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Permalink

<https://escholarship.org/uc/item/15x880mh>

Journal

Journal of Bone and Mineral Research, 32(6)

ISSN

0884-0431

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Publication Date

2017-06-01

DOI

10.1002/jbmr.3104

Peer reviewed



Published in final edited form as:

J Bone Miner Res. 2017 June ; 32(6): 1237–1242. doi:10.1002/jbmr.3104.

Proximal femur volumetric bone mineral density and mortality: 13 years of follow-up of the AGES-Reykjavik Study

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Abstract

Bone mineral density (BMD) has been linked to mortality, but little is known about the independent contribution of each endosteal bone compartment and also the rate of bone loss to risk of mortality. We examined the relationships between (i) baseline trabecular and cortical volumetric (v) BMD at the proximal femur, and (ii) the rate of trabecular and cortical bone loss and all-cause mortality in older adults from the AGES-Reykjavik study. The analysis of trabecular and cortical vBMD and mortality was based on the baseline cohort of 4,654 participants (aged 66 years) with a median follow-up of 9.4 years; the association between rate of bone loss and mortality was based on 2,653 participants with bone loss data (median follow-up of 5.6 years). Analyses employed multivariable Cox-proportional models to estimate hazard ratios (HRs) with time-varying fracture status; trabecular and cortical variables were included together in all models. Adjusted for important confounders, Cox models showed that participants in the lowest quartile of trabecular vBMD had an increased risk of mortality compared to participants in other quartiles (HR=1.12, 95% confidence interval (CI) 1.01 to 1.25); baseline cortical vBMD was not related to mortality (HR=1.08, 95% CI 0.97 to 1.20). After adjustment for time-dependent fracture status, results were attenuated and not statistically significant. A faster loss (quartile 1 vs quartiles 2–4) in both trabecular and cortical bone was associated with higher mortality risk (HR =1.37 and 1.33,

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Disclosures

All authors declare that they have no conflicts of interest.

Author's roles: EAM was responsible for the study concept and design, analysis, and interpretation of data, and drafted the manuscript. ME participated in the analysis and interpretation of data, and in the critical revision of the manuscript. TA, TL, and KS were responsible for the acquisition of participants and data, and approved the final version. OM participated in the analysis of the data, and approved the final version. VG, GS, SS, LL, GE, and TBH were responsible for the study concept and design, acquisition of participants and data, critical revision of the manuscript or important intellectual content and approval of the final version. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

respectively); these associations were independent of major potential confounders including time-dependent incident fractures (HR =1.32 and 1.34, respectively). Overall, data suggest that faster bone losses over time in both the trabecular and cortical bone compartments are associated with mortality risk and that measurements of change in bone health may be more informative than single-point measurements in explaining mortality differences in older adults.

Keywords

All-cause mortality; bone loss; trabecular; cortical; computed tomography

Introduction

Substantial evidence has shown associations between low bone mineral density (BMD) and mortality.⁽¹⁾ In the past, these associations have been observed independently of risk of fracture and other aging-related co-morbidities,⁽²⁾ assessed with dual-energy X-ray absorptiometry (DXA), and focused predominantly on women. Although DXA is an excellent clinical tool, it does not provide specific assessments of 3D trabecular and cortical tissue or bone geometry. These distinctions are particularly relevant for the proximal femur structure, which is comprised of both trabecular and cortical bone, and which has been widely linked to adverse health effects. Importantly, an accelerated decrease in trabecular compared to cortical bone loss at the proximal femur with age has been documented.^(3,4) Moreover, due to its central anatomical location, both the surface-to-volume ratio and the bone formation rate per bone surface are greater in the trabecular than in cortical bone, therefore trabecular bone has higher turnover than cortical bone.⁽⁵⁾ Despite this, cortical bone loss also plays an important role in the pathogenesis of bone fragility. Clearly trabecular and cortical compartments have major and individual effects on bone strength and they provide valuable insights into the development of skeletal fragility. However, the association between these compartments and mortality risk is unknown.

The focus on low areal BMD (aBMD) and mortality also neglects the possible role of bone size/geometry; its confounding effect has not been considered in previous studies. The occurrence of periosteal apposition with aging had been suggested by previous cross-sectional and longitudinal studies^(4,6). Failure to recognize the effect of femoral geometry on bone strength when quantifying mortality risk associated with bone health in old age may disregard valuable information.

Moreover, longitudinal data on femoral bone loss are scarce⁽⁷⁻⁹⁾ and have been limited to aBMD estimates using DXA. Thus, and while genetic, metabolic, endocrine and behavioral factors have been proposed to explain the associations between age-related loss of bone strength and fragility fractures, the nature of the association with mortality, and the mechanisms involved are still not clearly elucidated. No study has explored the intriguing link between cortical and trabecular bone loss and mortality. Therefore, using volumetric quantitative computed tomographic (vQCT) images we investigated whether trabecular and cortical BMD at baseline as well as the rate of volumetric bone loss over a period of 5-year follow-up are associated with total mortality in a well-characterized large population-based

cohort of older men and women. Also, we wanted to explore whether such associations were independent of age, sex, hip size, fractures and other potentially important risk factors. We hypothesized that low volumetric BMD (vBMD) in both compartments and a greater rate of volumetric bone loss would be independent predictors of mortality risk in older adults.

Material and Methods

Study design and participants

The present study is based on the Age, Gene/Environment Susceptibility (AGES) - Reykjavik Study, a single-center prospective population study of Icelandic older men and women. Specifically, data come from the baseline examination (AGES) and one follow-up examination (AGES II), occurring on average 5.2 years later. Design and recruitment have been described in detail.⁽¹⁰⁾ A complete description of the number of participants (supplemental Figure 1) and criteria for exclusion are reported on Supplemental Data. Written informed consent was obtained from all participants, and the study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the Institutional Review Board of the Intramural Research Program of the National Institute of Aging.

Procedures

Our endpoint was all-cause mortality, which was ascertained by the Icelandic Heart Association (IHA), with permission of the Icelandic Data Protection Authority, using the complete, adjudicated registry of deaths available from the Icelandic National Roster maintained by Statistics Iceland (<http://www.statice.is/Statistics/Population/Births-and-deaths>) through 4 October 2015. For baseline analysis, survival time was calculated as the number of days between a participant's entry to the study at baseline (in 2002–2006) until the date of death from all causes, or until the end of follow-up in the cohort. For bone loss analysis, we calculated an individual's time at risk from the date of participation in the follow-up survey (AGES II) until the date of death, or until the end of follow-up in the cohort.

Left hip was scanned and analyzed with a four-row detector CT system (Sensation; Siemens Medical Systems, Erlangen, Germany), following a standardized protocol, and encompassed the proximal femur from a level 1 cm superior to the acetabulum to a level 3–5 mm inferior to the lesser trochanter at settings of 120 kVp, 140 mAs, 1-mm slice thickness, pitch=1, pixel size of 0.977 mm. Scans were performed at baseline and repeated after an average follow-up of 5.2 years (range 2.7–8.2). Proximal femur vQCT images were processed to extract measures of trabecular and cortical vBMD (g/cm^3), and bone size (CSA in cm^2) as previously published.⁽¹¹⁾ Assessments of covariates are described in the Supplemental Data.

Statistical analysis

Mean \pm SD or percentages for categorical variables were used to summarize subject characteristics. Comparisons among groups were assessed by independent T-test for continuous variables and by the chi-squared test for categorical data. To estimate annual percent change (%) in each bone parameter we divided the inter-visit difference relative to

absolute baseline, divided by the number of years between the visits, as follows: [(follow-up value – baseline value)/baseline value * time between CT scans] * 100.

Mortality rates per 1000 person-years were calculated. All analyses were based on Cox-proportional hazard regression models, which estimated the association of baseline trabecular and cortical vBMD and mortality over the next 13.1 years, and the associations of rate of change in trabecular and cortical vBMD and mortality over the next 8.4 years. Trabecular vBMD and cortical vBMD (both baseline values and %) were moderately to weekly correlated (Pearson's correlations of $r=0.51$ for baseline vBMD and $r=0.17$ for %); thus, we included both vBMD measurements together as independent variables for the Cox's proportional hazard regression models. Because prior studies have suggested differences in vBMD between men and women we tested for potential sex-differences between baseline trabecular and cortical vBMD and mortality by including interaction terms in the Cox models; these interaction terms were non-significant (all p -values >0.275), subsequent analyses were pooled by sex.

For baseline vBMD measures, the hazards ratios (HRs, with 95 % confidence intervals (CI)) for mortality were calculated for the lowest quartile (representing lower bone density) compared with the three highest combined. For the longitudinal bone measurement analyses, we calculated the mortality HR associated with having a faster rate of bone loss, defined as being in the quartile of fastest bone loss in our sample compared with the other three quartiles of the annual percent change in bone.

The proportional hazard assumption was tested by evaluating interaction terms with time, using the Schoenfeld residuals, and by examining complementary log-log plots (i.e., $\log(-\log(\text{survival}))$ versus $\log(\text{time})$). HRs reported here did not violate the proportionality assumption and thus were constant over follow-up time.

Proximal femur minimum and maximum CSAs were included in all models to account for bone size and the possible effect on bone strength although they were not significant predictors of mortality ($P = 0.10$) in the multivariate models. To be consistent through regression analyses, the same predictors that were significant in the baseline (AGES analytical sample) model were included in the bone loss analysis (AGES II).

Significance testing was two-sided and based on a 5% probability level. All analyses were conducted using Stata version 12 (STATA Corp, College Station, TX, USA).

Covariates—Several potential confounding covariates were taken into account in the analyses. These were selected from an extensive list of variables available in the AGES dataset and thought to be associated with bone loss and mortality, based on biological plausibility or previous literature findings (see Appendix for full list of variables explored). Variables were selected to be included in the Cox models if they were significantly related ($P < 0.05$) to both vBMD and mortality and if they had a significant contribution to the multivariate model (retention threshold of $P < 0.10$) were included in the final analyses. These variables were: Model 1 adjusted for sex, age, proximal femur minimum cross-sectional area (femoral neck) and maximum cross-sectional area. Model 2 additionally

adjusted for health variables including baseline history of diabetes, and chronic lung disease, CAC score, creatinine, cognitive status and self-reported health status. Model 3 additionally adjusted for lifestyle factors: 25OHD, smoking status, physical activity level, weight change from age 50, and self-reported history of previous fracture which was obtained from the baseline questionnaire. Model 4 adjusted for all covariates in Model 3 plus time-varying fracture status in order to further account for the potentially important influence of fracture occurrences in explaining the links between bone health and mortality.

Sensitivity Analysis—In sensitivity analysis we further adjusted for some additional variables were significantly associated with mortality in previous studies and in our sample, including body mass index, high-sensitivity C-reactive protein, history of valvular heart disease, arthritis, Parkinson disease, and cancer. In addition, we repeated the analysis using vBMD as continuous (per SD decrease), and also after excluding participants with early fatal events (in the first 3 years of follow-up). We also conducted sensitivity analyses to account for potential bias due to selective participation and survival in the follow-up study visit using inverse probability weights.⁽¹²⁾ In brief, we estimated via logistic regression models the probability of being alive and seen at the follow-up study examination. Using these probabilities, we computed analytical weights that are the inverse of the probability of the conjunction of surviving and participating at follow-up. These inverse probability weights were then applied to the Cox regression models (for full description see Supplemental Data).

Results

Characteristics of the study participants

The baseline characteristics of the participants who did and did not survive during follow-up are detailed in Table 1. Participants who did not survive were on average older, weaker, and more likely to be male, a current smoker, to report a history of chronic diseases, and less likely to exercise. In addition, vBMD at both bone compartments was significantly lower in the participants who did not survive compared to those who survived.

For the baseline AGES cohort, during a mean follow-up period of 9.4 (SD, 3.2) years, 2,108 (45.3%) participants died (48.3 per 1,000 person-years), and of these 1,021 (48.4%) were women (40.1 per 1,000 person-years); during this period 1130 participants, 327 men (16%) and 803 women (31%), sustained at least one fracture. For the AGES II cohort, the mean follow-up period was 5.6 (SD, 1.6) years, and during this period 683 (25.7%) participants died (45.7 per 1,000 person-years) and of those, 305 (44.7%) were women (35.6 per 1,000 person-years). Bone fracture incidence was 10.8% (287 fracture cases from AGES II examination until 15th of March 2015), of those 7.1% were men and 13.7% were women.

Baseline vBMD and risk of mortality

Table 2 summarizes the risk of mortality between the lowest quartile of vBMD for each of the trabecular and cortical bone compartments at proximal femur (versus the highest three quartiles for each one compartment measure). Risk of death was 1.21 times higher for participants in the lower quartile of trabecular vBMD, compared to participants in the other three quartiles, after adjusting for age and sex and hip size (model 1; 95% CI 1.09–1.35;

$p < 0.001$). Adjusting for all significant shared risk factors, including reported history of bone fractures (models 3), attenuated the estimated risk but it remained significantly elevated (HR 1.12, 95% CI 1.01–1.25; $p = 0.033$ in model 3) and independent of cortical vBMD. This association was further attenuated and not statistically significant when fracture status modeled as a time-varying covariate was taken into account (HR 1.07, 95% CI 0.96, 1.19; $p = 0.24$ in model 4). We found a trend of association between being in the lowest quartile of baseline cortical vBMD and higher risk of mortality, although these associations did not reach statistical significance (Table 2). In the fully-adjusted model with time-varying fracture status, mortality HR was 1.05 (95% CI 0.94–1.16; $p = 0.38$) for participants in the lower quartile of cortical vBMD (compared to Q2-Q4).

Bone loss and risk of mortality

The average time between the baseline visit (AGES) and visit 2 (AGES II) was 5.2 years (range 2.7–8.2 years). Among participants who attained both study visits (AGES II study sample), those who died during follow-up (range 0.17 – 8.42 years) had a significantly higher loss in total hip trabecular vBMD (1.7%/year) compared to survivors (1.4 %/year). The annual rate of cortical vBMD change was also significantly different ($p < 0.001$) per survival status. Participants with $>2\%$ trabecular vBMD loss per year (corresponding to the fastest quartile of trabecular bone loss with average 3.2% loss per year) had a mortality rate of 61 per 1,000 person-years compared with 41 per 1,000 persons-years among participants with a $<2\%$ trabecular vBMD loss per year (Q2-Q4, average 0.9% loss per year). Similar increased mortality rates were observed for the fastest versus other quartiles of cortical BMD (63 vs 40 per 1,000 persons-years).

After adjusting for potential confounders, faster bone loss at both cortical and trabecular compartments of the endosteal surface were independently associated with increased mortality (Table 3). Specifically, among participants with the faster trabecular bone loss, the HR for mortality was 1.37 (95% CI, 1.15–1.64) compared with the other participants (model 3, Table 3). For cortical bone loss, when participants in the faster quartile of bone loss at the proximal femur were compared with those in the other three quartiles of cortical bone change, the model 3 (full-adjusted) HR was 1.33 (95% CI 1.13–1.57). These associations remained significant - although slightly attenuated for trabecular bone loss - when fracture status modeled as a time-varying covariate was included (model 4).

In sensitivity analyses (Supplemental Table 1) results were similar to main analyses, including the model which further included inverse probability weights for censoring.

Discussion

In this large prospective study of community-dwelling older adults faster trabecular and cortical bone loss were associated with greater risk of mortality over thirteen years of follow-up. After adjusting for demographics, hip size, health behaviors and chronic conditions, there was 32% increased risk of mortality among older adults with a faster trabecular bone loss compared to those in the other three quartiles of trabecular bone change. Similar results were also observed for cortical bone loss (34% increased risk), and the associations between vBMD and mortality were observed even after adjusting for major

shared risk factors. Conclusions remained similar when fracture status during follow-up was included as a time-varying covariate.

To our knowledge, this is the first study to examine the contribution of each of the trabecular and cortical bone compartments to all-cause mortality risk. Some observational studies have shown that lower aBMD is independently associated with all-cause mortality in elderly populations.^(2,13–15) For example, in a previous report using a large cohort of Swedish men and women, Nordström and colleagues⁽¹³⁾ found that each 1 SD reduction in aBMD of the femoral neck was associated with a 54% increase in mortality in the fully-adjusted model. Results from a meta-analysis of 10 prospective cohort studies showed that each 1 SD decrease in aBMD at all sites was associated with a 1.17-fold (95% CI: 1.13–1.22) increase in total mortality.⁽¹⁾

Our results showed that lower trabecular vBMD at baseline was found to predict long-term mortality after adjusting for demographics, hip size, health behaviors, chronic conditions and history of bone fractures. Szulc et al.⁽¹⁵⁾ showed that lowest versus three upper quartiles of total hip aBMD predicted mortality independently of major incident osteoporotic fractures despite the fact that neither incident nor prevalent major osteoporotic fractures predicted mortality in the multivariate models. Another study⁽²⁾ demonstrated that low aBMD was associated with an increased risk of mortality and removal of women who fractured during follow-up did not change this association. The majority of other prior studies did not explore whether the relationship between BMD and mortality was independent of fractures (neither incident nor prevalent), although it is well-established that hip fracture patients have an excess mortality rate compared to the general population.⁽¹⁶⁾ One strength of our study is the inclusion of data on history of previous fracture (occurring before the bone assessment) as well as information on time-dependent occurrence of fracture throughout follow-up. Our results show that for baseline bone analyses, adjusting for history of fracture occurring before baseline bone assessment did not alter the association between trabecular vBMD and mortality; however, adjusting for time-varying follow-up fracture following baseline attenuated this association, suggesting that fractures at older age might explain some of the links between baseline BMD and mortality. Our results showed that lower cortical bone at baseline was not associated with long-term mortality, although the vBMD change analyses showed that higher cortical bone loss was associated with a higher risk of mortality independently of relevant confounders. Thus, it is likely that the baseline bone values reflect all relevant events during participant's life course (including achievement of peak bone mass and menopause for women), whereas recent changes of vBMD are more likely to be a marker of current metabolic or other factors/processes associated with a higher risk of mortality. However, we cannot exclude the possibility that the lack of association found between baseline cortical bone and mortality may be due to measurement error in assessment of cortical bone, such as of the effect of partial volume averaging on cortical bone measurements, as previously described by our group.⁽¹⁷⁾ Our cortical vBMD results should be interpreted in the light of this limitation, and further studies are necessary to clarify this finding.

We found that a higher rate of bone loss at both bone compartments was associated with increased risk of all-cause mortality. Studies examining the effect of bone loss on mortality

are sparse and the existing evidence are from the same prospective cohort, the Dubbo Osteoporosis Epidemiology Study.⁽⁷⁻⁹⁾ In general all three studies demonstrated that aBMD loss at the hip/femoral neck was associated with an increased risk of mortality. Our results show that in the fully-adjusted model the highest quartile of trabecular bone loss was associated with a 32% increased mortality compared to those in the other three least quartiles of trabecular bone change. The highest quartile of cortical bone loss was also significantly associated with increased mortality risk (34%). Finally, the associations of trabecular and cortical bone loss and mortality were still observed in Cox regression models weighted to account for the potential selection nature of the follow-up cohort. The associations in weighted models were slightly stronger than in un-weighted model three, reflecting a scenario of mild selection bias wherein the associations were underestimated in the un-weighted healthier follow-up sample.

The factors mediating the association between vBMD changes during aging and mortality risk are poorly known, but higher rates of bone loss are hypothesized to be a marker of metabolic / cytokine changes rather than being a causal pathway to mortality. Our findings suggest that bone loss is associated with increased mortality, adjusting for history of fractures as well as fractures occurring during follow-up. Fractures occurring throughout mortality follow-up, as observed in the cross-sectional analyses, was a significant and major predictor of mortality (HR= 1.57, p<0.001). Genetic factors may play a role in the link between the two bone compartments and mortality risk. A genome-wide association study reported different genetic variants associated with cortical and trabecular vBMD,⁽¹⁸⁾ and they may be under distinct biologic and environmental factors.⁽¹⁹⁾ The modest correlation between trabecular and cortical vBMD found in our cohort also supports the notion that the determinants of these two bone parameters may differ. Future research would be needed to understand the so-far undetermined mechanisms regulating compartment-specific bone loss and how they relate with mortality risk.

The hypothesis that reduced skeletal loading, vascular calcification and several pathological disorders are the primary basis for the bone-mortality linkage may be oversimplified. In our study, the link with mortality was observed even after accounting for coronary artery calcium score, chronic lung disease, and other possible common denominators such as decreased physical activity and cognition, diabetes, smoking and poor health status; although we cannot exclude the potential for residual confounding. Other shared pathways that cause both bone loss and mortality such as muscle loss or inflammation are likely to be implicated in this association. As we did not consider these potentially confounding factors, their influences cannot be excluded. The major strengths of our study were the exploration of both single-time bone measurements as well as changes in bone measurements over time at older age, large sample size, long follow-up time, analyses accounted for history of status as well as time varying fracture status, and detailed baseline data that enabled us to accurately control for lifestyle, medical history, and several other factors. We also explored both the cross-sectional and longitudinal (bone loss) relationship with mortality risk. Whereas QCT has been previously used in fracture risk studies, it has not been used in prospective studies of mortality risk. Our research had some limitations. In addition to the spectrum of covariates included in the present study, other factors such as endogenous sex steroids, genetic markers, and cytokines associated with bone regulation were not measured.

These endocrine and genetic factors could provide some additional clues to the complex bone-mortality relationship. Our study is based on a single Icelandic community and our results may not be generalizable to other populations, including other Caucasian groups with different characteristics or other ethnicities.

In conclusion, the results illustrate that both cortical and trabecular bone loss were associated with higher risk of mortality. Advancing age is associated with bone loss and structural damage, however the potential specific biologic factors that lead to both bone structure regulation and mortality risk is an important topic for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Institutes of Health contract N01-AG-1-2100, the Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

References

1. Qu X, Huang X, Jin F, et al. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol.* 2013; 166(2):385–93. [PubMed: 22112679]
2. Bauer DC, Bauer DC, Palermo L, et al. Quantitative ultrasound and mortality: a prospective study. *Osteoporos Int.* 2002; 13(8):606–12. [PubMed: 12181617]
3. Johannesdottir F, Aspelund T, Reeve J, et al. Similarities and differences between sexes in regional loss of cortical and trabecular bone in the mid-femoral neck: the AGES-Reykjavik longitudinal study. *J Bone Miner Res.* 2013; 28(10):2165–76. [PubMed: 23609070]
4. Riggs BL, Melton LJ 3rd, Robb RA, et al. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J Bone Miner Res.* 2004; 19(12):1945–54. [PubMed: 15537436]
5. Parfitt AM. Misconceptions (2): turnover is always higher in cancellous than in cortical bone. *Bone.* 2002; 30(6):807–9. [PubMed: 12052445]
6. Lauretani F, Bandinelli S, Griswold ME, et al. Longitudinal changes in BMD and bone geometry in a population-based study. *J Bone Miner Res.* 2008; 23(3):400–8. [PubMed: 17997708]
7. Bliuc D, Nguyen ND, Alarkawi D, et al. Accelerated bone loss and increased post-fracture mortality in elderly women and men. *Osteoporos Int.* 2015; 26(4):1331–9. [PubMed: 25600473]
8. Kado DM, Browner WS, Blackwell T, Gore R, Cummings SR. Rate of bone loss is associated with mortality in older women: a prospective study. *J Bone Miner Res.* 2000; 15(10):1974–80. [PubMed: 11028450]
9. Nguyen ND, Center JR, Eisman JA, Nguyen TV. Bone loss, weight loss, and weight fluctuation predict mortality risk in elderly men and women. *J Bone Miner Res.* 2007; 22(8):1147–54. [PubMed: 17635040]
10. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol.* 2007; 165(9):1076–87. [PubMed: 17351290]
11. Marques EA, Gudnason V, Sigurdsson G, et al. Are bone turnover markers associated with volumetric bone density, size, and strength in older men and women? The AGES-Reykjavik study. *Osteoporos Int.* 2016; 27(5):1765–76. [PubMed: 26630978]

12. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology*. 2012; 23(1):119–28. [PubMed: 21989136]
13. Nordstrom A, Eriksson M, Stegmayr B, Gustafson Y, Nordstrom P. Low bone mineral density is an independent risk factor for stroke and death. *Cerebrovasc Dis*. 2010; 29(2):130–6. [PubMed: 19955736]
14. Suzuki T, Yoshida H. Low bone mineral density at femoral neck is a predictor of increased mortality in elderly Japanese women. *Osteoporos Int*. 2010; 21(1):71–9. [PubMed: 19499274]
15. Szulc P, Maurice C, Marchand F, Delmas PD. Increased bone resorption is associated with higher mortality in community-dwelling men ≥ 50 years of age: the MINOS study. *J Bone Miner Res*. 2009; 24(6):1116–24. [PubMed: 19113925]
16. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010; 152(6):380–90. [PubMed: 20231569]
17. Sigurdsson G, Aspelund T, Chang M, et al. Increasing sex difference in bone strength in old age: The Age, Gene/Environment Susceptibility-Reykjavik study (AGES-REYKJAVIK). *Bone*. 2006; 39(3):644–51. [PubMed: 16790372]
18. Paternoster L, Lorentzon M, Lehtimäki T, et al. Genetic determinants of trabecular and cortical volumetric bone mineral densities and bone microstructure. *PLoS Genet*. 2013; 9(2):e1003247. [PubMed: 23437003]
19. Cauley JA, Blackwell T, Zmuda JM, et al. Correlates of trabecular and cortical volumetric bone mineral density at the femoral neck and lumbar spine: the osteoporotic fractures in men study (MrOS). *J Bone Miner Res*. 2010; 25(9):1958–71. [PubMed: 20572023]

Table 1

Demographic and clinical characteristics for both analytical samples (AGES and AGESII) according survival status by 2015.

Variables	AGES Analytical Sample (n=4,654)		AGES II Analytical Sample (n=2,653)	
	Dead (n=2,108)	Alive (n=2,546)	Dead (n=683)	Alive (n=1,970)
	Mean (SD)			
Age, yrs	78.59 (5.52)	74.23 (4.45)	77.13 (5.23)	73.79 (4.22)
% Weight change from age 50 ^a	0.91 (13.28)	6.93 (12.10)	2.93 (12.31)	7.06 (11.83)
CAC score ^b	955.8 (1221.5)	473.5 (768.2)	835.6 (1069.2)	479.51 (791.3)
Creatinine, µmol/L	96.26 (33.91)	85.81 (20.10)	93.53 (23.70)	86.30 (20.20)
25OHD, nmol/L	52.33 (24.95)	54.40 (22.80)	53.03 (24.09)	55.18 (22.89)
Proximal femur vQCT variables				
Trabecular vBMD, g/cm ³	0.058 (0.036)	0.066 (0.034)	0.064 (0.036)	0.068 (0.034)
Cortical vBMD, g/cm ³	0.519 (0.040)	0.523 (0.037)	0.523 (0.040)	0.525 (0.037)
Minimum CSA, cm ²	10.86 (2.25)	10.58 (2.18)	10.90 (2.20)	10.63 (2.14)
Maximum CSA, cm ²	28.75 (4.57)	27.70 (4.38)	29.01 (4.52)	27.83 (4.42)
	% (No.)			
Female	48.4 (1,021)	62.4 (1,588)	44.7 (305)	59.9 (1,180)
Current smoker	15.1 (318)	10.3 (261)	13.8 (94)	9.9 (196)
Moderate-high PA level	13.6 (286)	21.1 (536)	16.5 (113)	22.1 (435)
Previous any fracture	51.1 (1077)	53.7 (1366)	48.3 (330)	53.5 (1053)
Poor health status	40.1 (845)	24.4 (620)	69.0 (471)	21.9 (431)
Impaired cognitive status	23.9 (504)	7.4 (188)	12.2 (83)	5.5 (109)
Diabetes ^c	15.0 (316)	9.9 (253)	14.2 (97)	9.3 (184)
Chronic lung disease	13.0 (274)	8.3 (211)	13.2 (90)	7.7 (152)

^a Percent weight change was calculated using midlife weight data from the Reykjavik Study and baseline AGES-Reykjavik weight measurements as follows: (AGES weight – midlife weight / midlife weight) x 100.

^b A higher score indicates higher calcification.

^c Diabetes mellitus was defined as the self-reported history of diabetes, use of glucose-modifying medications or fasting blood glucose > 7.0 mmol/l.

CAC= coronary artery calcium, CSA= cross-sectional area, PA= physical activity, vQCT= volumetric quantitative computed tomographic, vBMD= volumetric bone mineral density.

Table 2

Associations of proximal femur trabecular and cortical vBMD (by lowest versus the highest three quartiles of vBMD) with mortality in participants from the AGES-Reykjavik Study, 2002–2006 (n= 4,654).

AGES analytical sample (no. of deaths = 2,108)			
QCT Proximal femur vBMD	Model	HR	95% CI
Trabecular (Q1 <0.037 g/cm ³)	1	1.21	1.09, 1.35
	2	1.20	1.08, 1.34
	3	1.12	1.01, 1.25
	4	1.07	0.96, 1.19
Cortical (Q1 <0.496 g/cm ³)	1	1.06	0.96, 1.18
	2	1.10	0.99, 1.22
	3	1.08	0.97, 1.20
	4	1.05	0.94, 1.16

Trabecular and cortical variables were included together in all COX models. Bolded values are significant.

Model 1 is adjusted for sex, age, proximal femur minimum cross-sectional area (femoral neck) and maximum cross-sectional area; **Model 2** is adjusted for all of the factors in model 1 plus health variables including baseline history of diabetes and chronic lung disease, coronary artery calcium score, Creatinine, cognitive status and self-reported health status; **Model 3** is additionally adjusted for lifestyle factors including 25OHD, smoking status, physical activity level, weight change from age 50, and self-reported history of previous fracture. **Model 4** is additionally adjusted for fracture status as a time-varying covariate.

Table 3

Adjusted HRs of mortality by quartile of bone change (faster rate of bone loss versus the other three quartiles of the annual percent change in bone) in participants from the AGES II, 2007–2011 (n= 2,653).

AGES II analytical sample (no. of deaths = 683)			
QCT Proximal femur bone loss,	Model	HR	95% CI
Trabecular (Q1 -2.25 %/year)	1	1.48	1.25, 1.76
	2	1.48	1.24, 1.76
	3	1.37	1.15, 1.64
	4	1.32	1.11, 1.58
Cortical (Q1 -0.13 %/year)	1	1.41	1.20, 1.66
	2	1.37	1.16, 1.61
	3	1.33	1.13, 1.57
	4	1.34	1.14, 1.58

Trabecular and cortical variables were included together in all COX models. Bolded values are significant.

Model 1 is adjusted for sex, age, proximal femur minimum cross-sectional area (femoral neck) and maximum cross-sectional area; **Model 2** is adjusted for all of the factors in model 1 plus health variables including baseline history of diabetes and chronic lung disease, coronary artery calcium score, Creatinine, cognitive status and self-reported health status; **Model 3** is additionally adjusted for lifestyle factors including 25OHD, smoking status, physical activity level, weight change from age 50, and self-reported previous fracture; **Model 4** is similar to model 3 but is additionally adjusted for fracture status as a time-varying covariate.