Plasma Parathyroid Hormone and the Risk of Cardiovascular Mortality in the Community

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Background—Diseases with elevated levels of parathyroid hormone (PTH) such as primary and secondary hyperparathyroidism are associated with increased incidence of cardiovascular disease and death. However, data on the prospective association between circulating PTH levels and cardiovascular mortality in the community are lacking.

Methods and Results—The Uppsala Longitudinal Study of Adult Men (ULSAM), a community-based cohort of elderly men (mean age, 71 years; n=958), was used to investigate the association between plasma PTH and cardiovascular mortality. During follow-up (median, 9.7 years), 117 participants died of cardiovascular causes. In Cox proportional-hazards models adjusted for established cardiovascular risk factors (age, systolic blood pressure, diabetes, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, antihypertensive treatment, lipid-lowering treatment, and history of cardiovascular disease), higher plasma PTH was associated with higher risk for cardiovascular mortality (hazard ratio for 1-SD increase in PTH, 1.38; 95% confidence interval, 1.18 to 1.60; P<0.001). This association remained essentially unaltered in participants without previous cardiovascular disease and in participants with normal PTH (<6.8 pmol/L) with no other signs of a disturbed mineral metabolism (normal serum calcium, 2.2 to 2.6 mmol/L; normal glomerular filtration rate, >50 mL·min⁻¹·1.73 m⁻² and without vitamin D deficiency, plasma 25-OH vitamin D >37.5 nmol/mL). Interestingly, elevated plasma PTH (>5.27 pmol/mL) accounted for 20% (95% confidence interval, 10 to 26) of the population-attributable risk proportion for cardiovascular mortality.

Conclusions—Plasma PTH levels predict cardiovascular mortality in the community, even in individuals with PTH within the normal range. Further studies are warranted to evaluate the clinical implications of measuring PTH in cardiovascular risk prediction and to elucidate whether PTH is a modifiable risk factor. (Circulation. 2009;119:2765-2771.)

Key Words: cardiovascular diseases • mortality • parathyroid hormone • population • prognosis

Parathyroid hormone (PTH) is a key regulator of mineral metabolism, the homeostasis of calcium, phosphate, vitamin D, and bone turnover. Patients with elevated PTH resulting from primary or secondary hyperparathyroidism have been shown to be at higher risk for cardiovascular morbidity and mortality. Multiple lines of evidence from experimental and clinical studies suggest that PTH could be causally involved in pathological processes leading to cardiovascular disease. Moreover, several investigators have reported that other mineral metabolism abnormalities such as vitamin D deficiency, hypercalcemia, hyperphosphatemia, and osteoporosis are associated with higher risk for cardiovascular disease. Still, the prospective association between circulating PTH and incident cardiovascular disease in the community has not been reported.

Clinical Perspective on p 2771

Because PTH is an important regulatory hormone of the mineral metabolism, we hypothesized that higher PTH could be a relevant marker for mineral metabolism abnormalities predisposing to an increased risk for cardiovascular disease. Accordingly, we investigated associations between plasma PTH levels and cardiovascular and all-cause mortality in a large, prospective, community-based cohort of elderly men, with prespecified subgroup analyses in participants without previous cardiovascular disease at baseline and in participants with plasma PTH within the normal range. We also investigated whether the association between plasma PTH and cardiovascular and all-cause mortality was independent of established cardiovascular risk factors and of factors involved in mineral metabolism.
Methods

Study Population

The Uppsala Longitudinal Study of Adult Men (ULSAM) was initiated in 1970. All 50-year-old men born in 1920 to 1924 and living in Uppsala, Sweden, were invited to a health survey focusing on identifying cardiovascular risk factors.16 (described in detail at http://www.pubcare.uu.se/ULSAM). The present analyses are based on the third examination cycle of the ULSAM cohort when participants were ∼71 years of age (1991 to 1995; n = 1221). Of these, 958 participants had valid measurements of plasma PTH and the established cardiovascular risk factors. Analyses were also performed in the following prespecified subgroups: participants without previous cardiovascular disease at baseline (n = 617), participants with plasma PTH within the normal range (<6.8 pmol/L; n = 886), and participants with normal plasma PTH and no other signs of a disturbed mineral metabolism (normal serum calcium [2.2 to 2.6 mmol/L], normal glomerular filtration rate [≥50 mL·min⁻¹·1.73 m²] and without vitamin D deficiency [plasma 25-OH vitamin D >37.5 nmol/L; n = 646]). All participants gave written consent, and the Ethics Committee of Uppsala University approved the study.

Baseline Examinations

At baseline, venous blood samples were drawn after an overnight fast and stored at −70°C until analysis.17 Intact plasma PTH was measured with solid-phase 2-site chemiluminescent immunoenassy with an Immulite 2500 (Diagnostics Product Corporation, Los Angeles, Calif). Serum calcium was measured with spectrophotometry with a complexometric method using orthonitrophosphoric acid. Serum albumin was measured with spectrophotometry using bromine cresol green. Albumin-corrected serum calcium was calculated as follows: serum calcium + 0.019 · (46 − serum albumin). Serum phosphate was measured with spectrophotometry using a complexometric method with ammonium molybdenum. Hitachi 717 or 911 (Hitachi, Tokyo, Japan) was used for biochemical analysis. Plasma 25-OH vitamin D was determined with high-performance liquid chromatography, together with atmospheric pressure chemical ionization and mass spectrometric detector, at Vitas AS, Oslo, Norway (http://www.vitas.no), with an HP 1100 liquid chromatograph (Agilent Technologies, Palo Alto Calif). Serum cystatin C was measured by latex-enhanced reagent (N Latex Cystatin C, Dade Behring, Deerfield, Ill) with a Behring BN ProSpec analyzer (Dade Behring).18 Glomerular filtration rate was calculated from serum cystatin C results (in milligrams per liter) by the following formula: y = 77.24 + 2.622, which has been shown to be closely correlated with iohexol clearance.19 Renal dysfunction was defined as glomerular filtration rate <50 mL·min⁻¹·1.73 m² according to the current definition used in clinical practice in Sweden for individuals >50 years of age. Fasting plasma glucose and serum cholesterol values were measured by routine laboratory analysis.16 Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin I, and C-reactive protein (CRP) were measured as previously described.17 Basic laboratory analyses were performed at the time of the baseline investigation. Circulating levels of PTH, 25-OH vitamin D, NT-proBNP, troponin I, cystatin C, and CRP were run in batch analyses in samples that had been stored at −70°C for 10 to 15 years until analysis. Height, weight, body mass index, ECG, and supine systolic and diastolic blood pressures were measured under standardized conditions.16 Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L, 2-hour postload glucose levels ≥11.1 mmol/L, or the use of oral hypoglycemic agents or insulin.20 Smoking status, current smoking versus nonsmoking, was obtained from a questionnaire. Participants reported their leisure-time physical activity on a standardized questionnaire. Participants reported their leisure-time physical activity on a standardized questionnaire. Previous cardiovascular disease was defined as history of any cardiovascular disease in the follow-up.16

Dietary intake of calcium and vitamin D was recorded using a 7-day precoded food diary following the instructions of a dietitian. Daily intakes were calculated with a computer program and the Swedish National Food Administration database (SLV Database, 1990).

Outcomes

The Swedish Cause of Death Register was used to define all-cause and cardiovascular mortality (ICD-9 codes 390 to 459 or ICD-10 codes 100 to 199). The completeness of ascertainment and accuracy of classification in the Swedish Cause of Death Register have been shown to be high.22

Statistical Analyses

Logarithmic transformation was performed to achieve normal distribution for skewed variables (PTH, phosphate, troponin I, NT-proBNP, cystatin C, and CRP). The relations of serum levels of PTH to cardiovascular and all-cause mortality were investigated with Cox proportional-hazard regression in the whole cohort in 3 sets of models: model A, crude model; model B, adjusted for established risk factors for cardiovascular disease (age [continuous], systolic blood pressure [continuous], diabetes [diabetic], smoking [diabetic], body mass index [continuous], total cholesterol [continuous], high-density lipoprotein cholesterol [continuous], antihypertensive treatment [diabetic], lipid-lowering treatment [diabetic], and history of cardiovascular disease [diabetic]); and model C, adjusted for established risk factors for cardiovascular disease (model B) and factors associated with mineral metabolism (serum calcium [continuous], serum phosphate [continuous], vitamin D deficiency [diabetic]; plasma 25-OH vitamin D <37.5 nmol/L), glomerular filtration rate [continuous], dietary intake of calcium [continuous], dietary intake of vitamin D [continuous], month of examination [categorical; modeled as dark months (November, December, January, and February), intermediate months (September, October, March, and April) and light months (May, June, July, and August)], and leisure-time physical activity [categorical]).

In secondary analyses, we also investigated whether the association between PTH and cardiovascular mortality was confounded by other distinct pathophisiological pathways that are not primarily reflected by the established risk factors, ie, inflammation (CRP), renal dysfunction (cystatin C), ventricular dysfunction (NT-proBNP), and myocardial cell damage (troponin I). We also investigated the association between PTH and cardiovascular mortality after excluding participants with hyperphosphatemia (defined as serum phosphate >1.4 mmol/L; n = 909) and participants with previous cardiovascular disease at baseline (n = 541). In our primary analysis, we modeled PTH as a continuous variable (expressed as a 1-SD increase). We also used multivariate models comparing risk in PTH quartiles 2, 3, and 4 with that in quartile 1 (lowest) and thus in 4 models (modeled as quartile 4 versus 1 to 3 [PTH >5.27 pmol/L]). To gain additional insights into the potential nonlinearity of the association between plasma PTH and CVD mortality, we examined the Cox regression model using penalized splines with 4 df (knots at 10th percentile [2.17 pmol/L], median [4.00 pmol/L], and 90th percentile [6.74 pmol/L] of PTH). Assumptions of linearity were further assessed by adding a quadratic term of plasma PTH to multivariable model B.

Proportional-hazards assumptions were confirmed by Schoenfeld tests. Additionally, we performed tests for effect modification by the established cardiovascular risk factors in model B by including multiplicative interaction terms with these variables and plasma PTH. None of the interaction terms reached statistical significance (P > 0.09 for all).

The population-attributable risk proportion was calculated as follows: p · (HRexposed − HRunexposed)/HRexposed, where p is the proportion of cases that were exposed and HR is the hazard ratio adjusted for the established cardiovascular risk factors in multivariable model B.23

Estimates of C statistic for Cox regression models were calculated,24 and differences in C statistics after the addition of plasma PTH to a model with established risk factors were estimated.25 To assess the calibration of the Cox models, the Grimmsey and Borgan26 calibration test, comparing the observed and model-based estimated expected number of events within 5 risk score groups, was computed. We
also performed likelihood ratio tests to evaluate whether the global model fit improved after the addition of plasma PTH.

Backward stepwise regression analyses between PTH and all covariates in multivariable model C also were performed to assess which covariates were independently associated with PTH levels at baseline. The statistical software packages STATA 10.0 (Stata Corp., College Station, Tex) and SAS version 9.1 for Windows (SAS Institute, Cary, NC) were used.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Baseline characteristics in the whole sample and in the different subsamples are shown in Table 1. In backwards stepwise regression analyses between PTH and the variables in model C, higher PTH levels were independently associated with vitamin D deficiency, lower prevalence of smoking and diabetes, lower glomerular filtration rate, higher prevalence of previous cardiovascular disease, and lower serum levels of cholesterol and calcium (P < 0.033 for all; see Table I of the online-only Data Supplement for details).

Plasma PTH, Cardiovascular Disease, and All-Cause Mortality

During follow-up (median, 9.7 years; range, 1.2 to 12.4 years), 277 participants died; 117 of the deaths were due to cardiovascular disease. The incidence rates in the whole sample and in the different subsamples are shown in Table 2.

Cox Regression Models

Multivariable associations are presented in Table 3, and crude associations are presented in online-only Data Supplement.
Table II. In the whole cohort, a 1-SD increase in plasma PTH was associated with a 37% to 38% higher risk for cardiovascular mortality in the crude (model A) and multivariable (model B) models. Further adjustment for factors associated with mineral metabolism attenuated the association somewhat (model C; HR for 1-SD increase, 1.24; 95% confidence interval [CI], 1.04 to 1.47; \( P = 0.02 \)). The association between higher plasma PTH and higher risk for cardiovascular disease remained essentially unaltered in the multivariate models and threshold models, in the subsample with participants without previous cardiovascular disease at baseline, in participants with normal PTH, and in participants with normal PTH and no other signs of a disturbed mineral metabolism (normal serum calcium 2.2 to 2.6 mmol/L, normal glomerular filtration rate, >50 mL \( \cdot \) min \(^{-1} \) \( \cdot \) 1.73 m \(^{-2} \) and without vitamin D deficiency, plasma 25-OH vitamin D \( \geq 37.5 \) nmol/L). In the whole sample, the association between plasma PTH and cardiovascular mortality remained significant even after the addition of cystatin C (HR for 1-SD increase, 1.29; 95% CI, 1.1 to 1.6; \( P < 0.001 \)), NT-proBNP (HR for 1-SD increase, 1.19; 95% CI, 1.0 to 1.4; \( P = 0.03 \)), troponin I (HR for 1-SD increase, 1.32; 95% CI, 1.1 to 1.5; \( P < 0.001 \)), or CRP (HR for 1-SD increase, 1.34; 95% CI, 1.2 to 1.6; \( P < 0.001 \)) to multivariable model B. The association between plasma PTH and cardiovascular mortality showed no deviation from linearity when a quadratic term of PTH was introduced (\( P = 0.52 \)).

The association between plasma PTH and all-cause mortality portrayed a pattern similar to that for cardiovascular mortality but with weaker associations (Table 3 and online-only Data Supplement Table II).

Models that included plasma PTH showed better global fit compared with models with only the established risk factors, as evaluated by likelihood ratio tests (\( P < 0.001 \)). Examination of

Table 3. Relations of Plasma PTH to Cardiovascular and All-Cause Mortality: Multivariable Cox Regression (Model B)

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Whole Sample (n=958)</th>
<th>Without Previous CVD (n=617)</th>
<th>Normal Plasma PTH (n=868)</th>
<th>Normal Mineral Metabolism (n=646)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiovascular Mortality</td>
<td>All-Cause Mortality</td>
<td>Cardiovascular Mortality</td>
<td>All-Cause Mortality</td>
</tr>
<tr>
<td>Continuous models</td>
<td>1-SD increase</td>
<td>1.38 (1.18–1.60)†</td>
<td>1.20 (1.08–1.35)†</td>
<td>1.40 (1.05–1.86)†</td>
</tr>
<tr>
<td>Multicategory models</td>
<td>Q1 (&lt;2.96 pmol/L)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>0.78 (0.43–1.34)</td>
<td>0.84 (0.59–1.21)</td>
<td>1.03 (0.45–2.35)</td>
<td>0.85 (0.55–1.36)</td>
<td>0.82 (0.45–1.48)</td>
</tr>
<tr>
<td>Q2 (2.96–3.99 pmol/L)</td>
<td>0.99 (0.56–1.72)</td>
<td>1.00 (0.71–1.42)</td>
<td>1.07 (0.48–2.40)</td>
<td>0.93 (0.59–1.48)</td>
</tr>
<tr>
<td>Q3 (4.00–5.27 pmol/L)</td>
<td>1.83 (1.10–3.04)*</td>
<td>1.48 (1.06–2.06)*</td>
<td>1.96 (0.94–4.09)</td>
<td>1.48 (0.96–2.29)</td>
</tr>
<tr>
<td>Q4 (&gt;5.27 pmol/L)</td>
<td>1.98 (1.35–2.92)†</td>
<td>1.55 (1.20–2.02)†</td>
<td>1.90 (1.04–3.45)*</td>
<td>1.59 (1.11–2.26)*</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; Q, quartile. Data are adjusted for established risk factors for cardiovascular disease, model B (age, systolic blood pressure, diabetes mellitus, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, antihypertensive treatment, lipid-lowering treatment, and history of cardiovascular disease). Normal plasma PTH was defined as <6.8 pmol/L; normal mineral metabolism was defined as normal plasma PTH and no other signs of a disturbed mineral metabolism (normal serum calcium 2.2 to 2.6 mmol/L, normal glomerular filtration rate, >50 mL \( \cdot \) min \(^{-1} \) \( \cdot \) 1.73 m \(^{-2} \) and without vitamin D deficiency, plasma 25-OH vitamin D >37.5 nmol/L).

\*\( P < 0.05 \), †\( P < 0.001 \), ‡\( P = 0.06 \).
other signs of a disturbed mineral metabolism such as abnormal serum calcium, renal dysfunction, or vitamin D deficiency, suggesting that plasma levels of PTH portray prognostic information even in the absence of clinically overt primary or secondary hyperparathyroidism. Interestingly, elevated plasma levels of PTH accounted for 20% of the population-attributable risk proportion for cardiovascular mortality, indicating that our findings could have substantial public health implications.

Comparison With the Literature
The finding that increased plasma PTH predicts cardiovascular mortality is in accordance with previous studies in patients with primary hyperparathyroidism and secondary hyperparathyroidism caused by chronic kidney disease. We are aware of 1 study that has reported the association of circulating PTH and the risk for cardiovascular disease in the community. However, that study was limited by a cross-sectional study design and the fact that the assessment of cardiovascular disease was based on a questionnaire. Thus, the prospective association between plasma PTH and cardiovascular mortality in a community-based sample has not previously been reported. Moreover, no previous studies have reported that higher PTH is associated with higher incidence of cardiovascular events even in individuals with PTH in the normal range. Our finding that higher plasma PTH is associated with a higher risk for total mortality is in accordance with a prior study in institutionalized frail elderly.

Potential Mechanisms
Several mechanisms may explain the link between PTH and cardiovascular mortality in our study. First, PTH has been directly implicated in atherogenesis via vascular calcification and vascular remodeling. Second, PTH appears also to have detrimental effects on the myocardium via induction of left ventricular hypertrophy, cardiac calcification, and fibrosis. Third, higher PTH is associated with both established cardiovascular risk factors and more recently described risk factors such as inflammation markers, renal dysfunction, and cardiac pathology. The fact that PTH remained significantly associated with CVD mortality in all multivariable models suggests that confounding by these factors is not the sole explanation for our findings. However, although no major confounding by the cardiovascular risk factors was detected in our multivariable modeling, we cannot rule out the possibility of residual confounding or confounding by unmeasured factors.

Finally, because PTH is one of the key regulatory hormones in the mineral homeostasis, it is possible that the plasma levels of PTH reflect other abnormalities along the same pathway such as vitamin D deficiency, hypercalcemia, hyperphosphatemia, or renal failure that predispose to a higher risk for cardiovascular mortality. However, the interplay between the circulating levels of PTH, calcium, phosphate, vitamin D, and renal function is complex. Because elevated PTH levels could be considered an intermediate in the causal pathway between renal failure or vitamin D deficiency and cardiovascular disease and because hypercalcemia and hyperphosphatemia could be considered to be in

Discussions
In the present community-based sample of elderly men, higher plasma levels of PTH were associated with higher risk for cardiovascular mortality independently of established cardiovascular risk factors and factors associated with mineral homeostasis. The results remained essentially unaltered in participants with PTH within the normal range without elevation, plasma PTH: 0.714 versus 0.687, C-statistic increment: 0.026, 95% CI, 0.002 to 0.051). In the subsample with participants without previous cardiovascular disease, the estimate of the increment in the C statistic was similar but with slightly wider CIs (C statistic with versus without plasma PTH: 0.691 versus 0.665, P=0.08; C-statistic increment: 0.026, 95% CI, −0.003 to 0.056).

Calibration
The P values for the Grønnesby and Borgan statistics indicated good calibration for the models both with and without plasma PTH (P>0.20).

Figure, Association between plasma PTH and cardiovascular mortality in the total sample. Solid line shows estimated hazard ratios (with 95% confidence limits) for cardiovascular mortality in relation to plasma PTH levels as a function of penalized regression splines. Q indicates quartile.

Population-Attributable Risk Proportion
Elevated PTH (as defined by the quartile 4 versus 1 to 3 cutoff, plasma PTH >5.27 pmol/L) accounted for 20% (95% CI, 10 to 26) of the population-attributable risk proportion for cardiovascular mortality. The population-attributable risk proportion for PTH above the median (PTH >4.00 pmol/L) was 22% (95% CI, 3.3 to 35) and for the top tertile of PTH (PTH >4.75 pmol/L) was 23% (95% CI, 12 to 31).

Discrimination
The C statistic increased significantly for the prediction of cardiovascular mortality when plasma PTH was incorporated into a model with the established risk factors (C statistic with versus without plasma PTH: 0.714 versus 0.687, P=0.03; C-statistic increment: 0.026, 95% CI, 0.002 to 0.051). In the subsample with participants without previous cardiovascular disease, the estimate of the increment in the C statistic was similar but with slightly wider CIs (C statistic with versus without plasma PTH: 0.691 versus 0.665, P=0.08; C-statistic increment: 0.026, 95% CI, −0.003 to 0.056).
the causal pathway between higher PTH and cardiovascular disease, it is not possible to fully disentangle the individual contribution of these factors to the development of cardiovascular disease in the present observational study. Nevertheless, our data clearly show that plasma PTH is a strong risk marker for cardiovascular mortality independently of these factors and in individuals without signs of clinically overt mineral metabolism abnormalities.

Clinical Implications
The idea of a causal role for PTH in the development of cardiovascular disease is further supported by intervention trials in which PTH lowering, by parathyroidectomy, renal transplantation or treatment with calcimetics (PTH-lowering agents), reduces the incidence of cardiovascular disease in patients with primary or secondary hyperparathyroidism. Ongoing large randomized intervention trials will evaluate whether a reduction of PTH levels by calcimetics treatment will reduce the incidence of cardiovascular events in patients with secondary hyperparathyroidism caused by renal failure. To date, we are aware of no evidence suggesting that reducing the levels of PTH will reduce cardiovascular risk in the general population. Thus, our data should not be construed as implying a direct benefit of a reduction of PTH levels. Still, if validated, our data could motivate additional interventional studies evaluating the potential of PTH lowering, perhaps by vitamin D supplementation or by treatment with calcimetics, in the primary prevention of cardiovascular disease in the community. However, because our observational data do not allow us to fully determine whether PTH per se is a causal factor or whether PTH levels merely reflect other abnormalities along the mineral metabolism pathway that predispose to a higher risk for cardiovascular mortality, our study is not ideal for providing a clear direction for future interventional studies.

Another potential clinical implication of our data is the use of PTH in the risk prediction of cardiovascular disease. The significant C-statistic increment in the whole cohort indicates that the addition of plasma PTH to a model with established cardiovascular risk factors represents a substantial improvement in model performance. The improvement in risk prediction was confirmed through the use of tests of model calibration and global model fit. However, the clinical value of an improved risk prediction would be greater in a sample without prevalent cardiovascular disease. In the present study, the estimate of the C-statistics increment was similar in the subsample without previous cardiovascular disease at baseline compared with the whole sample but did not quite reach statistical significance, most likely because of the lower statistical power given the smaller study sample with fewer events during follow-up. Thus, the clinical utility of using PTH in cardiovascular risk prediction in a primary preventive setting in the community needs to be evaluated in future large-scale studies. Moreover, it is essential that future studies investigate whether a reduction in PTH levels corresponds to a reduction in cardiovascular events in this setting.

Study Strengths and Limitations
Strengths of this investigation include the large, homogeneous, community-based study population with a large number of events during a long follow-up, as well as the detailed characterization of study participants with regard to cardiovascular risk factors and mineral metabolism factors.

Limitations include the unknown generalizability to women or other age and ethnic groups because we examined only men of the same age with a similar ethnic background. Further studies are needed to explore whether plasma PTH also is associated with cardiovascular mortality in women, in younger individuals, and in other ethnicities. Moreover, plasma PTH levels and other factors involved in mineral metabolism were measured only at the baseline examination, and it is unclear how well a single measurement reflects the PTH levels during the 10-year follow-up. Yet, any potential bias by variations in PTH levels over time would most likely conservatively bias our risk estimates.

Conclusions
Higher plasma PTH is associated with a higher risk for cardiovascular mortality even in individuals without signs of a disturbed mineral metabolism in the community. Further studies are needed to validate our findings and to evaluate the clinical implications of PTH lowering in the primary prevention of cardiovascular disease.

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Disclosures
Dr Lind reports grant support from AstraZeneca. The other authors report no conflicts.

References


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### Supplementary Table 1
The cross sectional association between plasma PTH and established cardiovascular risk factors and factors involved in mineral metabolism: Stepwise regression

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficients (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Deficiency</td>
<td>0.23 (0.071-0.38)</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.14 (-0.22--0.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.13 (-0.23--0.035)</td>
<td>0.008</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (ml/min/1.73 m²)*</td>
<td>-0.0032 (-0.0055-0.009)</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous Cardiovascular Disease</td>
<td>0.071 (0.0057-0.14)</td>
<td>0.033</td>
</tr>
<tr>
<td>Serum Cholesterol (mmol/l)</td>
<td>-0.066 (-0.097--0.035)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin-Corrected Serum Calcium (mmol/l)</td>
<td>-0.79 (-1.1--0.45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are regression coefficients and 95% confidence interval for change in log* PTH per unit increase in continuous variables and increase in log* PTH for presence vs. absence for dichotomous variables (Vitamin D-deficiency, smoking, diabetes and previous cardiovascular disease) * Natural logarithm.
## Supplementary Table 2 Relations of plasma PTH to cardiovascular and all-cause mortality: Crude Cox regression (Model A)

<table>
<thead>
<tr>
<th></th>
<th>Whole sample</th>
<th>Without previous CVD</th>
<th>Normal plasma PTH</th>
<th>Normal mineral metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiovascular mortality</td>
<td>All-cause mortality</td>
<td>Cardiovascular mortality</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95%CI)</td>
<td>Hazard ratio (95%CI)</td>
<td>Hazard ratio (95%CI)</td>
<td>Hazard ratio (95%CI)</td>
</tr>
<tr>
<td><strong>Continuous models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SD increase</td>
<td>1.37 (1.19-1.57)‡</td>
<td>1.18 (1.06-1.31)†</td>
<td>1.24 (0.95-1.62)</td>
<td>1.12 (0.95-1.32)</td>
</tr>
<tr>
<td><strong>Multicategory models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;2.96 pmol/l)</td>
<td>referent</td>
<td>referent</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td>Q2 (2.96-3.99 pmol/l)</td>
<td>0.73 (0.41-1.33)</td>
<td>0.81 (0.56-1.15)</td>
<td>0.82 (0.37-1.8)</td>
<td>0.80 (0.51-1.26)</td>
</tr>
<tr>
<td>Q3 (4.00-5.27 pmol/l)</td>
<td>0.95 (0.55-1.65)</td>
<td>0.96 (0.68-1.35)</td>
<td>0.88 (0.40-1.95)</td>
<td>0.86 (0.55-1.35)</td>
</tr>
<tr>
<td>Q4 (&gt;5.27 pmol/l)</td>
<td>1.83 (1.13-2.96)*</td>
<td>1.38 (1.01-1.90)*</td>
<td>1.42 (0.70-2.87)</td>
<td>1.25 (0.83-1.90)</td>
</tr>
<tr>
<td><strong>Threshold models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 vs. Q1-3 (&gt;5.27 pmol/l)</td>
<td>2.04 (1.41-2.96)*</td>
<td>1.50 (1.17-1.93)†</td>
<td>1.56 (0.88-2.79)</td>
<td>1.41 (1.00-2.00)*</td>
</tr>
</tbody>
</table>
| SD= standard deviation, Q= quartile. * p<0.05, † p<0.01, ‡ p<0.001, § p=0.06