. We found a statistically significant association between osteopenic and osteoporotic BMD-levels of the
200 distal forearm and increased mortality rate in both women and men.

201

202 The strengths of the present study include the population-based design, standardized objective measures of bone
203 mineral density and grip strength, a large sample size and a long follow-up of 22 years with updated time of
204 death from as recently as November 2016. The population consists of people living in both rural and urban areas
205 and the study had a high attendance rate (about 78%).

206

207 However, the study is not without limitations. Self-reported variables challenge the internal validity of any study
208 [34, 35]. State of health, presence of chronic diseases, level of physical activity, education and smoking habits
209 are self-reported variables and might be subject to over- or under-estimation due to recall bias [36] or socially
210 desirable responding (SDR) [37]. This can in turn lead to an under-estimation of the potential association
211 between variables. Though this could be the case with some of the variables mentioned above, the outcome in
212 the current analysis was the registry-based hard endpoint of deaths while our main exposure variables (BMD and
213 grip strength) were measured objectively.

214

215 We controlled for variables that were measured at baseline in 1994/5. During the follow-up of 22 years, it is
216 likely that some variables changed, especially the presence of chronic diseases since it is well known that
217 comorbidity increases in older age. The participants may also have experienced significant changes in BMD
218 during follow-up that could be associated with excess mortality. This could be subject for further research.

219

220 We created our own reference values in order to define osteopenia and osteoporosis for our population, but the
221 association between BMD as a continuous variable and mortality was also analyzed, allowing the reader to study
222 the whole spectrum of BMD independent of our categorization into osteoporosis, osteopenia and normal BMD.
223 Modern methods for BMD-testing has changed over the past 22 years and we were unsuccessful in retrieving
224 external reference-values for SXA of the distal forearm. There are both strengths and limitations in creating our
225 own reference values. We have no guarantee that our reference groups are similar to those used in other studies
226 and the variation within the reference group warrants the size of 1 SD which in turn make out the cut-off values.
227 However, this resulted in 28 percent of the women being categorized as osteoporotic and this is comparable to
228 other findings in Caucasian women [7], considering that the oldest old were not included in this study. A
229 strength of creating a reference group from the same study is that they share the same geographical and cultural
230 affiliation, we know how the BMD has been measured and tests are performed by the same professionals,
231 following the same protocols as in the main analyses.

232 Dementia and other cognitive impairments increase the risk of mortality. 6.1 % of all deaths in Norway in 2016
233 were registered with dementia as the underlying cause of death [38]. Cognitive assessments were not
234 incorporated in Tromsø 4 so we could not control for cognitive impairments or dementia at baseline in our
235 analysis, however, later study waves including the same population revealed that a low proportion of the
236 participants had cognitive impairments, with 7.3% scoring low on one or more of the cognitive tests in addition

237 to self-report of memory problems. Out of these, only one participant had dementia. It is therefore unlikely that
238 dementia confounded the association we found between osteoporosis/osteopenia and mortality.

239

240 Our findings indicate that BMD measurements of the distal forearm has a predictive value in mortality risk
241 assessment and mortality can be predicted using the commonly accepted T-values of -1 and -2.5 for osteopenia
242 and osteoporosis, though only demonstrated on a group level. In evaluating an individual's mortality risk,
243 osteopenia and osteoporosis should be viewed as independent risk factors of death that will add to the total risk
244 along with other known risk factors.

245

246 The association between mortality and osteoporosis was slightly stronger in men while the association with
247 osteopenia was somewhat stronger in women, indicating that smaller deficiencies in BMD might be more serious
248 in women. However, the between-gender differences are not large enough to make such assumptions based on
249 this material. The association between osteoporosis and increased mortality was still significant in both men and
250 women after adjusting for fractures, indicating that there might be a more complex relationship between low
251 BMD and mortality risk than we are currently aware of. Several authors have found an inverse relationship
252 between BMD and risk of cardiovascular disease and -death [39, 40]. Although we controlled for myocardial
253 infarction and angina, these variables were measured at baseline and more cases probably occurred during
254 follow-up, potentially more often among those with low BMD.

255

256 That our main analysis also show significantly higher mortality for osteopenic BMD-values suggests that it
257 might be valuable to initiate treatment measures already at this stage, though previous research debates the cost-
258 effectiveness of pharmacological treatment of osteopenia purely based on T-scores [41, 42]. Low BMD is mainly
259 seen as a risk factor of fractures, and it has been debated whether expensive medication is the right way to
260 prevent fractures as opposed to means of falls prevention [43]. However, one intervention does not exclude the
261 other, and falls prevention should be emphasized regardless of any medical prescriptions. In Norway,
262 osteoporosis appears to be both under-diagnosed and under-treated according to Devold et al. [44] who found
263 that one year after experiencing a hip fracture, only 14.6 percent of women and 4.2 percent of men used some
264 form of anti-osteoporotic medication. Grey et al. [29] found a significant reduction of mortality risk associated
265 with use of fracture-preventing medication in their meta-analysis and the effect was largest in older, frailer

266 individuals. The decision to prescribe medication should in any case be based on a full assessment of the
267 person's fracture risk and potential benefits of treatment.

268 In our study, a general population was screened for low BMD independent of prior indication of a BMD-
269 deficiency. There are currently no routines for general screening of BMD in Norway, but our findings indicate
270 that general BMD measurements can be of value in identifying individuals with higher risk of mortality.
271 Schousboe et al. [45] found that universal BMD-screening of the population combined with alendronate
272 therapy for those found to have osteoporosis is highly cost-effective for women aged 65 and older and may
273 be cost saving for ambulatory women aged 85 and older.

274 Based on our study, we cannot conclude whether treatment of low BMD will help decrease risk of
275 mortality or if the BMD deficiency is merely a marker for frailty. In practical terms, measured osteopenia
276 and osteoporosis in the distal forearm reveals individuals with increased risk of mortality, which warrants
277 closer follow-up of these individuals by health care personnel.

278 In a previous analysis from the Tromsø 4 study wave, high grip strength was associated with lower risk of
279 mortality [20], yet grip strength did not attenuate or modify the higher mortality risk for participants with
280 osteoporosis or osteopenia in our analyses. Thus, these variables seem to be independently associated with
281 mortality.

282

283 In elderly people, most wrist fractures occur in individuals with low BMD who are relatively healthy and active
284 and have good neuromuscular function [46]. BMD is commonly measured after a low-energy trauma fracture.
285 Even though a wrist fracture in itself has not been found to increase the risk of mortality [24], our findings
286 indicate that an underlying BMD-deficiency in the forearm can have more serious implications, and measures
287 should be taken accordingly with respect to current medical guidelines for prevention of fractures and treatment
288 of osteoporosis.

289

290

291 **Conclusion**

292 Women and men with distal forearm BMD-values consistent with both osteoporosis and osteopenia had an
293 increased all-cause mortality compared to people with normal BMD-values, independent of lifestyle- and health-
294 related variables. The association between BMD and all-cause mortality was not modified by hand grip strength.

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298 **References**

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Table 1. BMD-values of women and men aged 50-79 years in the Tromsø 4 study, categorized as “normal”, “osteopenia” and “osteoporosis” and number of deaths within age groups of 5 years.

Age group	N	Mean BMD (SD)	% Normal	% Osteopenia	% Osteoporosis	n (%) Deaths
Women	3 945	0.403 (0.069)	38.3	33.7	28.0	1538 (39.0)
50-54	1 050	0.453 (0.050)	70.2	25.3	4.5	135 (12.9)
55-59	840	0.421 (0.055)	46.1	39.5	14.4	175 (20.8)
60-64	695	0.393 (0.060)	27.5	41.9	30.7	247 (35.5)
65-69	752	0.365 (0.064)	16.4	34.7	48.9	475 (63.2)
70-74	577	0.352 (0.063)	12.0	29.8	58.2	477 (82.7)
75-79	31	0.341 (0.081)	16.1	22.6	61.3	29 (93.5)
Men	2 845	0.533 (0.067)	55.4	30.6	14.0	1638 (57.6)
50-54	225	0.564 (0.050)	77.8	20.0	2.2	40 (17.8)
55-59	793	0.552 (0.056)	67.6	27.1	5.3	258 (32.5)
60-64	700	0.539 (0.061)	56.1	32.7	11.1	378 (54.0)
65-69	606	0.520 (0.069)	46.4	33.7	20.0	468 (77.2)
70-74	494	0.501 (0.073)	36.0	34.4	29.6	467 (94.5)
75-79	27	0.492 (0.099)	44.4	25.9	29.6	27 (100.0)

N=total number of participants, BMD =Bone Mineral Density, n= number of participants who died during the follow-up period

Table 2. Number or proportions (%) of participants in the Tromsø 4-study in groups: “Normal BMD”, “Osteopenia” and “Osteoporosis” at baseline in 1994/1995. Number of deaths, person years (py) and mortality rate per 1 000 py during 22 years follow up. Each variable listed in women and men.

	N	Normal BMD	Osteopenia	Osteoporosis	Trend*
Women					
Number of participants	3 945	1 512	1 329	1 104	
Number of deaths	1 501	327	498	676	<0.001
Person years (py)	3 945	30 032	24 572	18 112	
Mortality rate per 1 000 py	3 945	10.9	20.3	37.3	
Age (years)	3 945	56.5 (6.1)	61.1 (6.8)	66.1 (5.8)	<0.001
BMD (g/cm ²)	3 945	0.472 (0.032)	0.398 (0.019)	0.316 (0.037)	<0.001
BMI (kg/m ²)	3 937	26.6 (4.5)	26.2 (4.5)	25.2 (4.4)	<0.001
Grip strength (bar)	3 931	0.79 (0.20)	0.73 (0.18)	0.66 (0.18)	<0.001
Smoking	3 941				0.138
Never smoker, %		43.2	45.4	40.9	-
Current smoker, %		30.2	27.9	32.5	-
Previous smoker, %		26.6	26.7	26.7	-
L-phys.act.<1 hour/week, %	3 938	25.4	26.3	29.6	0.044
H-phys.act.<1 hour/week, %	3 903	81.9	86.0	90.4	<0.001
Low education, %	3 915	55.2	60.8	70.2	<0.001
Self-reported health status	3 939				<0.001
Poor %		2.5	3.1	4.9	-
Not so good %		42.6	46.5	52.5	-

Good %		47.9	44.6	38.9	-
Very good %		7.0	5.9	3.6	-
Stroke %	3 929	1.2	2.1	2.5	0.042
Angina %	3 936	4.6	6.4	10.1	<0.001
Myocardial infarction %	3 932	1.9	3.2	4.0	0.004
Diabetes %	3 929	2.3	3.5	3.2	0.132
Asthma %	3 927	8.0	8.9	9.0	0.577
Men					
Number of participants	2 845	1 575	870	400	
Number of deaths	1 596	740	530	326	<0.001
Person years (py)	2 845	26 944	13 760	5 068	
Mortality rate per 1 000 py	2 845	27.5	38.5	64.3	
Age (years)	2 845	61.2 (6.2)	63.4 (6.1)	66.8 (5.6)	<0.001
BMD (g/cm ²)	2 845	0.581 (0.036)	0.501 (0.019)	0.419 (0.039)	<0.001
BMI (kg/m ²)	2 843	26.6 (3.2)	25.6 (3.3)	24.9 (3.8)	<0.001
Grip strength (bar)	2 831	0.89 (0.21)	0.83 (0.20)	0.72 (0.19)	<0.001
Smoking					<0.001
Never smoker, %	2 844	20.9	17.5	12.8	-
Current smoker, %	2 844	27.4	33.0	40.8	-
Previous smoker, %	2 844	51.7	49.5	46.5	-
L-phys.act.<1 hour/week, %	2 828	25.1	25.0	27.5	0.603
H-phys.act.<1 hour/week,%	2 814	70.9	74.3	78.4	0.006
Low education, %	2 833	47.2	45.9	52.3	0.131
Self-reported health status	2 841				0.014
Poor %		3.2	2.8	6.0	-
Not so good %		39.8	38.4	42.7	-
Good %		50.9	53.4	47.7	-
Very good %		6.1	5.4	3.5	-
Stroke %	2 834	2.7	3.2	6.3	0.002
Angina %	2 836	12.2	12.2	14.3	0.515
Myocardial infarction %	2 836	9.8	10.7	12.3	0.325
Diabetes %	2 834	3.8	3.6	3.0	0.779
Asthma %	2 833	7.4	6.1	9.1	0.161

Abbreviations: L/H-phys.act. = Light/Hard physical activity, BMD = Bone Mineral Density, py = person years

"<1 hour/week" contains both alternatives "none" and "less than one". "Low education" = 7 years or less.

*Trend gives p-values based on linear regression for the continuous variables (Normal BMD coded 0, osteopenia coded 1 and osteoporosis coded 2) and chi square test for the categorical ones.

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) of mortality for BMD categories: “Normal”, “Osteopenia” and “Osteoporosis” during 22 years follow-up from 1994/1995 to November 2016. Model 1-4 progressively adjusted for age, lifestyle- and health related covariates.

Model adjusted for	BMD	N	Women			N	Men		
			HR	95% CI			HR	95% CI	
Model 1: Age	Normal	3 818	1.00			2 747	1.00		
	Osteopenia		1.17	1.01	1.35		1.14	1.02	1.28
	Osteoporosis		1.42	1.23	1.64		1.62	1.41	1.85
Model 2: Model 1 + BMI, education, physical activity, smoking	Normal	3 818	1.00			2 747	1.00		
	Osteopenia		1.17	1.01	1.36		1.13	1.01	1.27
	Osteoporosis		1.35	1.17	1.57		1.45	1.26	1.67
Model 3: Model 2 + self-reported health and chronic diseases*	Normal	3 818	1.00			2 747	1.00		
	Osteopenia		1.18	1.02	1.36		1.14	1.01	1.28
	Osteoporosis		1.34	1.16	1.55		1.42	1.23	1.64
Model 4: Model 3 + grip strength	Normal	3 818	1.00			2 747	1.00		
	Osteopenia		1.17	1.01	1.35		1.13	1.00	1.27
	Osteoporosis		1.32	1.14	1.53		1.37	1.19	1.58

*Chronic diseases include angina, asthma, stroke, myocardial infarction and diabetes. N=number of subjects included in analysis.

Table 4. Hazard ratios (HR) with 95% confidence intervals (CI) of mortality for BMD categories: “Normal”, “Osteopenia” and “Osteoporosis” and after sustaining a hip fracture or osteoporotic fracture during 15 years follow-up from 1994/1995 to March 2010. Model 1 minimally adjusted without fractures. Model 2 and 4 minimally adjusted and model 3 and 5 fully adjusted for age, lifestyle- and health related covariates in addition to hip fractures (model 2 and 3) and osteoporotic fractures(model 4 and 5).

Model adjusted for	BMD	N	Women			N	Men		
			HR	95% CI			HR	95% CI	
Model 1: Age	Normal	3 809	1.00			2 745	1.00		
	Osteopenia		1.25	1.02	1.54		1.06	0.92	1.23
	Osteoporosis		1.46	1.19	1.79		1.54	1.30	1.82
Model 2: Model 1 + hip fracture	Normal	3 809	1.00			2 745	1.00		
	Osteopenia		1.24	1.01	1.53		1.05	0.90	1.21
	Osteoporosis		1.40	1.14	1.72		1.52	1.28	1.79
Model 3: Model 2 + BMI, education, physical activity, smoking, self-reported health, grip strength and chronic diseases*	Normal	3 809	1.00			2 745	1.00		
	Osteopenia		1.24	1.01	1.52		1.00	0.86	1.16
	Osteoporosis		1.30	1.05	1.61		1.25	1.05	1.49
Model 4: Age, osteoporotic fracture	Normal	3 809	1.00			2 745	1.00		
	Osteopenia		1.24	1.01	1.52		1.04	0.90	1.21
	Osteoporosis		1.42	1.15	1.74		1.50	1.27	1.77
Model 5: Model 4 + BMI, education, physical activity, smoking, self-reported health, grip strength and chronic diseases*	Normal	3 809	1.00			2 745	1.00		
	Osteopenia		1.23	1.00	1.51		1.00	0.86	1.17
	Osteoporosis		1.30	1.05	1.61		1.23	1.04	1.47

*Chronic diseases include angina, asthma, stroke, myocardial infarction and diabetes. N=number of subjects included in analysis.

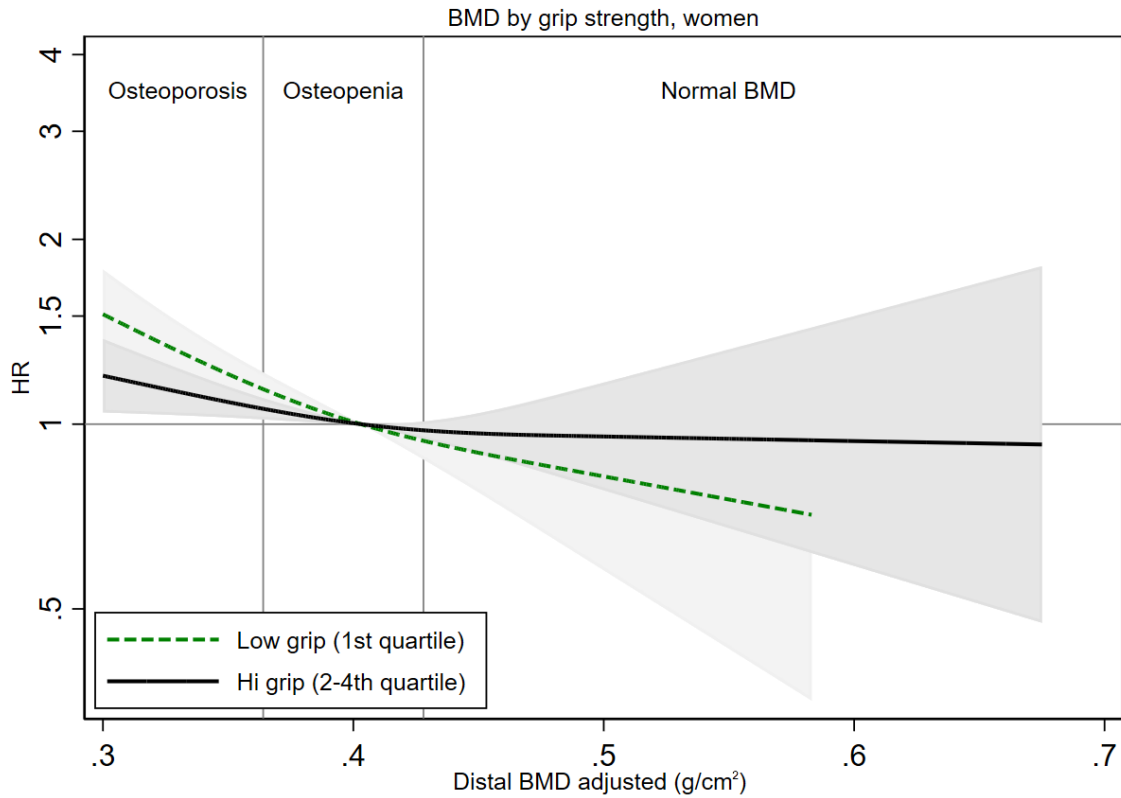


Figure 1: Mortality hazard ratios with 95% confidence intervals across the range of distal forearm BMD in women with low grip strength (dashed curve) and in women with normal or high grip strength (solid curve). Mediating effect not significant.

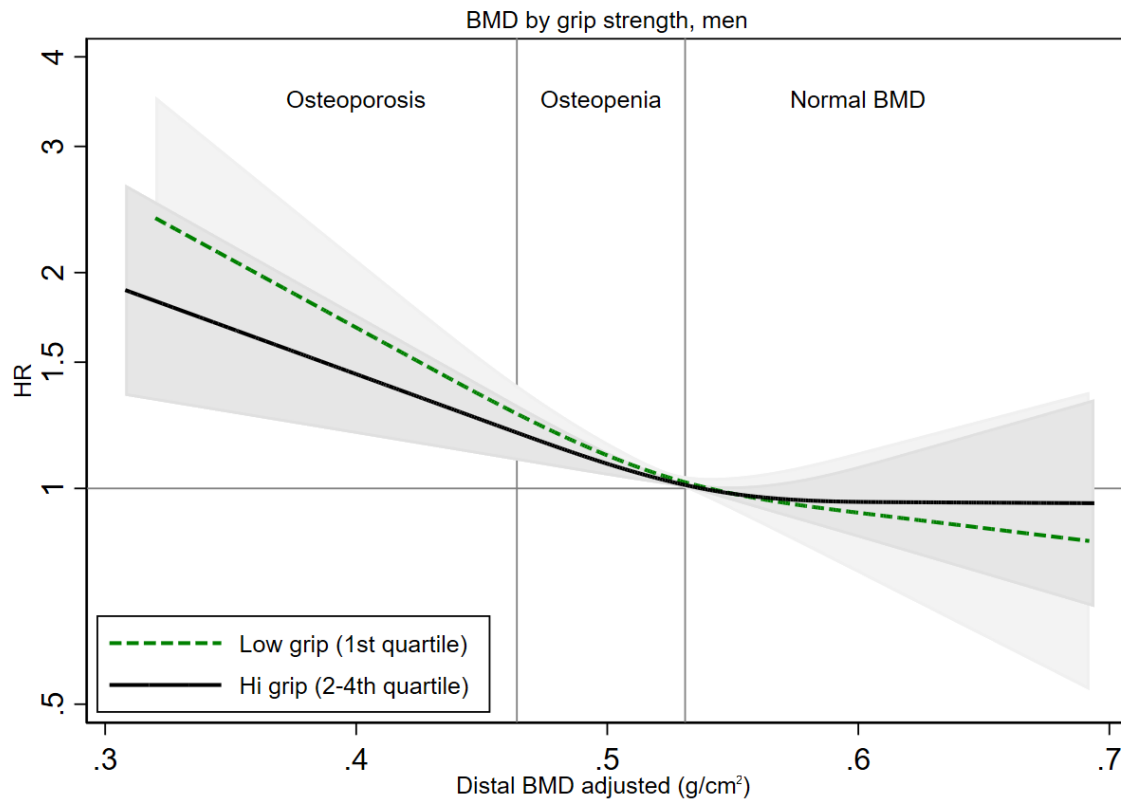


Figure 2: Mortality hazard ratios with 95% confidence intervals across the range of distal forearm BMD in men with low grip strength (dashed curve) and in women with normal or high grip strength (solid curve). Mediating effect not significant.