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# Parathyroid hormone and risk of heart failure in the general population

## A meta-analysis of prospective studies

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**Abstract**

Inconsistent findings have been reported on the association between the parathyroid hormone (PTH) level and risk of heart failure. We aimed to systematically evaluate the association between circulating level of PTH and risk of heart failure in the general population by conducting a meta-analysis. We made a comprehensive literature search in PubMed, Embase, VIP, CNKI, and Wanfang databases published until January 2016. Only prospective observational studies reporting the association between circulating level of PTH and risk of heart failure in the general population were selected. Pooled adjusted hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were calculated for the highest versus lowest PTH category. Six studies with 25,207 participants identified. Higher circulating level of PTH was associated with an increased risk of heart failure (HR: 1.38; 95% CI 1.09–1.74) in a random effect model. Subgroup analyses revealed that the risk of heart failure was more pronounced among men (HR: 1.75; 95% CI 1.38–2.22) than in both genders. However, the risk increment was not statistically significant (HR: 1.12; 95% CI 0.76–1.66) in the middle-aged population. Higher PTH level is independently associated with an exacerbated risk of heart failure in the general population.

**Abbreviations:** CI = confidence interval, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, PTH = parathyroid hormone.

**Keywords:** heart failure, meta-analysis, parathyroid hormone

## 1. Introduction

Heart failure is a globally public health concern, associated with considerable morbidity and mortality.[1] An estimated 5.7 million Americans have heart failure according to the data from NHANES 2009 to 2012,[2] and will afflict more than 8 million patients by 2030.[3] Heart failure affects approximately 4 million people, with 550,000 new cases diagnosed annually in China.[4] Many potential risk factors contribute to the development of heart failure. Modification of these risk factors may help to reduce the incidence of heart failure as well as decrease mortality in patients with established heart failure. Therefore, early identification of these modifiable risk factors remains crucial.

Parathyroid hormone (PTH) is secreted by the parathyroid glands that control calcium homeostasis. Excess of PTH may adversely affect cardiovascular health beyond the regulation of calcium and phosphate homeostasis.[5] To date, many observational studies have examined the relationship between circulating level of PTH and subsequent risk of heart failure in the general population[6–12] as well as adverse outcomes in patients with heart failure.[13–15] However, this association was not observed in all the studies. These conflicting findings among the studies may partly explain by differences in study population, lack of standardization of PTH assays, follow-up duration, gender difference, or adjustment for confounders. A well-designed meta-analysis revealed that higher circulating level of PTH was associated with excessive risk of cardiovascular events.[16] Moreover, a more recently published meta-analysis only focused on the association between higher circulating level of PTH and cardiovascular or all-cause mortality risk.[17]

No previous meta-analysis has examined the relationship between circulating level of PTH and subsequent risk of heart failure. Therefore, we conducted this meta-analysis of available prospective studies to investigate the association between circulating level of PTH and incident heart failure in the general population.

## 2. Materials and methods

### 2.1. Literature search

We performed this meta-analysis based on the guideline of the Meta-Analysis of Observational Studies in Epidemiology.[18] The ethical approval was not necessary for this meta-analysis because this study was only adopted the study-level data but not individual patients data. Two authors (FBM and WW) independently searched for all eligible prospective observational studies in Pubmed, Embase, VIP, China National Knowledge Infrastructure, and Wanfang databases published until January 2016. We combined the following search items: "parathyroid hormone" OR "hyperparathyroidism" and "heart failure" or "cardiac failure" and "follow-up" or "prospective," with no restriction of language. In addition, reference list of the included

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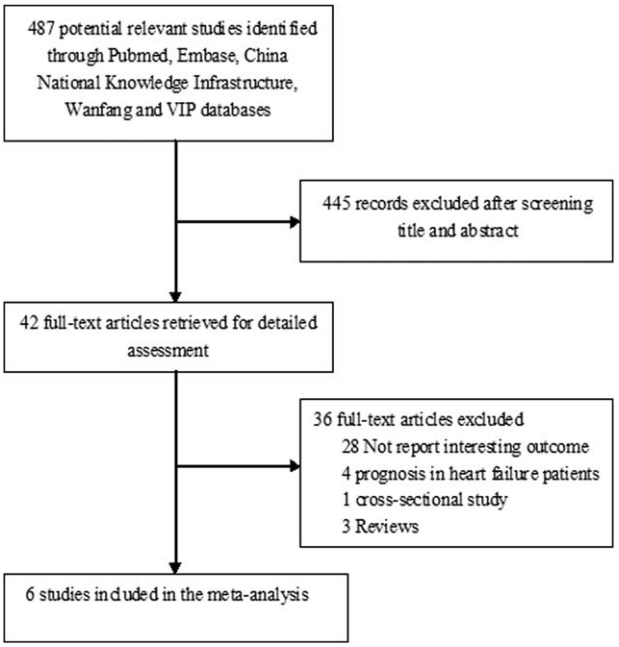


**Figure 1.** Flow diagram of the study selection.

studies and reviews on this topic was manually scanned for additional possible studies. If the outcomes were not reported in the original study, we contacted the corresponding author by e-mail.

### 2.2. Study selection

Studies that satisfied the following inclusion criteria were eligible: prospective observational studies that enrolled general population; studies that investigated the relationship between baseline circulating level of PTH and subsequent heart failure risk; and studies that reported adjusted hazard ratio (HR) and its corresponding 95% confidence intervals (CIs) of heart failure incidence. Studies that were cross-sectional design, abstract, or review were excluded.

### 2.3. Data extraction and quality assessment

Two independent authors (FBM and WW) used a standardized form to extract the relevant data from the selected studies. Any discrepancies between 2 authors were settled through discussion. The extracted data included first author's surname, years of publication, study design, geographic location, sample size, proportion of male, age of population, method of PTH assay, category of PTH comparison, number of events, most fully adjusted HR and 95% CI, follow-up duration, and variables adjusted. Two independent authors (FBM and WW) evaluated the quality of the included studies in accordance with the Newcastle-Ottawa Scale[19] that allowed a maximal score of 9 stars. Studies with a rating of 5 or more stars were regarded as moderate to good quality.

### 2.4. Statistical analyses

Analyses were conducted using the STATA 12.0 software package (STATA Corp LP, College Station, TX). Pooled risk estimates were expressed as the HR with 95% CI for the highest versus lowest PTH category. The likelihood of statistical heterogeneity across studies was assessed by Cochrane $Q$ test with significance set at 0.10 or less and $I^2$ statistic more than 50%. We selected the random effects model when pooled analysis resulted in significant heterogeneity; otherwise, a fixed-effect model was applied. We applied both Begg test[20] and Egger test[21] to explore potential publication bias. Subgroup analyses were performed according to the sample sizes (>1000 vs <1000), duration of follow-up (median or mean ≥10 years vs < 10 years), gender (male vs both gender), and age of patients (middle-aged vs older adults).

## 3. Results

### 3.1. Characteristics of the included studies

The detailed description of literature search and study selection process is shown in Figure 1. Six prospective studies[6–11] were retrieved from 334 citations. The included studies were published between 2010 and 2014. Three studies were from the United States,[7,10,11] 1 from Germany,[9] 1 from Sweden,[6] and 1 from the United Kingdom.[8] The sample size ranged from 864 to 10,392. The age of participants was over 35 years. Four studies[7,9–11] included both men and women and 2 studies[6,8] enrolled only men. The follow-up duration ranged from 8.2 to 19 years. All the included studies are adjusted for the estimated glomerular filtration rate and common cardiovascular risk factors. Newcastle-Ottawa Scale stars ranged from 5 to 8 and overall methodological quality of included studies was moderate to good. Characteristics of the included studies are summarized in Table 1.

### 3.2. Meta-analysis of incident heart failure

Relationship between circulating level of PTH and incident heart failure was reported in six studies. A total of 25,207 participants and 2561 heart failure events were analyzed. As shown in Figure 2, statistical heterogeneity ($I^2$=70.2%; $P$=0.005) was observed across six studies. Meta-analysis with a random effects model showed that higher circulating level of PTH was associated with an increased risk of heart failure (HR: 1.38; 95% CI 1.09–1.74). Furthermore, pooled HR for heart failure was 1.27 (95% CI 1.14–1.42) in a fixed-effect model. Begg test ($P$=0.452) and Egger test ($P$=0.203) did not provide evidence of substantial publication bias.

### 3.3. Subgroup analyses and sensitivity analyses

In the subgroup analyses (Table 2), the associations between higher circulating level of PTH and excessive risk of heart failure were not observed in the middle-aged persons (HR: 1.01; 95% CI 0.85–1.21), and over 10 years follow-up (HR: 1.28; 95% CI 0.95–1.71). Moreover, the risk of heart failure seemed more pronounced among men (HR: 1.75; 95% CI 1.38–2.22). The results of the sensitivity analyses showed only minimal changes in magnitude and direction of the pooled HR when anyone study was excluded from the meta-analysis, suggesting the robustness of our findings (data not shown).

## 4. Discussion

This meta-analysis suggests that higher circulating PTH is associated with an excessive risk of heart failure in the general population. Participants with increased circulating PTH had a

**Table 1**

**Characteristics of the included studies.**

| Study/year | Region | Design | Subjects (% male) | Age, y | PTH, pmol/L, comparison | PTH assay | Verification of HF | HF events HR (95% CI) | Follow-up, y | Adjusted for variables | Total NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hagström et al 2010[6] | Sweden | Prospective, community-based study | 864 (100) | Mean 71 | Highest vs lowest quintile >5.23 vs < 2.93 | Intact PTH by solid-phase 2-site chemiluminescent immunoassay | ICD-8: 427.0, 427.1, 428.99; ICD-9: 428; ICD-10: I50 or I11.0. | Congestive HF (75); 3.00 (1.37–6.61) | 8.74 | Hypertension, prior MI, LVH, DB, smoking, BMI, eGFR, hypercholesterolaemia, S-calcium, S-phosphate, S-albumin, vitamin D level, dietary calcium or vitamin D, PA and blood draw season. | 6 |
| Kestenbaum et al 2011[7] | The United States | Prospective study | 2312 (30) | >65 | Top vs low category ≥6.91 vs <6.91 | Serum intact PTH by 2-site immunoassay | Physician diagnosis plus symptoms and signs of HF, pulmonary edema on chest x-ray, or medical treatment for HF. | HF (504); 1.30 (1.05–1.61) | 14 | Age, race, sex, season of the year, clinic site, DB, antihypertensive drugs, smoking, education, PA, BMI, SBP, CRP, TC, HDL, calcium, phosphorus, cystatin C, and eGFR. | 8 |
| Wannamethee et al 2014[8] | United Kingdom | Prospective study | 3731 (100) | 60–79 | Top vs low category ≥6.02 vs < 6.02. | Intact PTH by electrochemiluminescence | Doctor-confirmed diagnosis of HF from primary care medical records | HF (287); 1.66 (1.30–2.13) | 13 | Age, smoking, social class, alcohol intake, PA, BMI, HDL,DB, preexisting MI/stroke, AF, eGFR, heart rate, LVH, SBP, antihypertensive drugs, FEV1, and CRP. | 7 |
| di Giuseppe et al 2014[9] | Germany | Prospective case–cohort study | 1449 (40.1) | 35–65 | Highest vs lowest quintile >5.12 vs < 2.24 | Intact PTH by ELISA kits | ICD-10: I50 | Congestive HF (221); 1.21 (0.71–2.07) | 8.2 | Age, sex, fasting status, waist circumference, BMI, alcohol, DB, CHD, sports, smoking, education, hypertension, hyperlipidemia, 25-hydroxyvitamin D, and eGFR. | 7 |
| Bansal et al 2014[10] | The United States | Prospective cohort study | 6459 (46.6) | 62.1 ± 10.3 | Top vs low category ≥6.91 vs < 6.91 | Intact PTH by 2-site immunoassay | Clinical symptoms or signs, a physician diagnosis of HF, and medical treatment for HF. | HF (180); 1.50 (1.03–2.19) | 8.46 | Age, sex, race/ethnicity, education, height, weight, smoking, PA, DB, eGFR, urine albumin to creatinine, SBP, antihypertensive drugs, calcium, phosphorus, FGF-23,and 25-hydroxyvitamin D. | 6 |
| Folsom et al 2014[11] | The United States | Prospective study | 10,392 (54.9) | 45–64 | Top vs low category ≥6.91 vs <6.91 | PTH by a sandwich immunoassay method | ICD-9: 428 | HF (1294); 0.99 (0.82–1.19) | 19 | Age, race, sex, season, drinking, ethanol intake, smoking, sports index, BMI, SBP, antihypertensive drugs, TC, eGFR, serum calcium, phosphorous, and 25-OH-vitamin D. | 8 |

AF = atrial fibrillation, BMI = body mass index, CHD = coronary heart disease, CRP = C-Reactive protein, CVD = cardiovascular disease, DB = diabetes mellitus, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, $FEV_1$ = forced expiratory volume in 1 second, FGF = fibroblast growth factor, HDL = high-density lipoprotein, HR = hazard ratio, ICD = International Classification of Disease, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale, PA = physical activity, PTH = parathyroid hormone, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride. To convert PTH values in picograms per milliliter into pmol/L, divided by 9.4.

**Table 2**

**Subgroup analyses of parathyroid hormone and risk of heart failure.**

| Subgroup | No. of studies | Pooled HR | 95% CI | Heterogeneity between studies |
|---|---|---|---|---|
| Sample size | | | | |
| <1000 | 1 | 3.00 | 1.37–6.59 | — |
| >1000 | 5 | 1.30 | 1.05–1.61 | $P=0.016$; $I^2=67.0\%$ |
| Gender | | | | |
| Men | 2 | 1.75 | 1.38–2.22 | $P=0.160$; $I^2=49.4\%$ |
| Men + women | 4 | 1.16 | 1.02–1.32 | $P=0.128$; $I^2=47.2\%$ |
| Age | | | | |
| Middle-aged | 2 | 1.01 | 0.85–1.21 | $P=0.488$; $I^2=0.0\%$ |
| Older adults | 4 | 1.49 | 1.29–1.72 | $P=0.149$; $I^2=43.8\%$ |
| Follow-up duration, y | | | | |
| <10 | 3 | 1.61 | 1.06–2.43 | $P=0.166$; $I^2=48.0\%$ |
| ≥10 | 3 | 1.28 | 0.95–1.71 | $P=0.004$; $I^2=82.1\%$ |

CI = confidence interval, HF = heart failure, HR = hazard ratio.

38% excessive risk of heart failure in the overall patients and 75% excessive risk of heart failure among men.

In the stratified analysis, gender of patients modified the magnitude of heart failure risk. Men with higher PTH were associated with 75% excessive risk of heart failure than the both gender groups. This finding implies that higher PTH levels appeared to have a pronounced impact on men. Given there are significant differences in etiology of heart failure,[22] women as a subgroup for statistical analysis is warranted in the future study. However, the exact mechanisms for the observed differences remain unclear. In addition, the magnitude risk estimate was reduced in studies with more than 10 year's follow-up, suggesting heart failure events mainly occurred in the early follow-up duration. Furthermore, subgroup analysis indicated that the effect of PTH on incident heart failure was not statistically significant in middle-aged population. Age of participants appeared to modify the relationship between PTH and risk of heart failure.

The role of PTH as a potential risk factor for heart failure has been widely investigated.[23] Several studies did not include in this meta-analysis also investigated the relationship between higher circulating PTH and heart failure. Consistent with the finding of our study, subjects with higher baseline PTH value had a 43% greater risk of heart failure in a cross-sectional study.[12] Higher PTH level was an independent risk factor for hospitalization[14,15] in heart failure patients. Moreover, higher PTH level was also associated with 90% excessive risk all-cause mortality in heart failure outpatients.[13] These findings suggest that circulating level of PTH predicts subsequent risk of heart failure in the general population as well as adverse outcomes in patients with heart failure. Possible mechanisms can explain the relationship between PTH and heart failure risk. Higher PTH promotes endothelial dysfunction[24] and increase aortic stiffness.[25] In addition, PTH is also linked to arterial hypertension[26,27] and left ventricular hypertrophy.[28]

Several potential limitations should be acknowledged. First, substantial heterogeneity ($I^2=70.2\%$; $P=0.005$) might reduce the reliability of our results. The differences in age, gender, sample size, follow-up duration, and severity of heart failure may be the sources of heterogeneity. Second, all the included studies enrolled the middle to older participants; therefore, our findings may not be generalized to younger population and women. Third, lack of repeated measurements of PTH level is a major limitation. A single baseline measurement may might have led to misclassification of participants or not accurately reflect the changes of PTH over time. Finally, included studies failed to adjust confounders in a consistent way. The lack of adjustment for phosphate, fibroblast growth factor-23 may have resulted in a slight overestimation of the risk estimate.

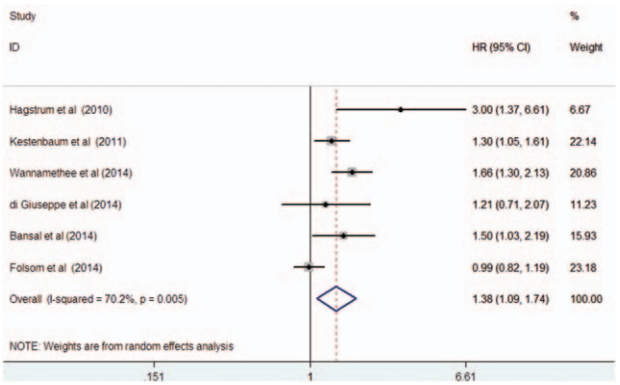


**Figure 2.** Hazard ratio and 95% confidence intervals of higher circulating level of parathyroid hormone and risk of heart failure in a random effect model.

## 5. Conclusions

This meta-analysis indicates that increased PTH level is independently associated with an increased risk of heart failure in the general population. This risk seems more pronounced among elderly men. However, well-designed randomized controlled trial should be carried out to evaluate whether reducing the levels of PTH will decrease heart failure risk or attenuate the disease progression.

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