Longitudinal Assessment of PTH in Community-Dwelling Older Women—Elevations Are Not Associated With Mortality

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Context: In older women, the magnitude of elevated parathyroid hormone (PTH) and its consequence is unclear.

Objective: To describe normal PTH profiles over time and the association with mortality.

Design and Participants: There were 1044 community-dwelling women in the Malmö Osteoporosis Prospective Risk Assessment cohort (OPRA) who attended baseline (age 75 years). Follow-ups were attended by 715 (age 80 years) and 382 (age 85 years).

Main Outcome Measures: PTH, estimated glomerular filtration rate (eGFR), 25-hydroxyvitamin D (25OHD) and mortality.

Results: At age 75 years, PTH levels for most (n = 877, 88%) were within the normal reference range (NRR) (i.e., <6.9 pmol/L). Longitudinally, between ages 75 and 80 years, PTH increased in 60% of all women (n = 390) but increases of up to 50% above baseline values (64%; n=250) still resulted in PTH levels within the NRR. These women had lower 25OHD levels (74 vs 83 nmol/L, P = 0.001). Only when increases were >50% was PTH elevated beyond the NRR (mean 7.1 ± 3.3). Here, a pronounced decline in eGFR (56 vs 61 mL/min/1.73 m², P = 0.002) was found, despite no further changes in 25OHD. Extending the observational period until age 85 years gave similar results. Baseline PTH levels above NRR were associated with mortality (hazard ratio, 1.4; 95% confidence interval (CI), 1.1-1.8; P = 0.007), although not after adjustment for covariates (P = 0.082).

Conclusions: Most women remained within normal PTH ranges despite large increases of up to 50%. PTH elevated above normal is not independently associated with mortality; impaired kidney function and low 25OHD status may be more prognostic in the very old.

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Freeform/Key Words: PTH, elderly women, kidney function, vitamin D, mortality

Abbreviations: 25OHD, serum 25-hydroxyvitamin D; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NRR, normal reference range; OPRA, Malmö Osteoporosis Prospective Risk Assessment; PTH, parathyroid hormone.
Although having a major role in calcium and phosphate homeostasis and being vital for bone health, we still lack a complete understanding of age-related changes in parathyroid hormone (PTH) and serum 25-hydroxyvitamin D (25OHD). Vitamin D is the major factor determining PTH levels in healthy adults [1]; furthermore, both PTH and vitamin D are closely linked to kidney function. PTH increases as kidney function declines, whereas vitamin D decreases [2, 3]. Given this relationship, chronic kidney disease (CKD) and vitamin D insufficiency [4, 5] are common with increasing age, and both are associated with increased mortality in older women [6, 7]. Studies also suggest that PTH itself is associated with cardiovascular disease risk [8, 9] and mortality [10]. Although an increase in serum PTH may lead to serious health implications, the influence of aging on PTH levels is not fully understood.

Thus, our understanding of the age-related changes in serum PTH levels, how to interpret PTH values overall, the relationship to standard reference ranges, and what can be considered normal or abnormal in older or very old women is clearly limited and warrants further investigation. Furthermore, no prospective study has yet investigated the association between PTH and mortality in such older women, an important omission because discrepancies between the sexes have been observed (e.g., an increased overall and cardiovascular mortality risk have been found with increased PTH in older men, but not in older women) [11].

The longitudinal population-based Malmö Osteoporosis Prospective Risk Assessment (OPRA) cohort of 1044 women, all aged 75 years at baseline and followed for up to 15 years with reassessments at ages 80 and 85 years, provides the possibility to understand the normal distribution of PTH levels over time in older community-dwelling women and whether PTH is associated with overall mortality risk.

The aim of the study is first to describe, in 75-year-old women, changes in PTH levels over time; second to evaluate the extent to which PTH levels and change in PTH levels are related to kidney function and vitamin D status; and finally to evaluate if elevated PTH is independently associated with mortality or reflects the interplay of poor kidney function and vitamin D insufficiency.

1. Subjects and Methods

A. Cohort

This study was performed in the OPRA cohort [12]. In brief, 1044 participants attended at baseline (1995 to 1999). They all were 75 years old at invitation and prospectively followed until 2012. The 5- and 10-year follow-ups were attended by 715 (age 80 years) and 382 women (age 85 years).

Collection of blood and serum, anthropometrics, and administration of a detailed lifestyle questionnaire were performed at all visits. Information on comorbidities was only available at 5-year follow up [7]. Date of death (but not cause) was available through the Swedish National Population Register (to a maximum of 91.5 years; October 2012).

Written informed consent was obtained from all participants, and the Regional Ethical Review Board in Lund approved the study, which was performed according to the principles of the Declaration of Helsinki.

B. Blood Biochemistry

Analyses for calcium, phosphate, and all biomarkers were performed at the Department of Clinical Chemistry, Malmö, Skåne University Hospital [13].

Serum PTH was measured using the Elecsys/Cobas PTH immunoassay (Roche Diagnostics, Mannheim, Germany) at baseline and 10 years [intra-assay coefficient of variability (CV) 1.6% to 7%]. At 5 years, measurements were performed using the Immulite 2000 Immunoassay Systems (Siemens Diagnostics, Eschborn, Germany) (intra-assay CV 5% to 7%). To ensure comparability between methods, duplicate measurements were performed, and adjustments were made. Normal PTH range is 1.6 to 6.9 pmol/L. Serum PTH was
available for 999 (75-year-old women), 692 (80-year-old women), and 348 (85-year-old women) participants. 25OHD (nmol/L) was assayed by liquid chromatography mass spectrophotometry linked to a high performance liquid chromatography (HPLC) system (previously described in Buchebner et al. [12]). 25OHD was available for 1011 (75-year-old women), 642 (80-year-old women) and 348 (85-year-old women) participants. Plasma creatinine [isotope dilution mass spectrometry (IDMS) traceable] and cystatin C were analyzed at all time points [6]. Estimated glomerular filtration rate (eGFR) used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for women based on cystatin C and creatinine [14] and was available for 963 (75-year-old women), 683 (80-year-old women) and 355 (85-year-old women) participants. We defined stages 3b through 5 (eGFR <45 mL/min/1.73 m²) as substantial impairment of kidney function [15].

C. Statistical Analyses

PTH data were approximately normally distributed, and vitamin D was normally distributed (Shapiro-Wilks test). PTH was used as a continuous variable, or categorized into quartiles (with quartile 1 as the lowest and quartile 4 as the highest).

Change in PTH concentration was calculated between ages 75 to 80 and 75 to 85 years. Individuals were then categorized according to whether PTH had remained stable/decreased or increased. PTH changes <1% were considered stable. To capture PTH increases within the normal range, additional analyses used percentage increases (1% to 10%, 11% to 20%, 21% to 30%, 31% to 40%, 41% to 50%, or >50%). Women with suspected primary/secondary hyperparathyroidism were not excluded because the cause of PTH elevation was not clinically confirmed. Primary hyperparathyroidism was suspected with normal kidney function (CKD stage 1 or 2) and sufficient 25OHD (>50 nmol/L) (n = 23 at 75 years; n = 24 at 80 years). Secondary hyperparathyroidism was assumed with substantially impaired kidney function (CKD stages 3b or 5) and 25OHD insufficiency (<50 nmol/L) (n = 4 at 75 years; n = 8 at 80 years).

Correlations between PTH, 25OHD, calcium, phosphate, body mass index, and smoking were estimated by Pearson correlation coefficient ($r$).

The relationship between PTH and mortality was investigated using Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Model 1 estimated mortality risk between women with PTH levels within the normal range (1.6 to 6.9 pmol/L) compared with women with PTH elevated to >6.9 pmol/L (reference category, normal range PTH). Model 2 used PTH quartiles (reference, quartile 1). HRs are presented unadjusted and adjusted for 25OHD, kidney function, phosphate, smoking, and comorbidities (only age 80 years) and calcium and vitamin D supplementation (n = 91 at baseline).

All analyses were performed using SPSS v22 (SPSS, Inc., Chicago, IL). $P$ values <0.05 were considered nominally significant.

2. Results

The biochemistry profiles of OPRA participants are shown in Table 1. PTH increased and eGFR decreased over time. The correlation between PTH and eGFR was similar at age 75 and 80 years ($r = -0.22$ and $r = -0.26$, $P < 0.001$), as was 25OHD ($r = -0.22$ and $r = -0.21$, $P < 0.001$) and body mass index ($r = 0.13$, $P < 0.001$ and $r = 0.08$, $P = 0.045$), respectively. Unexpectedly, PTH and calcium were not correlated, whereas PTH, smoking, and phosphate only correlated at age 80 years (Supplemental Appendix Table 1).

There were 715 women (69%) who attended the 5-year visit at age 80 years, 224 women (21%) who did not come to the follow-up visit because of various reasons, and 105 women (10%) died during the first 5 years of follow-up.

At age 85 years, 382 women (37%) of the initial cohort remained in the study, 353 (34%) did not come, and 309 women (29%) had died prior to the final examination. This has previously been described in more detail [6]. The cause of death of the participants was unknown.
Women who were alive at age 85 years had lower PTH levels than women who had died during follow-up (4.5 vs 4.9 pmol/L; \( P = 0.024 \)), and kidney function was better (71 vs 65 mL/min/1.73 m\(^2\); \( P < 0.001 \)), and 25OHD levels were higher (64 vs 59 nmol/L; \( P = 0.002 \)), respectively. Calcium levels however did not differ.

A. Normal Distribution of PTH Levels in Women at Age 75 and 80 Years

At age 75 years, most women (88%, \( n = 877 \)) had PTH within the normal reference range (NRR) (1.6 to 6.9 pmol/L). PTH levels <1.6 pmol/L were observed in 13 women; their eGFR, 25OHD, and phosphate were similar to those with PTH in the NRR (\( P = 0.24 \) to 0.53).

The remainder (11%) had PTH elevated above the NRR, and these women had lower eGFR (60 vs 70 mL/min/1.73 m\(^2\), \( P < 0.001 \)) and 25OHD (54 vs 63 nmol/L, \( P < 0.001 \)) than women with normal PTH, respectively (Table 2; Supplemental Appendix Table 2).

By age 80 years, most women still exhibited PTH in the NRR (74%, \( n = 512 \)). PTH below the NRR was detected in 47 women (7%), with eGFR, 25OHD, and phosphate similar to women with NRR PTH (\( P = 0.24 \) to 0.53). The proportion of women with PTH elevated above the NRR was almost doubled (19%), with lower eGFR (53 vs 63 mL/min/1.73 m\(^2\), \( P < 0.001 \)) and 25OHD (54 vs 63 nmol/L, \( P < 0.001 \)) than women with normal PTH, respectively. Contrary to the observations at 75 years, phosphate was also lower (1.06 vs 1.10 mmol/L, \( P = 0.004 \)) (Table 2; Supplemental Appendix Table 2). By age 85 years, the distribution was similar, with 76% within the NRR and 19% above the NRR.

B. Longitudinal PTH Change in Older Women

To explore PTH change at the individual level, we evaluated only those with longitudinal data available over 5 (\( n = 646 \)) or 10 years (\( n = 333 \)).

B-1. Longitudinal PTH change 75 to 80 years (i.e., 5 years)

At age 80 years, PTH had increased in 60% (\( n = 390 \)) of subjects over the 5-year period. Even so, most (64%; \( n = 250 \)) remained within the NRR despite PTH increases of up to 50% above baseline values (Table 3). These women had significantly lower 25OHD (74 \( \pm \) 29 vs 83 \( \pm \) 32 nmol/L, respectively; \( P = 0.001 \)) than those with stable PTH; however, eGFR, phosphate, and calcium remained unaltered (\( P = 0.07 \) to 0.88).

For those women with PTH increases of \( \geq \)50% compared with baseline (36%), mean PTH was now above the NRR (7.1 \( \pm \) 3.3 pmol/L). This elevation was associated with reduced kidney function (eGFR 56 \( \pm \) 15 vs 61 \( \pm \) 15 mL/min/1.73 m\(^2\), \( P = 0.002 \)) but no further reduction in
25OHD (77 ± 27 vs 74 ± 29 nmol/L, \( P = 0.31 \)) when compared with women whose PTH only increased by up to 50%, respectively. Phosphate and calcium remained unaltered (\( P = 0.23 \) to 0.99).

B-2. Longitudinal PTH change 75 to 85 years (i.e., 10 years)

Extending the observational period, half of the women at age 85 years had stable or decreased PTH levels (51%; \( n = 169 \)). Among those women whose PTH had increased with aging, we again observed that most (64%; \( n = 105 \)) remained within the NRR despite increases of up to 50% above baseline values. For the women with increases of >50% above baseline (36%), this resulted in a PTH concentration well above the NRR (mean, 9.5 ± 6.0 pmol/L) and considerably higher than the mean at age 75 years (Table 3). Associations to 25OHD, eGFR, calcium, and phosphate were similar to the first 5 years of follow-up.

C. PTH and Mortality

Finally, we investigated the association between PTH (normal vs elevated; quartiles), age, and mortality.

Measured at age 75 years, women with PTH elevated above the NRR had a higher mortality risk (HR, 1.4; 95% CI, 1.1 to 1.8; \( P = 0.007 \)). This increased risk remained after adjusting individually for smoking (HR, 1.5; 95% CI, 1.1 to 2.0; \( P = 0.003 \)), phosphate (HR, 1.4; 95% CI, 1.1 to 1.8; \( P = 0.010 \)), 25OHD (HR, 1.3; 95% CI, 1.0 to 1.7; \( P = 0.030 \)), but not eGFR (HR, 1.3; 95% CI, 0.9 to 1.7; \( P = 0.051 \)). With all confounders in the model (HR, 1.3; 95% CI, 0.9 to 1.6; \( P = 0.082 \)), eGFR accounted for the largest contribution to mortality risk [Fig. 1(a); Supplemental Appendix Table 4]. Adjustment for vitamin D and calcium supplementation did not alter the results. Mortality risk did not differ between the lowest and highest quartiles of baseline PTH (HR, 1.0; 95% CI, 0.8 to 1.3) and was essentially unchanged after adjustment.

| Characteristic       | PTH (1.6–6.9 pmol/L) (n = 877) | PTH (>6.9 pmol/L) (n = 109) | \( P \) Value\(^a\) | PTH (1.6–6.9 pmol/L) (n = 512) | PTH (>6.9 pmol/L) (n = 134) | \( P \) Value\(^a\) |
|----------------------|--------------------------------|-----------------------------|---------------------|--------------------------------|-----------------------------|---------------------|
| 25OHD (nmol/L)       | 63 ± 19                        | 54 ± 18                     | <0.001              | 80 ± 30                        | 70 ± 26                     | 0.001               |
| eGFR (mL/min/1.73 m\(^2\)) | 70 ± 15                 | 60 ± 17                     | <0.001              | 63 ± 13                        | 53 ± 16                     | <0.001              |
| Calcium (mmol/L)     | 2.4 ± 0.7                      | 2.4 ± 0.9                   | 0.193               | 2.4 ± 0.1                      | 2.4 ± 0.1                   | 0.334               |
| Phosphate (mmol/L)   | 1.12 ± 0.19                    | 1.13 ± 0.20                 | 0.765               | 1.10 ± 0.15                    | 1.06 ± 0.15                 | 0.004               |
| Height (cm)          | 161 ± 6                        | 160 ± 6                     | 0.539               | 159 ± 6                        | 159 ± 6                     | 0.558               |
| Weight (kg)          | 67 ± 11                        | 71 ± 13                     | 0.002               | 66 ± 11                        | 67 ± 12                     | 0.046               |
| BMI (kg/m\(^2\))     | 26 ± 4                         | 27 ± 5                      | 0.001               | 26 ± 4                         | 27 ± 4                      | 0.074               |
| Current smoker       | 127 ± 14                       | 7 ± 6                       | 0.020               | 58 ± 11                        | 7 ± 5                       | 0.036               |
| No. of comorbidities (80y) |                       |                             |                     |                                |                             |                     |
| None                 | n/a                            | n/a                         |                     |                                |                             |                     |
| One                  | n/a                            | n/a                         |                     |                                |                             |                     |
| Two                  | n/a                            | n/a                         |                     |                                |                             |                     |
| Three or more        | n/a                            | n/a                         |                     |                                |                             |                     |
| No. dead between 75 and 80 y |                       |                             |                     |                                |                             |                     |
| 75 and 80 y          | 72 (8)                         | 13 (12)                     | 0.194               | n/a                            | n/a                         |                     |
| 80 and 85 y          | n/a                            | n/a                         |                     |                                |                             |                     |

Values are mean ± standard deviation except for current smoker, number of comorbidities, and number dead, which are No. of cases (%). Information on comorbidities not available at age 75 years.

Abbreviations: BMI, body mass index; n/a, not applicable.

\(^a\) \( P \) value calculated using Pearson \( \chi^2 \) test, making comparison between PTH levels 1.6 to 6.9 vs >6.9 pmol/L.
Regarding PTH measured at 80 years, even at this older age, mortality risk did not differ with PTH level (unadjusted HR, 1.0; 95% CI, 0.7 to 1.2) or after adjustment (adjusted HR, 0.8; 95% CI, 0.6 to 1.1) [Fig. 1(b)]. Analyzing PTH quartiles, the results were largely similar.

To determine whether increasing PTH rather than an elevated PTH concentration per se was predictive of mortality, we analyzed only women with longitudinal 5-year data available (n = 646).

At the broadest level, we compared women with stable PTH with those with increased levels. Among women whose PTH levels had increased over 5 years of observation, mortality risk was 50% higher than women whose levels had remained stable (unadjusted HR, 1.5; 95% CI, 1.2 to 1.9; P = 0.001). As before, adjustment for 25OHD, eGFR, phosphate, and smoking abolished the association (adjusted HR, 1.1; 95% CI, 0.8 to 1.4). Quartile analysis gave approximately the same results (not shown).

We then looked closer at women whose PTH levels had increased, analyzing them by 10% increments. Mortality risk did not differ between the groups. Even for the women with PTH increases of >50% above baseline, mortality risk was not significantly different (unadjusted HR, 1.2; 95% CI, 0.8 to 1.6 and adjusted HR, 1.0; 95% CI, 0.7 to 1.4).

Table 3. Longitudinal Change in PTH Levels Over 5 and 10 Years With Increases Presented in Increments up to 250%

| Change in PTH Over Time | PTH Stabile/Decreased | PTH Increased 1%–10% | PTH Increased 11%–20% | PTH Increased 21%–30% | PTH Increased 31%–40% | PTH Increased 41%–50% | PTH Increased 1%–50% | PTH Increased 51% |
|-------------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-------------------|
| Over 5 y (i.e., between 75 and 80 y) (n = 646) | No. (%) 256 (40) 59 (9) 56 (8) 46 (7) 44 (7) 45 (7) 250 (38) 140 (22) | 3.5 ± 1.8 4.9 ± 2.0 5.3 ± 2.0 6.0 ± 2.8 5.4 ± 2.7 5.7 ± 1.8 5.5 ± 2.6 7.1 ± 3.38 |
| Over 10 y (i.e., between 75 and 85 y) (n = 333) | No. (%) 169 (51) 26 (8) 32 (9) 21 (6) 16 (5) 10 (3) 105 (31) 59 (18) | 3.3 ± 1.7 4.6 ± 2.3 5.3 ± 1.7 5.6 ± 2.0 5.8 ± 2.0 6.3 ± 1.6 5.5 ± 2.0 9.5 ± 6.08 |

Numbers are based on women who attended both visits at ages 75 and 80 years. PTH levels in picomole per liter. Reported values are No. (%) or mean ± standard deviation.

*Mean PTH levels are elevated beyond the normal range.

Regarding PTH measured at 80 years, even at this older age, mortality risk did not differ with PTH level (unadjusted HR, 1.0; 95% CI, 0.7 to 1.2) or after adjustment (adjusted HR, 0.8; 95% CI, 0.6 to 1.1) [Fig. 1(b)]. Analyzing PTH quartiles, the results were largely similar.

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### 3. Discussion

To address the knowledge gaps regarding the normal distribution of PTH over time in older women and the relationship between PTH and mortality, we performed this 15-year longitudinal, population-based, observational study in women aged 75 years at commencement. Our principal finding was that the most maintained PTH within normal range during advanced aging. Approximately half of the women had essentially unchanged PTH levels during follow-up until the age of 85 years, whereas even increases up to 50% remained within the normal range. Our second important finding was that PTH was not an independent predictor of mortality, but rather an indicator of impaired health in older women. PTH did become higher with advancing age [16, 17]; notably, however, substantial increases (i.e., >50%) were required to exceed the upper reference range. This indicates the reference interval is applicable in older women; however, less certain is the clinical relevance of this age-related increase.

Understanding the interrelationship between PTH, kidney function, and vitamin D is particularly relevant in older individuals from both a general and bone health perspective. We and others [18, 19] show PTH is inversely correlated to kidney function and vitamin D regardless of age, but we explored this in more depth. In keeping with the tight coupling between them, women whose PTH increased by up to 50%, while remaining within the normal...
Elevated PTH above normal range (i.e., >6.9 pmol/L) was not associated with mortality after adjustment for covariates. (a) PTH measured at age 75 years; maximum follow-up 15 years: using Cox proportional hazards model, HRs were estimated comparing normal vs high PTH levels and adjusted for 25OHD, eGFR, phosphate, and smoking. (b) PTH measured at age 80 years; maximum follow-up 11 years: using Cox proportional hazards model, HRs were estimated comparing normal vs high PTH levels and adjusted for 25OHD, eGFR, phosphate, smoking, and comorbidities. Cum, cumulative.

**Figure 1.** Elevated PTH above normal range (i.e., >6.9 pmol/L) was not associated with mortality after adjustment for covariates. (a) PTH measured at age 75 years; maximum follow-up 15 years: using Cox proportional hazards model, HRs were estimated comparing normal vs high PTH levels and adjusted for 25OHD, eGFR, phosphate, and smoking. (b) PTH measured at age 80 years; maximum follow-up 11 years: using Cox proportional hazards model, HRs were estimated comparing normal vs high PTH levels and adjusted for 25OHD, eGFR, phosphate, smoking, and comorbidities. Cum, cumulative.
range, had lower eGFR and 25OHD. Additional increases, taking PTH to above the normal range, saw a more pronounced decline in eGFR despite no further 25OHD decrease. This suggests loss of kidney function, and impairment of 1α-hydroxylase is the predominant upregulator of PTH in older adults [20]. Primary hyperparathyroidism has been associated with higher body weight, which might contribute to various negative health outcomes [21]. Although no independent association between elevated PTH and mortality was found in this study, women with PTH elevated above the normal range showed a small but significant increase in body weight.

The association between PTH and mortality is inconsistent. Reported associations with all-cause mortality (men and women) [22, 23] and cardiovascular mortality (mostly men) [11] suggest PTH as an independent predictor. We can only speculate that the clinical implications of elevated PTH might, to some extent, be sex-specific. Although the underlying mechanism is unknown, previous research shows that the clinical presentations of primary and secondary hyperparathyroidism differ between men and women. Although men are more likely to be asymptomatic, vitamin D deficiency and impaired kidney function seem to occur more frequently in men. On the other hand, among women, this tends to have a more profound impact on bone metabolism [24–26].

Hagström [9] reported that each standard deviation increase in PTH, even within the normal range, was associated with an almost 40% increase in cardiovascular mortality. Although predominantly including younger subjects, another study in severely frail subjects (mean age, 85 years) reported that even a subtle PTH elevation was associated with increased mortality [27]. In contrast, our study of community-dwelling older women shows that, regardless of assessment age, only PTH elevated above the normal range was associated with all-cause mortality, albeit not independently. Increases within the normal range, even if substantial, were not associated. Notably, the OPRA participants generally had fewer comorbidities, unlike the severely frail hospitalized individuals with a presumed high disease burden in other studies. More importantly, in the interplay between PTH–kidney function–vitamin D status, PTH itself makes a minor contributor to mortality [6, 7], and this study emphasizes the importance of kidney function on mortality risk in older women, seconded by vitamin D status. Subsequently, regarding the clinical implication of elevated PTH in older and very old women, we suggest that the interpretation of elevated PTH should be done in the context of the individuals’ health status, including assessment of kidney function and vitamin D status.

A strength of this study is the 15-year follow up, allowing investigation as the women become frailer with advancing age. We also had full data for 25OHD, eGFR, phosphate, and calcium. The participants were community-dwelling, average healthy older women, thus providing a less confounded interpretation of PTH distribution applicable to general medicine and the relationship with mortality. To our knowledge, no other studies investigating PTH in this age group have comparable sample size, follow-up, or such complete data at multiple time points. Even so, generalizations should be made cautiously [12], and causality cannot be addressed. Limitations are acknowledged. Information on comorbidities was not available at all time points, and cause of death was not available. We did not have access to detailed information on the women’s medication. Although overall the variables in our model explain only a small proportion of the risk of mortality (Supplemental Appendix Table 2), because PTH itself accounts for very little, we assume this is unlikely to change substantially even with the inclusion of multiple other factors and health conditions. Availability of calcitriol would have allowed for a more direct investigation of the association between PTH and vitamin D. Assessment of urine calcium and albumin would have given us a more complete picture of the PTH–calcium–25OHD axis.

In summary, in this population-based, longitudinal observational study of 75-year-old women, PTH increased with advancing age. The study provided insights to PTH profiles and its assumed association with mortality in a very old population. Most participants maintained PTH levels within the normal range despite substantial increases, with only one or two in 10 participants above the normal range. Elevated PTH was not independently associated with...
mortality, but rather a consequence of impaired health, possibly mirroring a state of increased frailty.

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