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Vitamin D, Parathyroid Hormone, and Cardiovascular Events Among Older Adults

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Objectives The aim of this study was to evaluate associations of 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) concentrations separately and in combination with incident cardiovascular events and mortality during 14 years of follow-up in the CHS (Cardiovascular Health Study).

Background Vitamin D deficiency and PTH excess are common in older adults and may adversely affect cardiovascular health.

Methods A total of 2,312 participants who were free of cardiovascular disease at baseline were studied. Vitamin D and intact PTH were measured from previously frozen serum using mass spectrometry and a 2-site immunoassay. Outcomes were adjudicated cases of myocardial infarction, heart failure, cardiovascular death, and all-cause mortality.

Results There were 384 participants (17%) with serum 25-OHD concentrations <15 ng/ml and 570 (25%) with serum PTH concentrations ≥65 pg/ml. After adjustment, each 10 ng/ml lower 25-OHD concentration was associated with a 9% greater (95% confidence interval [CI]: 2% to 17% greater) relative hazard of mortality and a 25% greater (95% CI: 8% to 44% greater) relative hazard of myocardial infarction. Serum 25-OHD concentrations <15 ng/ml were associated with a 29% greater (95% CI: 5% to 55% greater) risk for mortality. Serum PTH concentrations ≥65 pg/ml were associated with a 30% greater risk for heart failure (95% CI: 6% to 61% greater) but not other outcomes. There was no evidence of an interaction between serum 25-OHD and PTH concentrations and cardiovascular events.

Conclusions Among older adults, 25-OHD deficiency is associated with myocardial infarction and mortality; PTH excess is associated with heart failure. Vitamin D and PTH might influence cardiovascular risk through divergent pathways. (J Am Coll Cardiol 2011;58:1433–41) © 2011 by the American College of Cardiology Foundation

Disturbances in mineral metabolism are common in older adults and may adversely affect cardiovascular health (1,2). Older age is associated with lower circulating concentrations of 25-hydroxyvitamin D (25-OHD), impaired vitamin D activation within the kidney, and a rise in serum parathyroid hormone (PTH) concentrations (3,4). Disturbances in vitamin D and PTH metabolic axes may increase cardiovascular risk through diverse pathways (1,5,6). In experimental models, vitamin D deficiency activates the renin-angiotensin system, stimulates inflammatory cytokines, and promotes cardiomyocyte growth (7–9). PTH excess increases intracellular calcium in target tissues and is associated with hypertension, cardiac valve calcification, and left ventricular hypertrophy (10,11).

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Previous studies of mineral metabolism and cardiovascular risk have generally focused on middle-aged populations and have evaluated 25-OHD and PTH concentrations separately. In the present study, we evaluated 25-OHD and PTH concentrations together in a general population of 2,312 ambulatory older adults who were free of clinical cardiovascular disease at baseline. We assessed associations

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Abbreviations and Acronyms

GFR = glomerular filtration rate

PTH = parathyroid hormone

25-OHD = 25-hydroxyvitamin D

of mineral metabolism biomarkers with adjudicated cases of incident myocardial infarction, incident heart failure, cardiovascular death, and all-cause mortality during 14 years of follow-up. We hypothesized that lower 25-OHD and higher PTH levels would be associated with cardiovascular events and that associations would be strongest in the presence of both disturbances, because PTH represents an endogenous biologic marker of inadequate vitamin D stores (12,13).

Methods

Study population. The CHS (Cardiovascular Health Study) is a prospective cohort study of clinical and subclinical cardiovascular disease among older patients (14). In 1989 and 1990, the CHS enrolled 5,201 ambulatory men and women age 65 years and older from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. The CHS enrolled an additional 687 African American participants in 1992 and 1993. Exclusion criteria included the use of a wheelchair in the home, institutionalization, the need for a proxy respondent to provide informed consent, plans to move from the area within 3 years, and current treatment for cancer. Each center's institutional review board approved the study, and all participants provided informed consent.

We evaluated CHS participants at the time of their 1992 and 1993 examinations. To focus on incident cardiovascular events, we excluded participants who had prevalent cardiovascular disease at the time of the 1992 and 1993 CHS exams, defined as any 1 of the following conditions: coronary heart disease, heart failure, stroke, transient ischemic attack, claudication, atrial fibrillation, pacemaker, or implantable cardioverter-defibrillator (Fig. 1). CHS investigators determined prevalent cardiovascular conditions by review of medical records, electrocardiographic findings, participant responses to questionnaires, and interim events that occurred between the baseline and 1992 and 1993 CHS

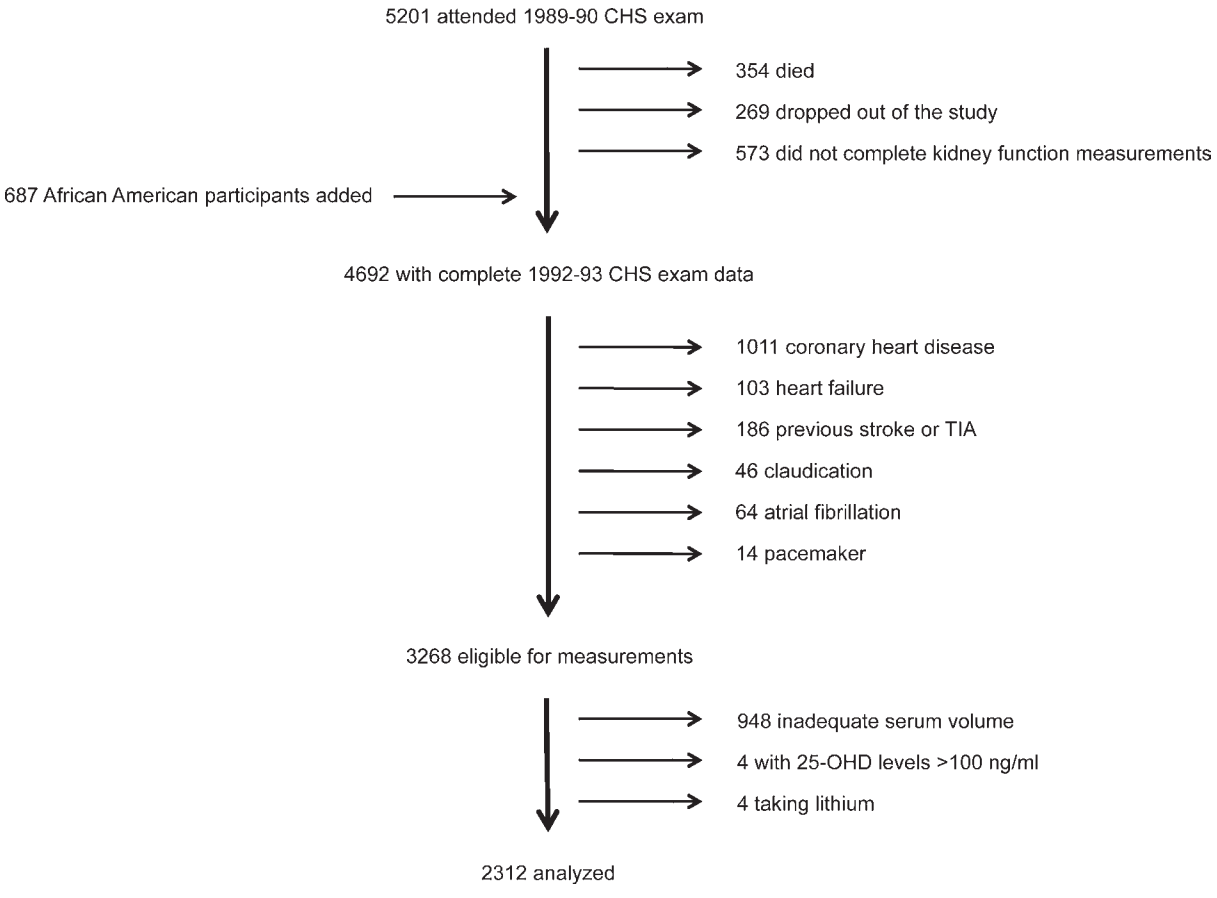

Figure 1 Flow Diagram of the Study Population

Exclusions are shown on the **right side** of the figure; additions to the study population are shown on the **left**.
CHS = Cardiovascular Health Study; TIA = transient ischemic attack; 25-OHD = 25-hydroxyvitamin D.