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# Bone Mineral Density and Parathyroid Hormone as Independent Risk Factors for Mortality in Community-Dwelling Older Adults: A Population-Based Prospective Cohort Study in Brazil. The São Paulo Ageing & Health (SPAH) Study

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**ABSTRACT**

Previous studies have shown a relationship between osteoporosis and increased mortality risk. However, none of these studies performed a concomitant evaluation of the parathyroid hormone (PTH)-calcium-vitamin D axis and bone mass to accurately determine the contribution of each of these parameters to survival in older subjects. Thus, we sought to investigate the association between bone parameters and mortality in a longitudinal, prospective, population-based cohort of 839 elderly subjects. Clinical data (including history of fractures and cardiovascular events) were assessed using a specific questionnaire. Laboratory exams, including serum 25OHD and PTH, were also performed. Bone mineral density (BMD) at the lumbar spine and hip were evaluated using DXA. All analyses were performed at baseline (2005 to 2007). Mortality was recorded during follow-up. Multivariate Cox proportional regression was used to compute hazard ratios for all-cause and cardiovascular mortality. Over a mean $4.06 \pm 1.07$ years, there were 132 (15.7%) deaths. These individuals were compared to 707 subjects who were alive at the end of the coverage period for mortality data collection. In a multivariate Cox proportional hazards model, age (HR 1.32; 95% CI, 1.13 to 1.55; $p = 0.001$, for each 5-year increase), male gender (HR 1.90; 95% CI, 1.30 to 2.79; $p = 0.001$), recurrent falls (more than two in the previous year; HR 1.65; 95% CI, 1.06 to 2.56; $p = 0.026$), diabetes mellitus (HR 2.17; 95% CI, 1.46 to 3.21; $p < 0.001$), low physical activity score (HR 1.78; 95% CI, 1.14 to 2.79; $p = 0.011$), prior cardiovascular event (HR 1.76; 95% CI, 1.18 to 2.63; $p = 0.006$), total hip BMD (HR 1.41; 95% CI, 1.15 to 1.72; $p = 0.001$, per each 1 SD decrease), and intact PTH (iPTH) (HR 1.06; 95% CI, 1.04 to 1.08; $p < 0.001$, per each 10 pg/mL increase) were independently associated with all-cause mortality. The subjects in the highest quartile of PTH (>49 pg/mL) were at a higher risk of cardiovascular death (HR 3.09; 95% CI, 1.36 to 6.99; $p = 0.007$) compared with the subjects in the lowest quartile (<26 pg/mL). Low BMD and higher PTH were significantly associated with mortality in community-dwelling older adults. These findings support the notion that careful screening of these bone parameters might lead to better management of older patients and improve outcomes in this population. © 2016 American Society for Bone and Mineral Research.

**KEY WORDS:** MORTALITY; ELDERLY; PARATHYROID HORMONE; BONE MINERAL DENSITY; RISK FACTORS

## Introduction

Osteoporotic fractures, particularly hip and vertebral fractures, are linked with adverse outcomes[1–3] including increased mortality.[1,4–6] Low bone mineral density (BMD) has also been associated with an increased mortality risk independent of fragility fracture.[7–10] However, the majority of studies concerning low BMD and mortality have focused on white populations[9,11]; a smaller number have included ethnic minorities.[12,13] Some epidemiological studies have also suggested that mineral metabolism biomarkers, especially low serum 25-hydroxyvitamin D (25OHD) concentrations and higher intact parathyroid hormone (iPTH) levels, separately or in combination, are related to mortality among institutionalized older adults[14] and community-dwelling elderly people without primary hyperparathyroidism.[15]

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Several biological mechanisms have been proposed to explain a possible causal relationship between vitamin D deficiency or elevated PTH and increased mortality risk, especially cardiovascular features, including atherosclerosis,[16,17] left ventricular hypertrophy,[18,19] and arterial stiffness and hypertension.[20]

However, these associations between bone parameters (BMD, 25OHD, and iPTH) and mortality in the general population are still controversial.[21,22] Moreover, previous studies of mineral metabolism and mortality risk have generally evaluated BMD, 25OHD, and iPTH concentrations separately. No study has performed a concomitant evaluation of the PTH-calcium-vitamin D axis and bone mass, and this is essential for determining the contribution of each of these parameters to survival in older subjects. Thus, in the present study, we investigated BMD, bone metabolism biomarkers, and clinical variables as potential independent predictors of all-cause and cardiovascular mortality in a population-based cohort of community-dwelling elderly men and women in Sao Paulo, Brazil.

## Subjects and Methods

### Subjects

From June 2005 to July 2007, a total of 1025 older subjects were enrolled in the São Paulo Ageing & Health (SPAH) Study, a prevalence survey of osteoporotic fractures. Details about the methodology have been described elsewhere.[23] Briefly, the SPAH recruited all residents ≥65 years from 66 census areas in the Butantã district, an urban neighborhood in the city of São Paulo (located in the south of Brazil). During the first stages of the study, all older adults living in the district were identified through census records. This sample was similar in age, gender, and social class characteristics to the entire Brazilian elderly population.[24] Only well-functioning elderly men and women who were able to visit the research center were recruited to participate in this study. All of the subjects completed an interviewer-administered lifestyle questionnaire, laboratory tests, BMD tests, and spinal radiographs performed on the same day.

Between 2010 and 2012, all of the subjects were invited to participate in a second evaluation. Individuals were recruited by telephone calls and door-to-door visits. They were brought from their homes to the research center via a shuttle service specifically hired for the study. Of the 1025 participants in the first study, 707 (69.0% of the original cohort) agreed to take part in the prospective assessment. Because of varying dates of completion of the baseline survey, the period between baseline and the second appraisal varied among the participants (range, 0.2 to 6.5 years, average 4.06 ± 1.07 years). The coverage period for mortality data collection was from the date of the baseline examination through December 31, 2012. At the end of that period, 132 (12.9%) individuals had died, and 168 (16.4%) could not be contacted because they were living outside of São Paulo (lost to follow-up). Those who could not be contacted were not known to be alive at the time that analysis was censored; thus, they were excluded from the study. Of the 725 subjects who agreed to participate in the second evaluation, 18 (1.8%) were excluded because of a lack of some baseline laboratory or BMD data. Figure 1 shows a flowchart of the study.

This study was approved by the Local Ethics in Research Committee of the São Paulo University School of Medicine, and all participants gave written informed consent.

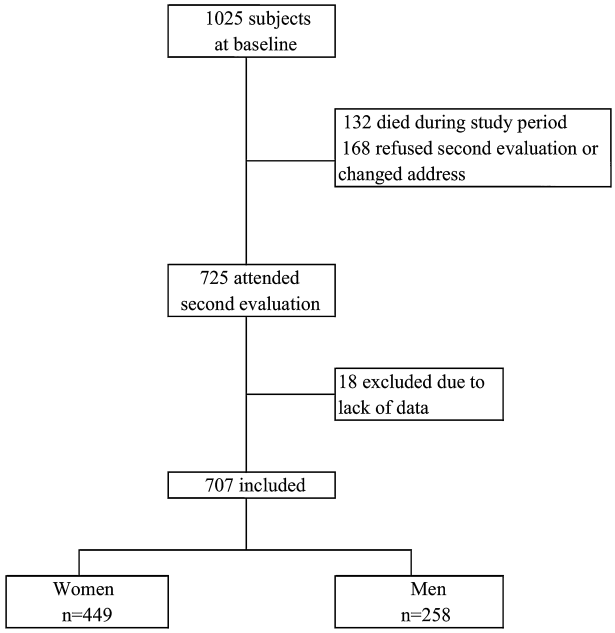


**Fig. 1.** SPAH study population. SPAH = São Paulo Ageing & Health.

### Baseline clinical assessment

At baseline, all of the participants[23,24] underwent a standardized interviewer-administered questionnaire that ascertained lifestyle and health behaviors, including age, dairy product consumption, smoking status, alcohol consumption, physical activity, previous nonvertebral fracture, hip fracture in first-degree relatives, falls during the previous year, comorbidities (including any cardiovascular event: myocardial infarction, unstable angina, or stroke), and current medication use. The individuals were asked to bring all medications to the baseline clinic visit. Details about the ascertainment of these baseline characteristics were provided previously.

Hypertension was determined based on self-reported physician-diagnosed hypertension, elevated average blood pressure measurement at examination (systolic ≥140 mmHg or diastolic ≥90 mmHg), or a history of recent blood pressure medication use. One to three blood pressure measurements were performed during data collection. Diabetes mellitus was defined as self-reported physician-diagnosed diabetes mellitus (except gestational diabetes only) or a fasting (12 hours) blood glucose of 126 mg/dL or greater. Hyperlipidemia was defined as self-reported physician-diagnosed high cholesterol, non-high-density lipoprotein (HDL) cholesterol of 160 mg/dL or greater, triglycerides of 200 mg/dL or greater, or current use of lipid-lowering medication.

The height, weight, and body mass index (BMI) of each participant were measured using standard protocols. BMI was calculated by dividing the participants' weight (kg) by their height squared ($m^2$).

### Baseline radiographic evaluation

At baseline, lateral radiographs of the thoracic and lumbar spine were obtained using a 40-inch tube-to-film distance centered at $T_7$ and $L_2$. To identify vertebral fractures, all X-ray images were analyzed independently by two rheumatologists D.S.D and L.G.M who were experienced in vertebral

fracture assessment. A consensus was reached between the readers for any difference of interpretation. The readers evaluated each $T_4$–$L_4$ vertebrae image to determine whether it contained a fracture, using Genant's semiquantitative approach.[25] The reliability between readers was analyzed using a random subsample of 60 X-ray images, as described. Interobserver agreement was 96%, and the kappa coefficient was 0.83.[23]

### Baseline laboratorial evaluation

Blood samples were collected under fasting conditions (between 8:00 a.m. and 10:00 a.m.) and stored at −70°C until analysis.

The concentrations of serum calcium (adjusted for the albumin concentration), phosphorus, alkaline phosphatase, creatinine, total cholesterol, HDL, triglycerides, albumin, and glucose were determined using standard automated laboratory methods.[23,24]

The estimated glomerular filtration rate (eGFR) was calculated using the Cockroft-Gault equation[25] and expressed categorically according to the U.S. National Kidney Foundation's (NKF's) modified classification for chronic kidney disease (CKD): stages 1 to 2, eGFR $>60$ mL/min/1.73 m$^2$ (reference group); stage 3a, eGFR 45 to 59 mL/min/1.73 m$^2$; stage 3b, eGFR 30 to 44 mL/min/1.73 m$^2$; stage 4, eGFR 15 to 29 mL/min/1.73 m$^2$; and stage 5, eGFR $<15$ mL/min/1.73 m$^2$.[26]

The serum concentration of 25OHD was measured using the radioimmunoassay technique (DiaSorin, Stillwater, MN, USA) with a lower detection limit of 5 ng/mL. iPTH serum concentrations were measured using immunoradiometric assay (ELSA-PTH; CIS bio international, Paris, France) with reference interval of 11 to 65 pg/mL (reference range of the kit tests).[23,24]

### BMD and body composition

At baseline, BMD was determined by dual energy X-ray absorptiometry (DXA) using Hologic QDR 4500A densitometry equipment (Discovery model; Hologic Inc. Bedford, MA, USA) at the following regions: lumbar spine, femoral neck, total hip, and total body. All DXA measurements were performed by the same experienced technologist V.C.[23,24]

### Outcomes

At the end of the field data collection, mortality data of the original SPAH cohort was collected from the death certificates ascertained by the publicly available databases of the Programa de Aprimoramento das Informações de Mortalidade no Município de São Paulo (PRO-AIM, Improvement Program of Information on Mortality in São Paulo) Foundation, the organ responsible for vital statistics, operating under the auspices of the São Paulo State Secretary of Economics and Planning. The underlying cause of death was coded using the 10th revision of the International Classification of Diseases (ICD-10). Cardiovascular (CVD) mortality was defined as ICD-10 codes I00 to I99 and non-CVD mortality as all other causes of death.

The outcome for the cohort was to examine the relationship between baseline characteristics (including mineral metabolism parameters) with incident all-cause mortality and specifically cardiovascular causes of death during the follow-up period.

### Statistical analysis

BMI was categorized according to Lipschitz's classification, namely: underweight, BMI $<22$ kg/m$^2$; normal range, BMI 22 to 27 kg/m$^2$; and overweight/obesity, BMI $>27$ kg/m$^2$.[27]

25OHD levels were analyzed as a continuous variable, as quartiles and as clinical categories, as suggested by Holick and colleagues[28]: normal ($\geq$30 ng/mL), insufficient ($>$20 to $<$30 ng/mL), or deficient ($\leq$20 ng/mL). iPTH was analyzed as quartiles. To investigate the influence of clinically high iPTH levels on the risk of mortality, the concentrations of iPTH were stratified as $\leq$65 versus $>$65 pg/mL because 65 pg/mL represents the upper limit of normal for the assay based on the central 95% of values of healthy subjects who had normal 25OHD concentrations.[29]

BMD was analyzed as a continuous variable, with the hazard ratio (HR) reported per SD decrease, as quartiles, and as clinical categories according to *T*-score at each site: normal, with a *T*-score at or below −1.0; osteopenia, with a *T*-score between −1 SD and −2.5 SD; or osteoporosis, with a *T*-score at or below −2.5.[30]

Appendicular skeletal muscle mass (ASM) was calculated as the sum of the lean soft-tissue mass of the arms and legs, assuming that all nonfat and nonbone tissue is skeletal muscle. Low ASM was defined using the ASM adjusted for fat criteria, which is appropriate for discriminating sarcopenia in the older Brazilian population, as we have described elsewhere.[31,32]

The subjects contributed follow-up time (person-years) from the date of participation in the baseline survey to the point of last contact, which was either the date of the second interviewer-administered questionnaire or the date of death. The association between each baseline variable and mortality outcomes was evaluated using a simple (unadjusted) Cox proportional hazards analysis. An actuarial analysis was used to plot Kaplan-Meier curves for survival by each variable, and the survival curves were compared using log-rank tests. Multivariable Cox proportional models were constructed to define which variables were independently associated with mortality. All variables were included in the preliminary model and backward likelihood ratio was used to determine those factors in the final model by stepwise selection method (Supporting Table 1). The entry criteria was $p < 0.05$ and the removal criteria was $p > 0.10$. Two different final multivariable models were defined: all-cause mortality and cardiovascular mortality.

Significance was set at $p < 0.05$. All analyses were performed using SPSS software version 20.0 for Windows (IBM Corp, Armonk, NY, USA).

## Results

During a mean of $4.06 \pm 1.07$ years of follow-up, there were 132 (15.7%) deaths among the 839 participants, of which 57 (43.2%) were related to CVD. The remaining 75 non-cardiovascular deaths could not be further stratified according to other causes (eg, cancer, infection) for valid analysis because of the small number of observations for each cause.

The baseline differences between the individuals who survived the follow-up and those who died are shown in Table 1. Compared with the surviving participants, the deceased subjects were older, were more frequently men, and had a lower BMI, a higher prevalence of recurrent falls, a low physical activity score, an alcohol intake $\geq$3 units/day, diabetes mellitus, and a prior cardiovascular event. These individuals also had a lower eGFR, lower 25OHD, higher iPTH, and lower BMD at the femoral neck and total hip.

**Table 1.** Baseline Characteristics of the SPAH Study Population (Surviving Versus Deceased Participants)

| Baseline characteristics | Alive throughout the study ($n = 707$) | Deaths during study ($n = 132$) | $p$[a] |
|---|---|---|---|
| Age (years), mean ± SD | 72.7 ± 4.7 | 76.2 ± 6.9 | <0.001 |
| Women, *n* (%) | 449 (63.5) | 67 (50.8) | 0.006 |
| White race, *n* (%) | 449 (63.5) | 94 (71.2) | 0.089 |
| Blood draw season, *n* (%) | | | 0.642 |
| Winter (June to August) | 168 (23.8) | 29 (22.0) | |
| Spring (September to November) | 189 (26.7) | 36 (27.3) | |
| Summer (December to March) | 190 (26.9) | 31 (23.5) | |
| Autumn (March to May) | 160 (22.6) | 36 (27.3) | |
| Weight (kg), mean ± SD | 67.6 ± 13.2 | 64.8 ± 15.3 | 0.292 |
| Height (cm), mean ± SD | 154.8 ± 8.9 | 155.7 ± 9.6 | 0.053 |
| BMI (kg/m$^2$), mean ± SD | 28.2 ± 5.0 | 26.5 ± 5.0 | 0.001 |
| Dietary calcium intake (mg/day), mean ± SD | 436.8 ± 307.7 | 432.1 ± 284.6 | 0.871 |
| Low physical activity score, *n* (%) | 45 (6.4) | 39 (29.6) | <0.001 |
| Recurrent falls (≥2 falls in the last year), *n* (%) | 91 (12.9) | 27 (20.5) | 0.021 |
| History of nonvertebral fracture, *n* (%) | 75 (10.6) | 18 (13.6) | 0.309 |
| Prevalent vertebral fracture, *n* (%) | 205 (29.0) | 48 (36.4) | 0.143 |
| Current smoking, *n* (%) | 80 (11.3) | 17 (12.9) | 0.363 |
| Alcohol intake, ≥3 units/day, *n* (%) | 107 (15.1) | 33 (25.0) | 0.005 |
| Diabetes mellitus, *n* (%) | 129 (18.2) | 45 (34.1) | <0.001 |
| Hypertension, *n* (%) | 441 (62.4) | 92 (69.7) | 0.076 |
| Dyslipidemia, *n* (%) | 406 (57.6)[b] | 56 (43.4)[c] | 0.98 |
| Any previous cardiovascular event, *n* (%) | 85 (12.0) | 38 (28.9) | <0.001 |
| eGFR (mL/min/1.73 m$^2$), mean ± SD | 59.1 ± 18.1 | 50.4 ± 22.4 | 0.007 |
| Albumin-corrected serum calcium (mg/dL), mean ± SD | 9.4 ± 0.5 | 9.4 ± 0.6 | 0.632 |
| Serum phosphate (mg/dL), mean ± SD | 3.4 ± 0.5 | 3.4 ± 0.6 | 0.151 |
| iPTH (pg/mL), mean ± SD | 39.1 ± 17.2 | 55.5 ± 75.1[d] | 0.014 |
| 25OHD (ng/mL), mean ± SD | 20.1 ± 9.3[e] | 17.9 ± 10.4[f] | 0.017 |
| Lumbar spine BMD (g/cm$^2$), mean ± SD | 0.890 ± 0.194 | 0.885 ± 0.205 | 0.778 |
| Femoral neck BMD (g/cm$^2$), mean ± SD | 0.708 ± 0.143 | 0.659 ± 0.148[g] | 0.019 |
| Total hip BMD (g/cm$^2$), mean ± SD | 0.849 ± 0.151 | 0.791 ± 0.171[h] | <0.001 |
| Low appendicular muscle mass, *n* (%) | 118 (16.8)[i] | 30 (22.7) | 0.099 |

eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone; 25OHD = 25-hydroxyvitamin D; BMD = bone mineral density.
[a]Values of $p$ are for comparisons of means (Student's $t$ test or Mann-Whitney test) or proportions (chi square test, Fisher's test, or likelihood ratio test).
[b]$n = 704$.
[c]$n = 129$.
[d]$n = 131$.
[e]$n = 701$.
[f]$n = 131$.
[g]$n = 131$.
[h]$n = 131$.
[i]$n = 704$.

## All-cause mortality

The association between baseline characteristics and all-cause mortality are presented in Table 2. Older age, male gender, lower BMI, low physical activity score, recurrent falls, clinical fracture (hip, humerus), alcohol consumption, diabetes mellitus, cardiovascular event, lower eGFR, higher iPTH, lower 25OHD, and lower total hip BMD were most strongly associated with all-cause mortality (all $p < 0.05$; Tables 2 and 3).

In the multivariate Cox proportional hazards models (Table 4), age, low physical activity score, recurrent falls, diabetes mellitus, and previous cardiovascular event maintained an independent association with all-cause mortality, even after controlling for potential confounders and intermediate variables.

Of the bone parameters, lower baseline total hip BMD and higher iPTH levels were also predictors of all-cause mortality in the multivariate analysis (Table 4). Additionally, the adjusted Kaplan-Meier curves (Fig. 2*A–D*) for all-cause mortality according to hip BMD and iPTH showed a divergence of mortality risk among the strata.

Compared with the subjects in the highest quartile (Q4: >0.940 g/cm$^2$) for total hip BMD, the participants in the lowest quartile (Q1: <0.728 g/cm$^2$) had a higher risk of all-cause mortality (HR 2.86; 95% CI, 1.48 to 5.54; $p = 0.002$), as did the subjects in the second quartile (Q2: 0.728 to 0.831 g/cm$^2$; HR 2.05; 95% CI, 1.10 to 3.81; $p = 0.024$). The participants in the third quartile for hip BMD (Q3: 0.832 to 0.940 g/cm$^2$) also had a trend toward a higher risk of all-cause mortality compared with those in the highest quartile for hip BMD (HR 1.83; 95% CI, 0.99 to 3.36; $p = 0.053$). Analyzing total hip BMD as a continuous variable did not alter this association (HR 1.41; 95% CI, 1.15 to 1.72; $p = 0.001$ per 1-SD decrease), nor did the clinical

**Table 2.** Unadjusted Risk of All-Cause and Cardiovascular Mortality During a Mean 4.06 Years of Follow-Up in SPAH Study Participants, According to Clinical Baseline Characteristics

| | | All-cause ($n = 132$) | | Cardiovascular ($n = 57$) | |
|---|---|---|---|---|---|
| Baseline characteristics | $n$ | Events $n$ (%) | Hazard ratio (95% CI) | Events $n$ (%) | Hazard ratio (95% CI) |
| Age | | | | | |
| <70 years | 250 | 30 (12.0) | Referent | 6 (2.4) | Referent |
| 70–74 years | 310 | 32 (10.3) | 0.85 (0.52–1.40) | 16 (5.2) | 2.12 (0.83–5.42) |
| 75–79 years | 166 | 26 (15.7) | 1.25 (0.74–2.11) | 14 (8.4) | **3.33 (1.28–8.67)** |
| ≥80 years | 113 | 44 (38.9) | **3.75 (2.35–5.96)** | 21 (18.6) | **8.89 (3.59–22.03)** |
| Male | 323 | 65 (20.1) | **1.56 (1.16–2.33)** | 30 (9.3) | **1.89 (1.12–3.13)** |
| White race | 543 | 94 (17.3) | 1.33 (0.91–1.93) | 37 (6.8) | 1.01 (0.58–1.73) |
| Blood draw season | | | | | |
| Winter (June to August) | 197 | 29 (14.7) | Referent | 15 (7.6) | Referent |
| Spring (September to November) | 225 | 36 (16.0) | 1.15 (0.71–1.88) | 16 (7.1) | 1.00 (0.50–2.03) |
| Summer (December to March) | 221 | 31 (14.0) | 1.08 (0.65–1.80) | 12 (5.4) | 0.81 (0.38–1.74) |
| Autumn (March to May) | 196 | 36 (18.4) | 1.52 (0.93–2.47) | 14 (7.1) | 1.16 (0.56–2.40) |
| BMI | | | | | |
| <22 kg/m$^2$ | 84 | 24 (28.6) | **1.93 (1.19–3.15)** | 10 (11.9) | **2.21 (1.02–4.78)** |
| 22–27 kg/m$^2$ | 305 | 50 (16.4) | Referent | 18 (5.9) | Referent |
| >27 kg/m$^2$ | 450 | 58 (12.9) | 0.78 (0.53–1.14) | 29 (6.4) | 1.08 (0.60–1.94) |
| Physical activity score | | | | | |
| Low | 84 | 39 (46.4) | **4.88 (2.93–8.12)** | 20 (23.8) | **12.01 (4.53–32.02)** |
| Moderate | 545 | 69 (12.7) | 1.16 (0.73–1.85) | 32 (5.9) | **2.58 (1.01–6.64)** |
| High | 210 | 24 (11.4) | Referent | 5 (2.4) | Referent |
| Recurrent falls (≥2 falls in the previous year) | 118 | 27 (22.9) | **1.63 (1.07–2.48)** | 12 (10.2) | 1.70 (0.90–3.21) |
| Prevalent nonvertebral fracture | | | | | |
| No fracture | 748 | 115 (15.4) | 1.00 | 47 (6.3) | Referent |
| Wrist | 51 | 3 (5.9) | 0.36 (0.12–1.15) | 1 (2.0) | 0.30 (0.04–2.15) |
| Humerus | 20 | 7 (35.0) | **2.72 (1.27–5.84)** | 5 (25.0) | **4.74 (1.88–11.94)** |
| Rib | 9 | 2 (22.2) | 1.13 (0.28–4.62) | 0 | — |
| Hip | 11 | 5 (45.5) | **4.21 (1.2–10.34)** | 4 (36.4) | **8.15 (2.93–22.72)** |
| Prevalent vertebral fracture | 253 | 48 (19.0) | 1.27 (0.49–1.82) | | 1.62 (0.96–2.74) |
| Smoking status | | | | | |
| Never | 448 | 63 (14.1) | Referent | 3 (0.7) | Referent |
| Current | 97 | 17 (17.5) | 1.27 (0.74–2.17) | 26 (26.8) | 0.51 (0.15–1.66) |
| Former | 294 | 52 (17.7) | 1.29 (0.89–1.86) | 28 (9.5) | 1.45 (0.85–2.48) |
| Alcohol intake ≥3 units/day | 140 | 33 (23.6) | **1.61 (1.08–2.39)** | 14 (10.0) | 1.56 (0.85–2.85) |
| Diabetes mellitus | 174 | 45 (25.9) | **2.13 (1.48–3.06)** | 21 (12.1) | **2.37 (1.38–4.06)** |
| Hypertension | 533 | 92 (17.3) | 1.43 (0.98–2.09) | 45 (8.4) | **2.21 (1.17–4.18)** |
| Dyslipidemia | 462 | 56 (12.1) | 0.72 (0.51–1.03) | 30 (6.5) | 0.93 (0.54–1.59) |
| Any previous cardiovascular event | 123 | 38 (30.9) | **2.64 (1.81–3.86)** | 18 (14.6) | **2.92 (1.67–5.11)** |
| Diary calcium intake above median (>349 mg) | 473 | 74 (15.6) | 1.00 (0.71–1.41) | 30 (6.3) | 0.88 (0.52–1.47) |

Bold values denote $p < 0.05$.
BMI = body mass index.

category (osteoporosis [$T$-score ≤ –2.5] at total hip versus normal BMD [$T$-score ≥ –1.0]: HR 3.51; 95% CI, 1.89 to 6.52; $p < 0.001$; and osteopenia [$T$-score < –1.0 and > –2.5] versus normal BMD: HR 2.03; 95% CI, 1.28 to 3.22; $p = 0.003$).

The subjects in the highest quartile for iPTH (Q4: >49 pg/mL) had a significantly increased risk of all-cause mortality (HR 1.75; 95% CI, 1.04 to 2.94; $p = 0.037$) compared with the participants in the lowest quartile (Q1: <26 pg/mL). There was no increased mortality risk between the highest quartile and the second quartile (Q2: 26 to 35 pg/mL) (HR 1.33; 95% CI, 0.75 to 2.35; $p = 0.334$) or between the highest quartile and the third quartile (Q3: 36 to 49 pg/mL; HR 1.24; 95% CI, 0.71 to 2.16; $p = 0.459$). Similar results were found when iPTH levels were analyzed as a continuous variable (HR 1.06; 95% CI, 1.04 to 1.08; $p < 0.001$, per each 10-pg/mL increase) or as clinical categories (>65 pg/mL versus ≤65: HR 2.25; 95% CI, 1.40 to 3.61; $p = 0.001$).

Although the multivariate model showed no significant association between 25OHD levels and the risk of all-cause mortality (Table 4), an additional analysis was done in order to make sure that vitamin D levels did not influence the relationship between iPTH and mortality. Because more than 50% of subjects did have 25OHD deficiency, the risk factors for mortality were determined after excluding the individuals with 25OHD <20 ng/mL ($n = 470$). Of 362 subjects with 25OHD ≥20 ng/mL, 49 (13,5%) had died during the study. As a result, the multivariate Cox proportional hazards models confirmed that iPTH maintained an independent association with all-cause mortality (HR 1.12; 95% CI, 1.03 to 1.21; $p = 0.007$, per each

**Table 3.** Unadjusted Risk of All-Cause and Cardiovascular Mortality During a Mean of 4.06 Years of Follow-Up in SPAH Study Participants, According to Laboratory and DXA Baseline Characteristics

| | | All-cause ($n = 132$) | | Cardiovascular ($n = 57$) | |
|---|---|---|---|---|---|
| Baseline characteristics | *n* | Events *n* (%) | Hazard ratios (95% CI) | Events *n* (%) | Hazard ratios (95% CI) |
| eGFR | | | | | |
| $<30$ mL/min/1.73 m$^2$ | 28 | 16 (57.1) | **5.66 (3.15–10.18)** | 12 (42.9) | **17.43 (7.33–41.45)** |
| 30–44.9 mL/min/1.73 m$^2$ | 168 | 41 (24.4) | **2.12 (1.36–3.31)** | 16 (9.5) | **3.36 (1.48–7.61)** |
| 45–59.9 mL/min/1.73 m$^2$ | 254 | 32 (12.6) | 1.05 (0.66–1.69) | 17 (6.7) | **2.29 (1.02–5.14)** |
| $\geq$60 mL/min/1.73 m$^2$ | 322 | 37 (11.5) | Referent | 9 (2.8) | Referent |
| Serum phosphate $>3.5$ mg/dL | 307 | 52 (16.9) | 1.15 (0.81–1.64) | 24 (7.8) | 1.31 (0.77–2.24) |
| iPTH, quartiles | | | | | |
| Q1 ($<28$ pg/mL) | 203 | 23 (11.3) | Referent | 8 (3.9) | Referent |
| Q2 (28–35 pg/mL) | 203 | 29 (14.3) | 1.28 (0.74–2.21) | 10 (4.9) | 1.26 (0.50–3.20) |
| Q3 (36–49 pg/mL) | 229 | 31 (13.5) | 1.13 (0.66–1.95) | 12 (5.2) | 1.26 (0.52–3.09) |
| Q4 ($>49$ pg/mL) | 204 | 49 (24.0) | **2.15 (1.31–3.53)** | 27 (13.2) | **3.43 (1.56–7.55)** |
| iPTH, clinical categories | | | | | |
| $\leq$65 pg/mL | 759 | 105 | Referent | 43 (20.7) | Referent |
| $>65$ pg/mL | 79 | 26 | **2.51 (1.65–3.89)** | 14 (6.7) | **3.32 (1.81–6.06)** |
| 25OHD, quartiles | | | | | |
| Q1 ($<13.0$ ng/mL) | 208 | 50 (24.0) | **1.94 (1.22–3.10)** | 22 (10.6) | 1.65 (0.84–3.22) |
| Q2 (13.1–18.3 ng/mL) | 208 | 26 (12.5) | 1.04 (0.61–1.78) | 11 (5.3) | 0.85 (0.39–1.88) |
| Q3 (18.4–25.0 ng/mL) | 208 | 28 (13.5) | 1.01 (0.60–1.71) | 10 (4.8) | 0.70 (0.31–1.58) |
| Q4 ($\geq$25.0 ng/mL) | 208 | 27 (13.0) | Referent | 14 (6.7) | Referent |
| 25OHD, clinical categories | | | | | |
| Deficient, $<20$ ng/mL | 470 | 82 (17.4) | 1.09 (0.64–1.83) | 34 (7.2) | 1.27 (0.54–3.04) |
| Insufficient, 20–29.9 ng/mL | 257 | 32 (12.5) | 0.72 (0.40–1.29) | 17 (6.6) | 1.08 (0.43–2.75) |
| Sufficient, $\geq$30 ng/mL | 105 | 17 (16.2) | Referent | 6 (5.7) | Referent |
| Lumbar spine BMD, quartiles | | | | | |
| Q1 ($<0.747$ g/cm$^2$) | 208 | 37 (17.8) | 1.26 (0.78–2.04) | 13 | 0.91 (0.44–1.92) |
| Q2 (0.747–0.872 g/cm$^2$) | 211 | 29 (13.7) | 0.88 (0.53–1.47) | 12 | 0.76 (0.35–1.61) |
| Q3 (0.873–1.005 g/cm$^2$) | 211 | 35 (16.6) | 1.12 (0.69–1.81) | 17 | 1.12 (0.56–2.24) |
| Q4 ($>1.005$ g/cm$^2$) | 209 | 31 (14.8) | Referent | 15 | Referent |
| Lumbar spine *T*-score, clinical categories | | | | | |
| Osteoporosis | 344 | 62 (18.0) | 1.21 (0.81–1.83) | 23 (6.7) | 0.95 (0.51–1.77) |
| Osteopenia | 264 | 34 (12.9) | 0.87 (0.55–1.39) | 17 (6.4) | 0.91 (0.47–1.79) |
| Normal | 231 | 36 (15.6) | Referent | 17 (7.4) | Referent |
| Femoral neck BMD, quartiles | | | | | |
| Q1 ($<0.594$ g/cm$^2$) | 230 | 44 (19.1) | 1.24 (0.77–2.02) | 17 (7.4) | 0.82 (0.41–1.64) |
| Q2 (0.594-0.689 g/cm$^2$) | 217 | 37 (17.1) | 1.05 (0.64–1.74) | 16 (7.4) | 0.79 (0.39–1.59) |
| Q3 (0.690-0.789 g/cm$^2$) | 214 | 24 (11.2) | 0.69 (0.40–1.21) | 9 (4.2) | 0.45 (0.20–1.02) |
| Q4 ($>0.789$ g/cm$^2$) | 177 | 26 (14.7) | Referent | 15 (8.5) | Referent |
| Femoral neck *T*-score, clinical categories | | | | | |
| Osteoporosis | 237 | 48 (20.3) | **1.83 (1.08–3.12)** | 20 (8.4) | 1.59 (0.72–3.49) |
| Osteopenia | 418 | 64 (15.3) | 1.37 (0.82–2.29) | 28 (6.7) | 1.27 (0.60–2.68) |
| Normal | 183 | 19 (10.4) | Referent | 9 (4.9) | Referent |
| Total hip BMD, quartiles | | | | | |
| Q1 ($<0.728$ g/cm$^2$) | 214 | 45 (21.0) | **2.10 (1.25–3.53)** | 17 (7.9) | 1.50 (0.70–3.20) |
| Q2 (0.728-0.831 g/cm$^2$) | 216 | 34 (15.7) | 1.50 (0.87–2.58) | 17 (7.9) | 1.44 (0.67–3.06) |
| Q3 (0.832-0.940 g/cm$^2$) | 205 | 31 (15.1) | 1.45(0.83–2.52) | 12 (5.9) | 1.06 (0.47–2.41) |
| Q4 ($>0.940$ g/cm$^2$) | 203 | 21 (10.3) | Referent | 11 (5.4) | Referent |
| Total hip *T*-score, clinical categories | | | | | |
| Osteoporosis | 94 | 27 (28.7) | **3.50 (2.10–5.84)** | 10 (10.6) | **3.17 (1.39–7.24)** |
| Osteopenia | 400 | 72 (18.0) | **1.92 (1.27–2.91)** | 34 (8.5) | **2.23 (1.17–4.22)** |
| Normal | 344 | 32 (9.3) | Referent | 13 (3.8) | Referent |
| Low appendicular skeletal mass (ASM) | 148 | 30 (20.3) | 1.36 (0.91–2.04) | 15 (10.1) | 1.67 (0.93–3.02) |

Bold values denote $p < 0.05$.

eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone; 25OHD = 25-hydroxyvitamin D; BMD = bone mineral density.

**Table 4.** Risk Factors Predictive of All-Cause Mortality in Community-Dwelling Older Adults in the SPAH Study Population, According the Multivariate Models

| Risk factors | HR[a] | 95% CI | *p* |
|---|---|---|---|
| Age (per 5-year increase) | 1.32 | 1.13 – 1.55 | 0.001 |
| Male gender | 1.90 | 1.30 – 2.79 | 0.001 |
| Low physical activity score | 1.78 | 1.14 – 2.79 | 0.011 |
| Recurrent falls | 1.65 | 1.06 – 2.56 | 0.026 |
| Diabetes mellitus | 2.17 | 1.46 – 3.21 | <0.001 |
| Any previous cardiovascular event[b] | 1.76 | 1.18 – 2.63 | 0.006 |
| iPTH (per each 10-pg/mL increase) | 1.06 | 1.04 – 1.08 | <0.001 |
| Total hip BMD (per 1-SD decrease) | 1.41 | 1.15 – 1.72 | 0.001 |

HR = hazard ratio; iPTH = intact parathyroid hormone; BMD = bone mineral density; eGFR = estimated glomerular filtration rate.

[a]Adjusted for the other variables from the model: [BMI (HR 0.96; 95% CI, 0.91–1.01; $p = 0.132$), previous fracture (HR 0.64; 95% CI, 0.35–1.20; $p = 0.167$), alcohol intake (HR 1.04; 95% CI, 0.64–1.69; $p = 0.887$), eGFR (HR 1.00; 95% CI, 0.99–1.01; $p = 0.710$), 25OHD (HR 1.01; 95% CI, 0.98–1.03; $p = 0.559$)]; plus season (HR 1.02; 95% CI, 0.60–1.72; $p = 0.947$), serum calcium (HR 0.85; 95% CI, 0.60–1.20; $p = 0.355$), and phosphorus (HR 1.32; 95% CI, 0.93–1.86; $p = 0.118$).

[b]Myocardial infarction, stroke, or instable angina.

10-pg/mL increase). Furthermore, after excluding subjects with more severe vitamin D deficiency (25OHD <15 ng/mL) ($n = 278$), similar results were obtained (HR 1.06; 95% CI, 1.03 to 1.09; $p < 0.001$, per each 10-pg/mL increase). Thus, the association between iPTH and all-cause mortality was shown to be independent of vitamin D levels even in patients with only normal serum vitamin D levels. The strength of relationship between 25OHD and iPTH was very weak (Spearman's rank correlation coefficient: $r = -0.187$; $p = 0 < 0.001$).

Moreover, the same analysis was performed with the renal function. After excluding 196 subjects with low eGFR (<45 mL/min/1.73 $m^2$), 576 individuals were analyzed, of whom 69 (12.0%) had died during follow-up. Again, iPTH was retained as predictor of all-cause mortality (HR 1.13; 95% CI, 1.05 to 1.21; $p = 0.001$, per each 10-pg/mL increase), independently of renal function. The strength of relationship between eGFR and iPTH was very weak (Spearman's rank correlation coefficient: $r = -0.105$; $p = 0.005$; Supporting Fig. 1).

### Cardiovascular mortality

The association between baseline characteristics and cardiovascular mortality are presented in Tables 2 and 3. Older age, male gender, lower BMI, low physical activity score, clinical fracture (hip, humerus), diabetes mellitus, hypertension, any cardiovascular event, lower eGFR, higher iPTH, and low total hip BMD were most strongly associated with cardiovascular mortality (all $p < 0.05$).

After adjusting for potential confounders, the multivariate Cox proportional hazards models (Table 5) retained age, male gender, low physical activity score, diabetes mellitus, and previous cardiovascular event as independent risk factors for cardiovascular death.

Higher iPTH levels and low BMD at the total hip were also predictors of cardiovascular mortality in multivariate Cox proportional hazards models. The adjusted Kaplan-Meier curves (Fig 3*A–C*) for cardiovascular mortality according to hip BMD and iPTH showed a significant difference in mortality risk among the strata.

Compared to subjects with a normal BMD at the total hip (*T*-score ≥ −1.0), those with osteopenia (*T*-score < −1.0 and > −2.5 at total hip) or osteoporosis (*T*-score ≤ −2.5) had an increased risk of cardiovascular mortality (HR 1.98; 95% CI, 1.00 to 3.96; $p = 0.054$ and HR 2.33; 95% CI, 0.87 to 6.22; $p = 0.091$, respectively).

The subjects in the highest quartile for iPTH (Q4: >49 pg/mL) were at a higher risk of cardiovascular death (HR 3.09; 95% CI, 1.36 to 6.99; $p = 0.007$) compared with the subjects in the lowest quartile (Q1: <26 pg/mL). As was the case for overall mortality, there was no significantly increased mortality risk for the individuals in the second quartile (Q2: 26 to 35 pg/mL; HR 1.51; 95% CI, 0.58 to 3.89; $p = 0.399$) or the third quartile (Q3: 36 to 49 pg/mL; HR 1.54; 95% CI, 0.61 to 3.89; $p = 0.366$) compared with those in the lowest quartile. The association between iPTH and mortality remained significant when iPTH was analyzed as a continuous variable (HR 1.07; 95% CI, 1.04 to 1.10; $p < 0.001$, per each 10-pg/mL increase) or when clinical categories were used (>65 pg/mL versus ≤65: HR 3.17; 95% CI, 1.63 to 6.16; $p = 0.001$).

Similar to overall mortality, an additional analysis was performed excluding individuals with vitamin D deficiency. Of 561 subjects with 25OHD ≥15 ng/mL, there were 57 (10.2%) deaths from cardiovascular causes during the study. As a result, the multivariate Cox proportional hazards models retained iPTH as an independent predictor of cardiovascular mortality (HR 1.11; 95% CI, 1.02 to 1.21; $p = 0.017$, per each 10-pg/mL increase).

Likewise, after excluding individuals with renal dysfunction (eGFR <45 mL/min/1.73 $m^2$), 26 (4.6%) of 576 individuals with eGFR ≥45 mL/min/1.73 $m^2$ died during follow-up. In this subsample, iPTH was also retained as risk factor for cardiovascular mortality (HR 1.15; 95% CI, 1.03 to 1.28; $p = 0.01$, per each 10-pg/mL increase) in the multivariate Cox proportional hazards models.

Hence, the association between iPTH and cardiovascular mortality was shown to be independent of vitamin D levels and renal dysfunction in this population.

## Discussion

This study demonstrated for the first time that, in addition to the established clinical risk factors for mortality in the elderly population, low bone density at the hip and higher plasma levels of PTH were independent predictors of all-cause and cardiovascular mortality in a population-based, prospective study of community-dwelling older adults. These effects were independent of recognized cardiovascular predictors of death and risk factors associated with mineral metabolism. Moreover, higher PTH was associated with a higher risk of mortality, even in individuals with PTH in the normal range (plasma levels 50 to 65 pg/mL) without other signs of disturbed bone metabolism, such as abnormal serum calcium, renal dysfunction, or vitamin D deficiency. These findings suggest that plasma levels of PTH provide prognostic information, even in the absence of primary or secondary hyperparathyroidism.

The SPAH is a longitudinal population-based study with several strengths, including a high participation rate and a homogeneous and well-characterized community-dwelling sample that is likely representative of the Brazilian elderly population.[33] Furthermore, in previous studies, the non-exclusion of vitamin

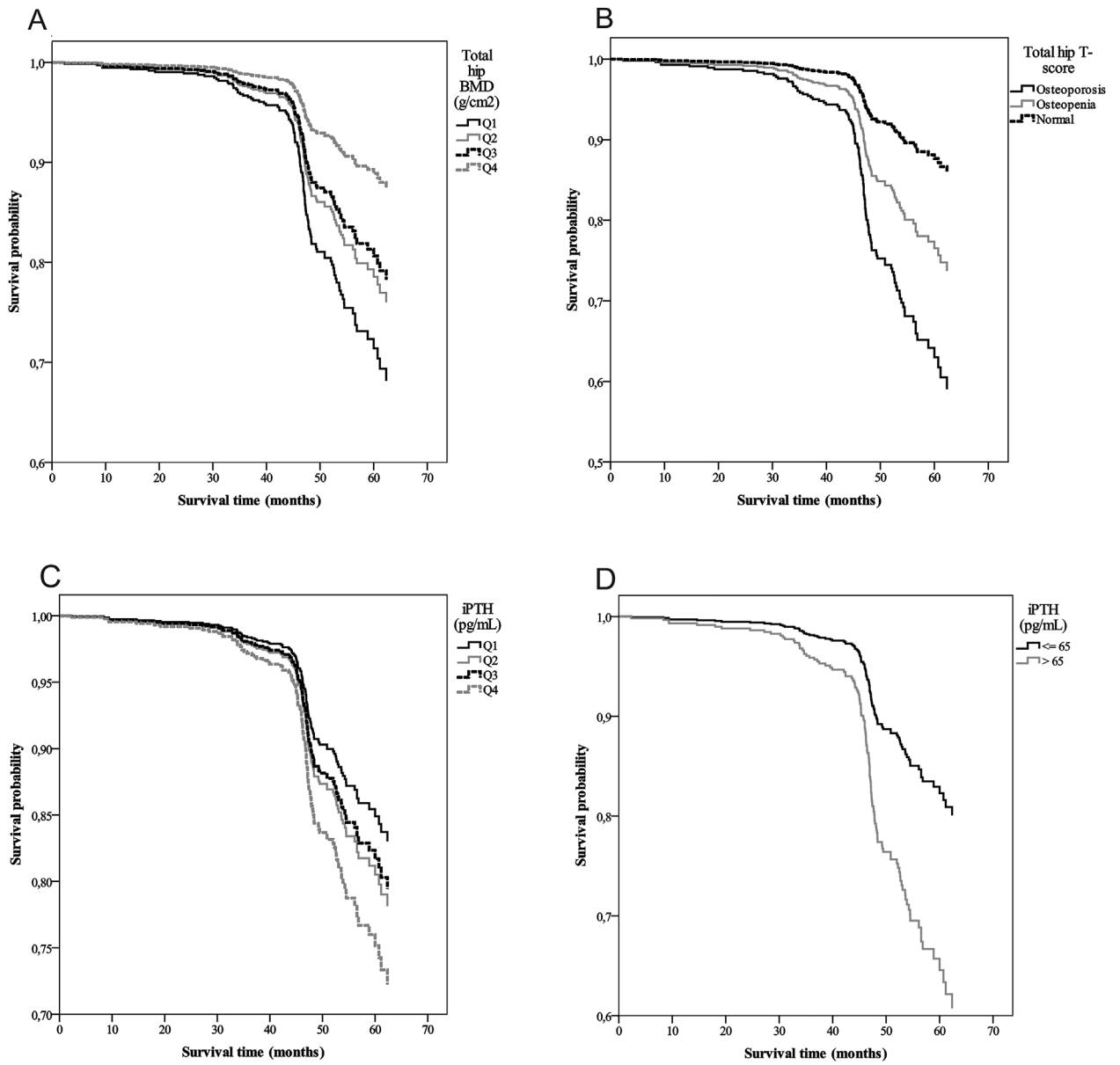


**Fig. 2.** Adjusted survival (Kaplan-Meier) plots for all-cause mortality according to BMD at the total hip and iPTH. Plots are adjusted for age, gender, body mass index, physical activity, recurrent falls, diabetes mellitus, cardiovascular event, osteoporotic fracture, season of blood draw, serum calcium and phosphate, 25OHD and eGFR. (*A*) Total hip BMD by quartiles. Q1 ($<0.728$ g/cm$^2$) versus Q4 (ref: $>0.940$ g/cm$^2$): $p = 0.002$; Q2 (0.728 to 0.831 g/cm$^2$) versus Q4: $p = 0.024$; Q3 (0.832 to 0. 940 g/cm$^2$) versus Q4: $p = 0.053$. (*B*) Total hip BMD by clinical categories. Osteoporosis versus normal (ref): $p < 0.001$; osteopenia versus normal: $p = 0.003$. (*C*) iPTH by quartiles. Q4 ($>49$ pg/mL) versus Q1 (ref: $<26$ pg/mL): $p = 0.037$; Q3 (36 to 49 pg/mL) versus Q1: $p = 0.459$; Q2 (26 to 35 pg/mL) versus Q1: $p = 0.334$. (*D*) iPTH by clinical categories. $>65$ pg/mL versus $\leq 65$ pg/mL: $p = 0.001$. BMD = bone mineral density; iPTH = intact parathyroid hormone; eGFR = estimated glomerular filtration rate.

D supplementation, bisphosphonate use, primary hyperparathyroidism, and chronic renal disease may hamper interpretation and misrepresent the influence of the pivotal role of PTH and BMD in mortality in the elderly population. Finally, we investigated a more comprehensive set of risk factors, including laboratory and BMD parameters, than those examined in other cohorts.[8,9,12,21,22]

Low proximal femoral BMD was found to be associated with an increased subsequent risk of death from all causes after controlling for age and other potential confounding factors. Several studies have found that baseline BMD is inversely related to subsequent mortality in elderly women and men.[7–9,11,12,34] Further, in a large cohort of white women 65 years of age and older, a greater decline in BMD was associated with increased mortality from all causes and CVD, regardless of initial BMD.[35]

The mechanism of this association is unknown. Studies in the elderly population have found a significant relationship between osteoporosis and mortality in excess, mostly caused by CVD/atherosclerotic diseases[35,36] and frailty syndrome.[37] Beyond the potential cardiovascular confounders, when studying BMD in relation to mortality, it is important to thoroughly

**Table 5.** Risk Factors Predictive of Cardiovascular Mortality in Community-Dwelling Older Adults From the SPAH Study Population, According the Multivariate Models

| Risk factors | HR[a] | 95% CI | *p* |
|---|---|---|---|
| Age (per 5-year increase) | 1.51 | 1.18–1.95 | 0.001 |
| Male sex | 2.00 | 1.05–3.85 | 0.030 |
| Low physical activity score | 2.08 | 1.10–4.00 | 0.024 |
| Diabetes mellitus | 2.25 | 1.24–4.08 | 0.007 |
| Any previous cardiovascular event[b] | 2.16 | 1.21–3.86 | 0.010 |
| iPTH (per 10-pg/mL increase) | 1.07 | 1.04–1.10 | <0.001 |

HR = hazard ratio; iPTH = intact parathyroid hormone; eGFR = estimated glomerular filtration rate; BMD = bone mineral density.

[a]Adjusted for the other variables from the model [BMI (HR 1.00; 95% CI, 0.92–1.09; $p = 0.977$), previous fracture (HR 1.24; 95% CI, 0.53–2.88; $p = 0.620$), hypertension (HR 1.55; 95% CI, 0.71–3.36; $p = 0.270$), eGFR (HR 1.01; 95% CI, 0.99–1.02; $p = 0.266$), 25OHD (HR 1.01; 95% CI, 0.97–1.03; $p = 0.806$), total femur BMD (HR 1.26; 95% CI, 0.16–10.0; $p = 0.825$)], plus season (HR 0.96; 95% CI, 0.42–2.22; $p = 0.929$), serum calcium (HR 0.59; 95% CI, 0.32–1.10; $p = 0.096$), phosphorus (HR 1.29; 95% CI, 0.75–2.28, $p = 0.758$).

[b]Myocardial infarction, stroke, or instable angina.

investigate whether a low BMD is not merely a marker of underlying illness.[11,12] A very ill person will undertake less physical activity, resulting in a lower BMD. In the SPAH population, however, two important parameters related to frailty (low physical activity score and recurrent falls) were predictors of mortality risk, independent of BMD. Other components of the frailty syndrome, such as low appendicular muscle mass and a history of clinical fractures, were not significantly associated with death in this population, most likely because they are confounders for the association between BMD and mortality. In fact, baseline hip and humerus fractures increased the unadjusted risk of overall mortality, but this association was altered by adjustment for BMD. Nevertheless, we did not specifically evaluate the lower limb disability index or self-assessed poor health, which are more precise markers of fragility. Moreover, the relationship between BMD and all-cause mortality was stronger than the relationship between BMD and cardiovascular deaths, although the borderline significance of the risk ratios for cardiovascular death according to the stratification by *T*-score (osteopenia or osteoporosis) might be related to the limited size of the sample, particularly the number of cardiovascular deaths. Analyzed as a group, the subjects with low bone mass (*T*-score $< -1$) had an increased risk of cardiovascular death compared with those with normal BMD. Consequently, further in vitro and in vivo research is needed to determine whether a biological mechanism exists for an independent association between BMD and mortality or whether BMD is a nonspecific indicator of frailty, ill health, or other comorbidities.

Studies investigating the association between circulating PTH and the death risk in elderly persons living in the community are scarce.[15,21,22] Here, we described the prospective association between plasma PTH and all-cause and cardiovascular mortality in a community-based sample. Moreover, our data confirmed two previous studies reporting that higher plasma PTH was associated with a higher incidence of death, even in individuals with PTH in the normal range.[15,22]

Several mechanisms have been proposed to explain the link between PTH and mortality, such as atherogenesis via vascular calcification,[38] the induction of left ventricular hypertrophy,[18,19] renal dysfunction,[39] and noncalcemic effects such as direct effects on vascular smooth muscle cells[40] and impaired myocardial energy utilization.[41] In this study, after adjustment for established cardiovascular risk factors and factors related to mineral homeostasis (including calcium, phosphorus, vitamin D levels, and renal function) in the SPAH study, PTH remained associated with a greater risk of overall and cardiovascular mortality, suggesting that confounding from these factors seems not to explain our findings. However, although no major confounding was detected in our multivariable model, we cannot rule out the possibility of residual confounding from unmeasured factors.

To date, there is no evidence that reducing PTH levels will decrease cardiovascular risk in the general population. Because our study was observational, our results do not allow us to fully determine whether PTH per se is a causal factor or to provide a direct benefit of a reduction of PTH levels. However, the results emphasize that further interventional studies are necessary to examine whether a reduction in PTH levels corresponds to a reduction in cardiovascular events in the community.

Although the lowest quartile of 25OHD levels (<13 ng/mL) was associated with mortality risk in the unadjusted analyses, the multivariate model showed no significant association between 25OHD levels and the risk of all-cause mortality in this cohort, regardless of whether 25OHD was analyzed as quartiles, as clinical categories, or as a continuous variable. This finding contrasts with recent large population-based studies[42–45] in which lower 25OHD levels were related to a higher mortality risk. A Mendelian randomization analysis of three large Danish cohorts including a impressive number of 95,766 participants suggested that genetically low plasma 25OHD concentrations (lower than 20 nmol/L, that is equivalent to 8 ng/mL) were associated with increased all-cause mortality.[46] These divergent results might be explained by some differences between the current study and previous reports. First, if the association between vitamin D status and mortality could be driven by subjects with 25OHD levels in this extremely low range (<10 ng/mL), we may not have had the ability to detect an effect because of the limited number of individuals with very low 25OHD levels (<20%). Second, unlike some studies,[42,47] in the SPAH population serum 25OHD was measured using a radioimmunoassay that is considered to overestimate the 25OHD level because the antibody used in the assay also binds 24,25-dihydroxyvitamin D; this limitation could influence the results toward the null hypothesis. Third, unlike some studies that included people with physical disabilities and thus reduced mobility,[14] the SPAH study included only well-functioning older subjects, many of whom still held jobs that required sun exposure, which may have been related to higher 25OHD levels. Alternatively, it may be that the limited size of the sample reduced the study's statistical power to detect the association between vitamin D status and mortality. Even though, our finding of non-association between lower 25OHD concentrations and cardiovascular mortality is similar to results of the recent Danish cohort study with sufficient statistical power to detect an association of vitamin D and cardiovascular deaths.[46]

Higher iPTH levels are most likely due to low vitamin D levels and/or impaired renal function. Nevertheless, the relationship between PTH and 25OHD levels is complex, and there is a modest association between these hormones.[22] In our data, 25OHD levels were not retained in the final multivariate models after adjustment for other confounders, including BMD and PTH.

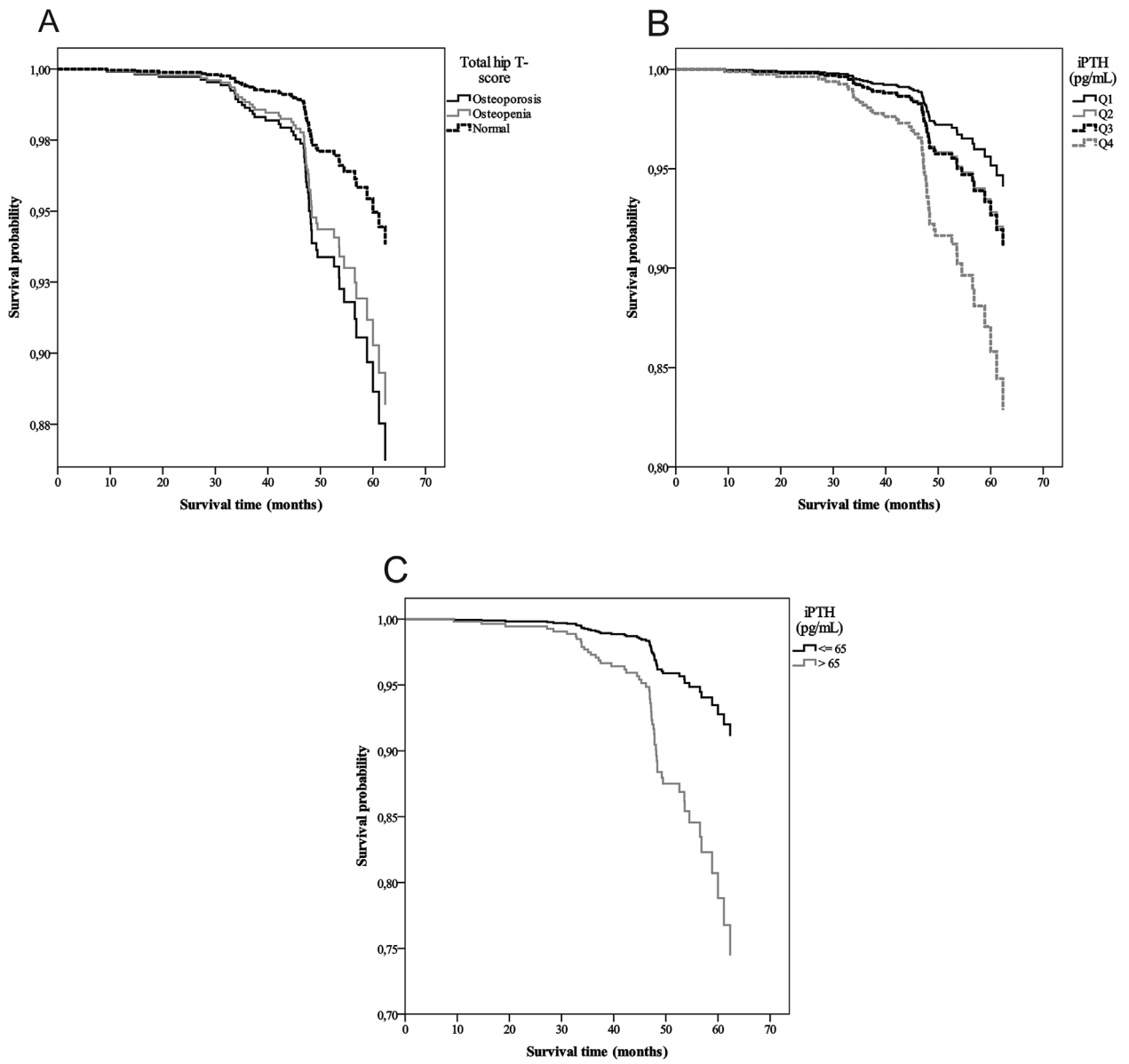


**Fig. 3.** Adjusted survival (Kaplan-Meier) plots for cardiovascular mortality according to BMD at the total hip and iPTH. Plots are adjusted for age, gender, body mass index, physical activity, recurrent falls, diabetes mellitus, cardiovascular event, osteoporotic fracture, season of blood draw, serum calcium and phosphate, 25OHD, and eGFR. (*A*) Total hip BMD by clinical categories. Osteoporosis versus normal (ref): $p = 0.091$; osteopenia versus normal: $p = 0.054$. (*B*) iPTH by quartiles. Q4 (>49 pg/mL) versus Q1 (ref: <26 pg/mL): $p = 0.007$; Q3 (36 to 49 pg/mL) versus Q1: $p = 0.366$; Q2 (26 to 35 pg/mL) versus Q1: $p = 0.399$. (*C*) iPTH by clinical categories. >65 pg/mL versus ≤65 pg/mL: $p = 0.001$. BMD = bone mineral density; iPTH = intact parathyroid hormone; eGFR = estimated glomerular filtration rate.

Even after excluding those individuals of lower levels of 25OHD and eGFR in this cohort, PTH remained as an independent predictor of mortality, suggesting that PTH may be a more important risk factor for mortality or may even mediate the relationship between 25OHD and mortality.

Limitations of the study include the limited sample size and the exclusion of individuals from the original SPAH cohort who were not known to be alive at the time of the censoring analysis. Moreover, plasma PTH levels and other variables involved in bone metabolism were measured only at the baseline assessment, and it is unclear how well a single measurement reflects the PTH levels during the follow-up.

In conclusion, this study showed that low BMD at the hip and higher plasma levels of PTH, but not vitamin D levels per se, were predictors of all-cause and cardiovascular mortality in healthy community-dwelling older adults, independent of vitamin D status, renal function, bone mass, and comorbidities. Taken together, these findings support the notion that more attention should be paid to these factors in clinical practice to improve the management of the elderly population.

## Disclosures

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Authors' roles: Study design: DSD, CPF, JBL, and RMRP. Study conduct: DSD, LGM, CPF, JBL, and RMRP. Data collection: DSD, LGM, CPF, JBL, VFC, and RMO. Data analysis: DSD and RMRP. Data interpretation: DSD, LGM, RMO, and RMRP. Drafting manuscript: DSD and RMRP. Revising manuscript content: DSD, LGM, MRM, and RMRP. Approving final version of manuscript and revised manuscript: DSD, LGM, CPF, JBL, VFC, RMO, MS, MRM, and RMRP. RMRP takes responsibility for the integrity of the data analysis.

## References

1. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O; European Vertebral Osteoporosis Study. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int. 2003;14(1):61–8.
2. Lopes JB, Fung LK, Cha CC, et al. The impact of asymptomatic vertebral fractures on quality of life in older community-dwelling women: the Sao Paulo Ageing & Health Study. Clinics (Sao Paulo). 2012;67(12):1401–6.
3. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med. 1998;128(10):793–800.
4. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. J Bone Miner Res. 2005;20(8):1349–55.
5. Melton LJ 3rd, Achenbach SJ, Atkinson EJ, Therneau TM, Amin S. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. Osteoporos Int. 2013;24(5):1689–96.
6. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ. 2009;181(5):265–71.
7. 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.
8. Van Der Klift M, Pols HA, Geleijnse JM, Van Der Kuip DA, Hofman A, De Laet CE. Bone mineral density and mortality in elderly men and women: the Rotterdam Study. Bone. 2002;30(4):643–8.
9. Pinheiro MM, Castro CM, Szejnfeld VL. Low femoral bone mineral density and quantitative ultrasound are risk factors for new osteoporotic fracture and total and cardiovascular mortality: a 5-year population-based study of Brazilian elderly women. J Gerontol A Biol Sci Med Sci. 2006;61(2):196–203.
10. Trivedi DP, Khaw KT. Bone mineral density at the hip predicts mortality in elderly men. Osteoporos Int. 2001;12(4):259–65.
11. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. Lancet. 1991;338(8763):355–8.
12. Mussolino ME, Gillum RF. Low bone mineral density and mortality in men and women: the Third National Health and Nutrition Examination Survey linked mortality file. Ann Epidemiol. 2008;18(11):847–50.
13. 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.
14. Sambrook PN, Chen JS, March LM, et al. Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin D status, bone mass, and renal function in the frail and very old: a cohort study. J Clin Endocrinol Metab. 2004;89(11):5477–81.
15. Hagström E, Hellman P, Larsson TE, et al. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. Circulation. 2009;119(21):2765–71.
16. Richart T, Li Y, Staessen JA. Renal versus extrarenal activation of vitamin D in relation to atherosclerosis, arterial stiffening, and hypertension. Am J Hypertens. 2007;20(9):1007–15.
17. Cardus A, Panizo S, Encinas M, et al. 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. Atherosclerosis. 2009;204(1):85–9.
18. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J. 2003;24(22):2054–60.
19. Schluter KD, Piper HM. Trophic effects of catecholamines and parathyroid hormone on adult ventricular cardiomyocytes. Am J Physiol. 1992;263(6 Pt 2):H1739–46.
20. Jorde R, Sundsfjord J, Haug E, Bonaa KH. Relation between low calcium intake, parathyroid hormone, and blood pressure. Hypertension. 2000;35(5):1154–9.
21. Jassal SK, Chonchol M, von Muhlen D, Smits G, Barrett-Connor E. Vitamin D, parathyroid hormone, and cardiovascular mortality in older adults: the Rancho Bernardo study. Am J Med. 2010;123(12):1114–20.
22. Cawthon PM, Parimi N, Barrett-Connor E, et al. Osteoporotic Fractures in Men (MrOS) Research Group. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. J Clin Endocrinol Metab. 2010;95(10):4625–34.
23. Lopes JB, Danilevicius CF, Takayama L, et al. Prevalence and risk factors of radiographic vertebral fracture in Brazilian community-dwelling elderly. Osteoporos Int. 2011;22(2):711–9.
24. Lopes JB, Figueiredo CP, Caparbo VF, et al. Osteoporotic fractures in the Brazilian community-dwelling elderly: prevalence and risk factors. J Clin Densitom. 2011;14(3):359–66.
25. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137–48.
26. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
27. Lipschitz DA. Screening for nutritional status in the elderly. Prim Care. 1994;21:55–67.
28. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol

Metab. 2011;96(7):1911–30. Erratum in: J Clin Endocrinol Metab. 2011;96(12):3908.

29. Boudou P, Ibrahim F, Cormier C, Chabas A, Sarfati E, Souberbielle JC. Third- or second-generation parathyroid hormone assays: a remaining debate in the diagnosis of primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90:6370–2.
30. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9(8):1137–41.
31. Domiciano DS, Figueiredo CP, Lopes JB, et al. Discriminating sarcopenia in community-dwelling older women with high frequency of overweight/obesity: the São Paulo Ageing & Health Study (SPAH). Osteoporos Int. 2013;24(2):595–603.
32. Figueiredo CP, Domiciano DS, Lopes JB, et al. Prevalence of sarcopenia and associated risk factors by two diagnostic criteria in community-dwelling older men: the São Paulo Ageing & Health Study (SPAH). Osteoporos Int. 2014;25(2):589–96.
33. Instituto Brasileiro de Geografia e Estatística (IBGE). Censo Demográfico 2010 [Internet]. [cited 2016 Feb 10]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/censo2010.
34. Johansson H, Odén A, Kanis J, et al. Low bone mineral density is associated with increased mortality in elderly men: MrOS Sweden. Osteoporos Int. 2011;22(5):1411–8.
35. 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;15:1974–80.
36. Sinnott B, Syed I, Sevrukov A, Barengolts E. Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. Calcif Tissue Int. 2006;78:195–202.
37. Johansson C, Black D, Johnell O, Oden A, Mellstrom D. Bone mineral density is a predictor of survival. Calcif Tissue Int. 1998;63:190–6.
38. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates endothelial expression of atherosclerotic parameters through protein kinase pathways. Am J Physiol Renal Physiol. 2007;292:F1215–8.
39. Vassalotti JA, Uribarri J, Chen SC, et al. Trends in mineral metabolism: Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis. 2008;51:S56–68.
40. Wang R, Wu L, Karpinski E, Pang PK. The changes in contractile status of single vascular smooth muscle cells and ventricular cells induced by bPTH- (1–34). Life Sci. 1993;52:793–801.
41. Baczynski R, Massry SG, Kohan R, Magott M, Saglikes Y, Brautbar N. Effect of parathyroid hormone on myocardial energy metabolism in the rat. Kidney Int. 1985;27:718–25.
42. Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med. 2008;168:1629–37.
43. Semba RD, Houston DK, Bandinelli S, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. Eur J Clin Nutr. 2010;64(2):203–9.
44. Semba RD, Houston DK, Ferrucci L, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. Nutr Res. 2009;29(8):525–30.
45. Kestenbaum B, Katz R, de Boer I, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. J Am Coll Cardiol. 2011;58(14):1433–41.
46. Afzal S, Brøndum-Jacobsen P, Bojesen SE, Nordestgaard BG. Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. BMJ. 2014;349:g6330.
47. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167(11):1159–65.