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Parathyroid hormone concentration and risk of cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—According to a recent meta-analysis, PTH excess is associated with increased cardiovascular disease (CVD) risk, but existing studies are limited. We examined in a prospective study the association of parathyroid hormone (PTH) with the incidence of CVD, taking into account vitamin D and other confounding variables.

Methods—The Atherosclerosis Risk in Communities Study measured PTH using a second-generation assay (Roche) in stored serum samples from 1990–1992 and related levels in 10,392 adults to incident cardiovascular outcomes [coronary heart disease (n = 808), heart failure (n = 1,294), stroke (n = 586), peripheral artery disease (n = 873), atrial fibrillation (n = 1,190), and CVD mortality (n = 647)] through 2010 (median follow-up = 19 years).

Results—Contrary to the hypothesis, PTH level was not associated positively with any CVD outcome. The associations of incident heart failure, peripheral artery disease, and CVD mortality with PTH actually were weakly inverse (p trend = 0.02 to 0.04) in the most fully adjusted models.

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Disclosures

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For example, the hazard ratios across PTH quartiles were 1.00, 1.07, 1.07, and 0.96 (p trend = 0.74) for coronary heart disease incidence and were 1.00, 0.69, 0.74, and 0.74 (p trend = 0.02) for CVD mortality. Patterns were similar when restricted to participants with normal baseline kidney function.

Conclusions—This large prospective study failed to support the hypothesis that elevated PTH is an independent risk marker for incident CVD. When our data were added to the previous meta-analysis, the pooled hazard ratio remained statistically significant but weakened.

Parathyroid hormone (PTH) helps regulate blood calcium concentrations. PTH levels are altered in primary hyperparathyroidism and secondarily with vitamin D deficiency, chronic kidney disease (CKD), and certain other conditions.

Elevated PTH has been linked to increased blood pressure and cardiac contractility, which may eventually lead to cardiomyocyte hypertrophy, apoptosis, and fibrosis of the left ventricle and other vascular smooth muscle.[1–5] Higher PTH has been associated with impaired endothelial function, increased aortic pulse pressure, and decreased large artery elasticity.[6] Elevated PTH may also predispose to valvular and myocardial calcification, especially in patients with moderate to severe CKD.[7] PTH can stimulate cytokine release from vascular smooth muscle cells and lymphocytes and thus may also affect the cardiovascular system via pro-inflammatory effects.[1,8–10]

Nevertheless, whether PTH is an independent cause of overt cardiovascular disease (CVD) is uncertain. A recent meta-analysis of 12 general cohort studies reported that PTH excess is associated with about a 1.45-fold increase (95% CI 1.24, 1.71) in the incidence of total CVD events, compared with low levels of PTH.[11] However, there was considerable between-study heterogeneity, with many individual cohorts showing no association of PTH with CVD. The Cardiovascular Health Study reported a modest positive association of PTH with heart failure incidence, but PTH was not associated with coronary heart disease (CHD) or total CVD independent of renal function.[12] Most prior studies, other than Cardiovascular Health Study, did not look at vitamin D simultaneously with PTH, or completely adjust for potential confounding variables, and data including African Americans are limited. Vitamin D is a potential confounder of PTH associations with CVD, because low vitamin D has been associated positively with CVD in some studies and is associated inversely with PTH.

We therefore examined the association of PTH with the incidence of multiple cardiovascular outcomes in the bi-racial Atherosclerosis Risk in Communities (ARIC) Study, taking into account vitamin D and other potential confounding variables.

Methods

This work was funded by the National Institutes of Health. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The study protocol was approved by the Institutional Review Boards of the collaborating institutions, and written informed consent was obtained from each participant.

Study population

In 1987–89, ARIC recruited and examined (visit 1) a cohort of 15,792 men and women aged 45 to 64 years in 4 U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland.[13] ARIC performed follow-up visit 2 in 1990–92 (93% return rate), visit 3 in 1993–95 (86%), visit 4 in 1996–98 (80%), and visit 5 in 2011–13 (65%). The present analysis used visit 2 as its start point for follow-up.

Measurements of risk factors and prevalent disease

Participants were asked to fast for 12 hours before their morning visit 2 appointments, and serum and plasma samples were obtained and stored at −80°C. Soon after the visit, central laboratories measured plasma total and HDL cholesterol by enzymatic methods, serum creatinine by Jaffe method, and serum glucose by a hexokinase assay. In 2012–13, a number of analytes were measured in a previously unthawed serum aliquot. PTH was measured on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation, Indianapolis, IN) using a sandwich immunoassay method (Roche Diagnostics). Serum PTH by the Elecsys method has excellent stability long-term at −80°C.[14] Using split samples collected at visit 2 and stored, we calculated the coefficient of variation, which was 9.7% for PTH. This coefficient of variation encompasses variability related to both sample processing and laboratory methods. 25-OH-vitamin D was measured using LC/MS/MS instrumentation (coefficient of variation 10.9%). Calcium and phosphorous were measured on a Roche Modular P Chemistry Analyzer (Roche Diagnostics) using colorimetric methods. The coefficient of variation was 2.4% for calcium and 3.0% for phosphorous. High sensitivity C-reactive protein was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics) (coefficient of variation 7%). Cystatin C was measured using Gentian Cystatin C reagent (coefficient of variation 3%). Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Epidemiology Collaboration formula, which incorporates both cystatin C and creatinine.[15]

Sitting blood pressures were measured thrice using a random-zero sphygmomanometer after 5 minutes of rest, and the second and third measurements were averaged. Names of the medications taken were recorded from medication bottles. Body mass index was calculated as weight (kg)/height $(m)^2$. Diabetes was defined as a fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose ≥ 200 mg/dl, a physician diagnosis of diabetes, or current use of anti-diabetic medication. The Baecke sport index (physical activity) was completed at visit 1.[16]

Prevalent CVD at visit 2 was identified using ARIC visit 1 or 2 electrocardiograms, ankle/brachial index, Gothenberg heart failure and Rose questionnaires, and self-reported medical histories, or as an adjudicated incident CVD event occurring before visit 2.

Identification and classification of incident CVD events

We identified incident CVD events occurring between ARIC visit 2 (1990–1992) and December 31, 2010. ARIC staff contacted participants annually by telephone to capture all hospitalizations and deaths related to possible CVD. They also surveyed lists of discharges

from local hospitals and death certificates from state vital statistics offices for potential CVD events. Abstractors reviewed medical records and recorded information to validate CVD outcomes. To help validate CHD outcomes, staff also attempted to interview next of kin, or obtain physician, medical examiner, or autopsy information. CHD events were validated by physician review, and were defined as a definite or probable myocardial infarction or definite fatal CHD by ARIC criteria[17] or as a coronary revascularization. For stroke classification, signs, symptoms, neuroimaging, and other diagnostic reports were used in a computer algorithm and by physician reviewers,[18] using criteria adapted from the National Survey of Stroke.[19] Heart failure was defined by a hospitalization with an ICD9 code of 428 or death with an underlying cause of ICD9 428 or ICD10 I50. ARIC has shown the validity of ICD-9 Code 428 to be moderately high, with a sensitivity of 93% for identifying acute decompensated heart failure.[20] Atrial fibrillation was based on electrocardiograms done at ARIC visits 3 and 4 or a hospital discharge diagnosis of atrial fibrillation or flutter.[21] Peripheral artery disease was ascertained from an ABI < 0.9 at ARIC visits 3 or 4 or from a list of hospital discharge diagnoses for peripheral artery disease during follow-up. CVD mortality comprised deaths with underlying causes attributed in ICD-9 to codes 390–459 or in ICD-10 to codes I00–I99.

Statistical analysis

Of the original 15,792 ARIC participants, we excluded those not attending ARIC visit 2 (n = 1,444); those with a CVD outcome prior to visit 2 (n = 2093) or incomplete information on these outcomes (n = 502). We then excluded, due to small numbers, the remaining participants in Minneapolis and Washington County who were not white (n = 39) and participants in any field center who were not white or African American (n = 37). We next excluded the remaining participants without measurements of PTH (n = 782) or extreme PTH values (>200 pg/mL, n = 9). Those without PTH measurements were similar ($p > 0.05$) to the remainder on the percentage who were African American and on mean values for alcohol intake, the sports index, body mass index, and total cholesterol; but those without PTH were ($p < 0.05$) more often male (55% vs 43%), ever smokers (66% vs 58%), and non-diabetic (84% vs 87%) and had higher mean age (59 vs 57 years) and systolic blood pressure (123 vs 121 mmHg). Finally, we excluded those with missing covariates for analyses (n = 494). This left 10,392 participants for the present analyses. For each CVD outcome, time at risk was computed from the visit 2 date to the earliest of the following: CVD event, date of death, date of last follow-up contact, or December 31, 2010.

Our main hypothesis was that PTH would be associated positively with CVD incidence outcomes: CHD, heart failure, stroke, peripheral artery disease, atrial fibrillation, and CVD mortality. For analyses, PTH was either categorized into quartiles or analyzed by a clinical cutpoint (<65 vs ≥65 pg/mL). For Table I, overall PTH quartiles were used to calculate means and prevalences of risk factors and cardiovascular conditions, stratified by race. Although PTH differed markedly between whites and African Americans, there was no significant interaction between race/ethnicity and PTH for any CVD outcome ($p>0.05$). Therefore, we pooled whites and African Americans for the remaining analyses. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals of incident CVD. We verified the proportional hazards assumption of the Cox

models by inspection of ln(−ln) survival curves for PTH categories. We tested trends in HRs across PTH quartiles by including an ordinal variable for each category in the Cox models. For all CVD outcomes, we tested multiplicative interactions of PTH with sex, vitamin D, calcium, phosphorous, and CKD status, categorized as eGFR ≥90 (normal), 60–90, and 15–59 ml/min/1.73 m^2 (none were <15). The only interaction that proved statistically significant ($p<0.01$) was PTH quartiles by serum calcium for stroke incidence. However, stratified analyses suggested that this interaction was unremarkable, and so it was not included in the main analysis.

We selected possible confounding variables for regression models based on previous prospective findings in ARIC. Covariates considered included age (years), sex, race, season of PTH blood draw, systolic blood pressure (mm Hg), antihypertensive medication use (yes or no), diabetes status (yes or no), smoking status (never, former, or current smokers of <15, 15–24, or 25+ cigarettes/d), sports index (range 1–5), drinking status (current, not), alcohol amount (g/d), body mass index (kg/m^2), total cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), lipid medication use (yes or no), and eGFR (ml/min). Ultimately, diabetes, HDL cholesterol, and lipid medication use were dropped as noncontributory to models of all CVD outcomes. Model 1 adjusted for demographics and season. Model 2 further adjusted for the other CVD risk factors. Model 3 further adjusted for serum vitamin D, calcium, and phosphorous (all continuous variables). We also repeated analyses (1) adjusted for C-reactive protein and NT-proBNP, (2) after restriction to those without CKD, and (3) after excluding people in the PTH quartile analysis with possible primary hyperparathyroidism (PTH > 65 pg/mL and serum calcium > 10.2 mg/dL)..

Results

Descriptive data

Among the 8013 whites and 2379 African Americans free of CVD, the median PTH values were lower in whites (38 pg/mL) than in African Americans (44 pg/mL), as were the 90th percentiles (58 and 70 pg/mL, respectively). In a sample of participants (n = 1,330), we had a second measurement of PTH taken three years later and measured in the same laboratory with the same method. The 3-year Spearman correlation of PTH level was 0.64.

Using similar quartile cutpoints in whites and African Americans (Table I), PTH showed notable and consistent positive associations with female sex, body mass index, and systolic blood pressure, and negative associations with current smoking, alcohol intake, and serum calcium, phosphorous, and 25-OH-vitamin D.

Analysis by PTH quartiles—Table II shows the number of CVD events and their associations with PTH quartiles. Contrary to our hypothesis, PTH level was not associated positively with any cardiovascular outcome. The associations of incident heart failure, peripheral artery disease, and CVD mortality with PTH quartiles were actually weakly inverse (p trend = 0.01 to 0.16) in Models 2 and 3. For example, the HRs for CVD mortality across PTH quartiles in Model 2 (Table II) were 1.00, 0.68, 0.74, and 0.73. Findings were similar when we excluded the few participants with possible primary hyperparathyroidism (n = 53). If we further adjusted for C-reactive protein and NT-proBNP, findings were similar

to Table II, except that the PTH association with atrial fibrillation even became slightly inverse (p trend 0.06 in Model 2 and 0.03 in Model 3).

When restricted to the 7,038 participants with normal baseline kidney function (eGFR>90 ml/min/1.73m^2), there were still weak inverse associations of PTH with heart failure, peripheral artery disease, and CVD mortality, and no association for other CVD outcomes. The HRs across PTH quartiles in Model 2 were 1.00, 0.93, 0.86, 0.82 for incident heart failure (p trend = 0.07); 1.00, 0.91, 0.88, and 0.72 for incident peripheral artery disease (p trend = 0.02); and 1.00, 0.52, 0.63 and 0.54 for CVD mortality (p trend < 0.001).

Analysis by a PTH clinical cutpoint—As shown in Table III, participants with PTH ≥ 65 pg/mL were not at increased CVD risk compared with participants with lower PTH values. This was also true when we further adjusted for NT-proBNP or restricted to those with normal kidney function.

Discussion

This large, population-based, prospective ARIC study of whites and African Americans did not find any independent positive associations of PTH with incident CVD outcomes, including CHD, stroke, heart failure, peripheral artery disease, atrial fibrillation, or CVD mortality. In fact, in the quartile analysis PTH was weakly inversely associated with incident heart failure, peripheral artery disease, and CVD mortality, overall and in those with normal baseline kidney function. These findings were not confounded by 25-OH-vitamin D concentrations.

Regardless of whether we analyzed by PTH quartiles or clinical cutpoints, our findings for CHD, heart failure, stroke, and CVD mortality contrast with a previous meta-analysis whose pooled risk ratio suggested a modest statistically significant, positive association between PTH and both fatal and nonfatal CVD.[11] The meta-analysis identified considerable between-study heterogeneity (i.e., differences in HR estimates), with most of the 12 individual cohorts showing no association. At least some heterogeneity was due to differences in populations, PTH assays, outcome definitions, and levels of control for potential confounding variables, including vitamin D. Furthermore, there was some evidence of publication bias, favoring smaller studies with significant results. Our study had careful methods and thorough confounder control, and our results seemingly would increase between-study heterogeneity in HR estimates. Our sample was initially younger than many other studies, and PTH elevations would be more common in older subjects. When we added our CHD and CVD mortality data for PTH quartile 4 versus 1 to those of the meta-analysis,[11] the pooled risk ratios (95% CI) contrasting extreme PTH categories remained statistically significant but fell from 1.45 (1.24–1.71) to 1.39 (1.17–1.64) for total CVD events and from 1.48 (1.14–1.92) to 1.37 (1.02–1.82) for fatal CVD events.

Previous cohort studies reported PTH was not independently associated with carotid atherosclerosis prevalence or progression[22] or with peripheral artery disease incidence.[23] Among cross-sectional studies,[24–27] sometimes in hemodialysis patients,[25,26] three have tended to show an inverse association and one a positive association of PTH with peripheral

artery disease. In ARIC, we found a weak inverse association of PTH with peripheral artery disease incidence. Overall, we found no association in ARIC between PTH and incident atrial fibrillation, in contrast with a positive association reported by one previous cross-sectional study.[28]

As described in the Introduction, elevated PTH is associated positively with numerous subclinical markers of cardiovascular disease, including left ventricular hypertrophy.[1–8] It therefore is surprising that our only statistically significant findings were inverse associations -- not positive, as hypothesized -- between PTH and CVD mortality, peripheral artery disease, and heart failure.

In this ARIC sample, high PTH was associated with female sex, higher body mass, higher blood pressure, non-smoking, less alcohol intake, and lower 25-OH-vitamin D; these associations have been described previously[4,29–31] and were carefully adjusted for in this analysis. PTH was somewhat higher in African Americans than whites, which has been previously documented.[29,32] Despite race differences in PTH level, we found no evidence that the largely null associations between PTH and incident CVD differed by race group. Associations of PTH with CVD also did not vary by CKD status or level of 25-OH-vitamin D.

Limitations of this study warrant consideration. Firstly, analyses were based on a single measure of PTH and were only moderately correlated with PTH measures taken three years later. Changes over time or within-person variation in PTH would likely weaken observed HRs. However, there was no evidence that the proportional hazards assumption was violated, suggesting that the long follow-up is not a major concern. Secondly, PTH and several other biomarkers were measured on serum stored for two decades. Evidence suggests that serum PTH by our method is stable when stored at −80°C,[14] but if deterioration occurred, it would be expected to weaken HRs. Our findings that coefficients of variation in split samples were low and that cross-sectional associations between PTH and CVD risk factors in ARIC were consistent with previous studies with shorter sample storage suggest that substantial deterioration of ARIC samples is unlikely. Thirdly, we used a second-generation PTH assay, which has cross reactivity with the inactive 7,84 PTH fragment[33] that is found in higher concentration in patients with renal failure. However, our sensitivity analysis restricted to participants with normal eGFR yielded similar results. It is possible, but seems unlikely, that differences among studies of PTH and CVD are due to different PTH assays. Fourthly, some of our CVD endpoints (e.g., heart failure, atrial fibrillation, and CVD mortality) partly or totally relied on ICD codes. Yet, the moderately high validity of the ICD-9 codes for heart failure and atrial fibrillation in ARIC has been documented.[20,21]

In conclusion, this large prospective study provides no support that elevated PTH is an independent risk marker for incident CVD. If anything, PTH was weakly inversely associated with CVD mortality. When our data were pooled with the previous meta-analysis,[11] the pooled association for all studies were still statistically significant but weakened. Future studies should try to further address whether this association is causal and possible mechanisms by which PTH might influence CVD incidence and risk factors.

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References

1. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol. 2006; 92:39–48. [PubMed: 16600341]
2. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int. 1999; 56:383–92. [PubMed: 10432376]
3. Perkovic V, Hewitson TD, Kelynack KJ, et al. Parathyroid hormone has a prosclerotic effect on vascular smooth muscle cells. Kidney Blood Press Res. 2003; 26:27–33. [PubMed: 12697974]
4. Amann K, Tornig J, Flechtenmacher C, et al. Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: evidence for a permissive action of PTH. Nephrol Dial Transplant. 1995; 10:2043–8. [PubMed: 8643165]
5. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J. 2003; 24:2054–60. [PubMed: 14613742]
6. Bosworth C, Sachs MC, Duprez D, et al. Parathyroid hormone and arterial dysfunction in the Multi-Ethnic Study of Atherosclerosis. Clin Endocrinol (Oxf). 2013; 79:429–36. [PubMed: 23402353]
7. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease -- a review. Eur Heart J. 2004; 25:1776–87. [PubMed: 15474692]
8. Martin-Ventura JL, Ortego M, Esbrit P, et al. Possible role of parathyroid hormone-related protein as a proinflammatory cytokine in atherosclerosis. Stroke. 2003; 34:1783–9. [PubMed: 12805493]
9. Somjen D, Weisman Y, Kohen F, et al. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation. 2005; 111:1666–71. [PubMed: 15795327]
10. Rigby WF, Denome S, Fanger MW. Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. J Clin Invest. 1987; 79:1659–64. [PubMed: 2884234]
11. van Ballegooijen AJ, Reinders I, Visser M, et al. Parathyroid hormone and cardiovascular disease events: A systematic review and meta-analysis of prospective studies. Am Heart J. 2013; 165:655–64. [PubMed: 23622902]
12. Kestenbaum B, Katz R, de Boer I, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. J Am Coll Cardiol. 2011; 58:1433–41. [PubMed: 21939825]
13. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989; 129:687–702. [PubMed: 2646917]
14. Cavalier E, Delanaye P, Hubert P, et al. Estimation of the stability of parathyroid hormone when stored at -80 degrees C for a long period. Clin J Am Soc Nephrol. 2009; 4:1988–92. [PubMed: 19820128]
15. Inker LA, Schmid CH, Tighiouart H, et al. for the CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367:20–9. [PubMed: 22762315]
16. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982; 36:936–42. [PubMed: 7137077]
17. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol. 1996; 49:223–33. [PubMed: 8606324]

18. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999; 30:736–43. [PubMed: 10187871]
19. The National Survey of Stroke. National Institute of Neurological and Communicative Disorders and Stroke. Stroke. 1981; 12(2 Pt 2 Suppl 1):I1–91. [PubMed: 7222163]
20. Rosamond WD, Chang PP, Baggett C, et al. Classification of heart failure in the Atherosclerosis Risk in Communities (ARIC) Study: a comparison of diagnostic criteria. Circ Heart Fail. 2012; 5:152–9. [PubMed: 22271752]
21. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2009; 158:111–7. [PubMed: 19540400]
22. Blondon M, Sachs M, Hoofnagle AN, et al. 25-hydroxyvitamin D and parathyroid hormone are not associated with carotid intima-media thickness or plaque in the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2013; 33:2639–45. [PubMed: 23814117]
23. Anderson JL, Vanwoerkom RC, Horne BD, et al. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? Am Heart J. 2011; 162:331–9. [PubMed: 21835295]
24. Pedone C, Scarlata S, Napoli N, et al. Relationship between bone cross-sectional area and indices of peripheral artery disease. Calcif Tissue Int. 2013; 93:508–16. [PubMed: 23995829]
25. Lee CC, Wu CJ, Chou LH, et al. Peripheral artery disease in peritoneal dialysis and hemodialysis patients: single-center retrospective study in Taiwan. BMC Nephrol. 2012; 13:100. [PubMed: 22943313]
26. O'Hare AM, Hsu CY, Bacchetti P, et al. Peripheral vascular disease risk factors among patients undergoing hemodialysis. J Am Soc Nephrol. 2002; 13:497–503. [PubMed: 11805180]
27. Fahrleitner A, Dobnig H, Obernosterer A, et al. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. J Gen Intern Med. 2002; 17:663–9. [PubMed: 12220361]
28. Rienstra M, Lubitz SA, Zhang ML, et al. Elevation of parathyroid hormone levels in atrial fibrillation. J Am Coll Cardiol. 2011; 57:2542–3. [PubMed: 21679857]
29. Paik JM, Farwell WR, Taylor EN. Demographic, dietary, and serum factors and parathyroid hormone in the National Health and Nutrition Examination Survey. Osteoporos Int. 2012; 23:1727–36. [PubMed: 21932115]
30. Paik JM, Curhan GC, Forman JP, et al. Determinants of plasma parathyroid hormone levels in young women. Calcif Tissue Int. 2010; 87:211–7. [PubMed: 20631996]
31. Taylor EN, Curhan GC, Forman JP. Parathyroid hormone and the risk of incident hypertension. J Hypertens. 2008; 26:1390–4. [PubMed: 18551015]
32. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med. 2013; 369:1991–2000. [PubMed: 24256378]
33. Eastell R, Arnold A, Brandi ML, et al. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Third International Workshop. J Clin Endocrinol Metab. 2009; 94:340–50. [PubMed: 19193909]

Table I

Participant characteristics according to quartiles of parathyroid hormone (PTH) concentration, by racial group, ARIC Visit 2, 1990–1992

	Whites PTH Quartile[†] (pg/mL)				African-Americans PTH Quartile[†] (pg/mL)			
Characteristic[‡]	**3.7–31.1**	**31.1–39.1**	**39.2–48.9**	**48.9–153.1**	**6.5–31.1**	**31.1–39.1**	**39.2–48.9**	**48.9–188.0**
n	2208	2109	1990	1706	391	491	607	890
Age, years	56.4 (5.6)	56.6 (5.5)	56.9 (5.7)	57.4 (5.7)	55.3 (5.6)	55.7 (5.8)	55.7 (5.6)	56.1 (5.8)
Female, %	53.4	53.0	55.2	59.9	50.1	61.1	61.6	75.5
Smoking status, % Never	35.7	39.2	42.2	45.7	33.0	44.4	48.8	54.3
% Current	31.6	19.5	14.3	11.5	44.0	23.2	21.4	18.4
Alcohol intake, g/day	6.5 (14.4)	6.0 (12.8)	5.7 (12.8)	4.6 (10.8)	6.9 (22.3)	3.8 (10.6)	3.1 (13.8)	2.9 (10.5)
Sports index score	2.56 (0.8)	2.60 (0.8)	2.57 (0.8)	2.46 (0.8)	2.14 (0.7)	2.21 (0.7)	2.20 (0.7)	2.14 (0.6)
Diabetes, %	9.7	9.7	9.3	11.3	22.6	22.0	22.9	20.1
Body mass index, kg/m^2	26.3 (4.3)	26.8 (4.5)	27.4 (4.7)	28.4 (5.6)	27.8 (5.2)	29.1 (5.7)	29.8 (5.7)	31.2 (6.7)
Systolic blood pressure, mmHg	117 (17)	119 (17)	120 (17)	122 (18)	124 (21)	124 (19)	125 (18)	129 (21)
Total cholesterol, mg/dL	212 (39)	209 (38)	208 (37)	208 (37)	205 (41)	209 (40)	212 (41)	209 (40)
eGFR, $ml/min/1.73m^2$	94.7 (14.3)	95.1 (14.2)	95.0 (14.5)	93.4 (15.9)	103.1 (18.3)	103.0 (17.5)	103.1 (17.2)	100.5 (20.0)
C-reactive protein, mg/L[*]	2.02	1.83	1.93	2.19	2.89	2.61	2.94	3.17
NT-proBNP, pg/mL[*]	46.8	48.6	48.9	54.4	35.0	33.9	31.9	38.8
Serum calcium, mg/dL	9.38 (0.4)	9.30 (0.4)	9.28 (0.4)	9.26 (0.4)	9.56 (0.4)	9.48 (0.4)	9.45 (0.4)	9.42 (0.5)
Serum phosphorous, mg/dL	3.61 (0.5)	3.52 (0.5)	3.48 (0.5)	3.39 (0.5)	3.69 (0.5)	3.68 (0.5)	3.60 (0.5)	3.53 (0.5)
Serum 25-OH-vitamin D, ng/mL	28.0 (8.5)	27.1 (8.3)	25.5 (7.5)	23.6 (7.9)	21.2 (7.0)	20.2 (6.7)	19.3 (6.5)	17.0 (6.3)

[*] Geometric Mean. Other values are arithmetic mean (SD) or prevalence.

[†] PTH quartiles are from the entire sample (whites plus African-Americans).

[‡] Due to the large sample size, many characteristics differ among PTH quartiles at $p \leq 0.01$; characteristics not differing by PTH quartile ($p>0.01$) are diabetes (for both racial groups) and for African-Americans: age, sports, total cholesterol, and C-reactive protein.

Table II

Hazard ratios (HR) and 95 percent confidence intervals for incident cardiovascular disease (CVD) outcomes according to parathyroid hormone (PTH) quartiles, ARIC, 1990–2010

	PTH (pg/mL) Quartile				
Outcome Model	**3.7–31.1 (N=2599)**	**31.1–39.1 (N=2600)**	**39.2–48.9 (N=2597)**	**48.9–188.0 (N=2596)**	**P for trend***
Coronary Heart Disease					
N Events	200	207	204	197	
Model 1 HR	1	0.98 (0.80–1.19)	0.97 (0.80–1.18)	0.94 (0.77–1.15)	0.54
Model 2 HR	1	1.07 (0.88–1.31)	1.07 (0.88–1.31)	0.97 (0.79–1.20)	0.79
Model 3 HR	1	1.07 (0.88–1.31)	1.07 (0.87–1.31)	0.96 (0.78–1.20)	0.74
Heart Failure					
N Events	322	298	307	367	
Model 1 HR	1	0.85 (0.72–0.99)	0.85 (0.73–1.00)	0.96 (0.82–1.12)	0.73
Model 2 HR	1	0.90 (0.77–1.05)	0.86 (0.73–1.01)	0.84 (0.71–0.98)	0.03
Model 3 HR	1	0.90 (0.77–1.06)	0.86 (0.73–1.01)	0.85 (0.72–1.00)	0.04
Stroke					
N Events	147	140	131	168	
Model 1 HR	1	0.87 (0.69–1.10)	0.79 (0.62–1.00)	0.94 (0.75–1.17)	0.47
Model 2 HR	1	0.93 (0.74–1.17)	0.84 (0.66–1.07)	0.92 (0.73–1.16)	0.38
Model 3 HR	1	0.93 (0.74–1.18)	0.84 (0.65–1.07)	0.91 (0.72–1.17)	0.36
Peripheral Artery Disease					
N Events	221	217	214	221	
Model 1 HR	1	0.92 (0.76–1.11)	0.89 (0.74–1.08)	0.87 (0.72–1.05)	0.14
Model 2 HR	1	1.01 (0.84–1.22)	0.98 (0.81–1.19)	0.87 (0.71–1.06)	0.16
Model 3 HR	1	0.98 (0.81–1.19)	0.93 (0.77–1.13)	0.81 (0.66–1.00)	0.04
Atrial Fibrillation					
N Events	291	300	290	309	
Model 1 HR	1	0.99 (0.84–1.17)	0.97 (0.83–1.15)	1.06 (0.90–1.25)	0.53
Model 2 HR	1	1.01 (0.86–1.19)	0.96 (0.81–1.13)	0.93 (0.78–1.10)	0.31
Model 3 HR	1	1.00 (0.85–1.17)	0.93 (0.79–1.11)	0.90 (0.75–1.07)	0.16
CVD Mortality					

	PTH (pg/mL) Quartile				
Outcome Model	**3.7–31.1 (N=2599)**	**31.1–39.1 (N=2600)**	**39.2–48.9 (N=2597)**	**48.9–188.0 (N=2596)**	**P for trend***
N Events	188	131	145	183	
Model 1 HR	1	0.63 (0.50–0.78)	0.68 (0.54–0.84)	0.77 (0.63–0.95)	0.04
Model 2 HR	1	0.68 (0.54–0.85)	0.74 (0.59–0.92)	0.73 (0.59–0.91)	0.01
Model 3 HR	1	0.69 (0.55–0.86)	0.74 (0.59–0.92)	0.74 (0.59–0.93)	0.02

Model 1: Cox proportional hazards model adjusted for age, race, sex, and season.

Model 2: Model 1 with additional adjustment for drinking status, ethanol intake, smoking status, sports index, body mass index, systolic blood pressure, use of antihypertensive medications, total cholesterol, and eGFR.

Model 3: Model 2 with additional adjustment for serum calcium, phosphorous, and 25-OH-vitamin D.

* Linear trend in quartiles.

Table III

Hazard ratios (HR) and 95 percent confidence intervals for incident cardiovascular disease (CVD) outcomes according to a parathyroid hormone (PTH) clinical cut-point, ARIC, 1990–2010

	PTH (pg/mL)	
Outcome Model	**3.7–64.9 (N=9620)**	**65.0–188.0 (N=772)**
Coronary Heart Disease		
N Events	738	70
Model 1 HR	1	1.19 (0.93–1.52)
Model 2 HR	1	1.03 (0.80–1.33)
Model 3 HR	1	1.03 (0.79–1.33)
Heart Failure		
N Events	1161	133
Model 1 HR	1	1.27 (1.06–1.52)
Model 2 HR	1	0.97 (0.80–1.17)
Model 3 HR	1	0.99 (0.82–1.19)
Stroke		
N Events	527	59
Model 1 HR	1	1.19 (0.91–1.57)
Model 2 HR	1	1.04 (0.79–1.37)
Model 3 HR	1	1.04 (0.78–1.38)
Peripheral Artery Disease		
N Events	786	87
Model 1 HR	1	1.27 (1.01–1.59)
Model 2 HR	1	1.09 (0.86–1.37)
Model 3 HR	1	1.06 (0.84–1.34)
Atrial Fibrillation		
N Events	1085	105
Model 1 HR	1	1.26 (1.03–1.54)
Model 2 HR	1	0.99 (0.81–1.22)
Model 3 HR	1	0.98 (0.79–1.20)
CVD Mortality		
N Events	586	61
Model 1 HR	1	1.08 (0.83–1.42)
Model 2 HR	1	0.85 (0.65–1.12)
Model 3 HR	1	0.87 (0.66–1.14)

Model 1: Cox proportional hazards model adjusted for age, race, sex, and season.

Model 2: Model 1 with additional adjustment for drinking status, ethanol intake, smoking status, sports index, body mass index, systolic blood pressure, use of antihypertensive medications, total cholesterol, and eGFR.

Model 3: Model 2 with additional adjustment for serum calcium, phosphorous, and 25-OH-vitamin D.