Introduction

Cardiovascular disease (CVD) – has become one of the major causes of death and disability in most countries of the world. Trends in CVD demographics indicate that CVD mortality has decreased, since the total number of deaths due to CVD declined over the past two decades. However, the incidence of CVD declined less indicating that CVD have become more likely to be non-fatal. The survivors of CVD often develop heart pump failure and loss of heart function in the following years. Consequently, the prevalence of cardiac diseases, including heart failure is expected to rise in the coming years. This poses a great burden on the public health system.

The identification of other, novel factors that can influence loss of heart function is of paramount importance for future cardiac disease prevention. Although much attention has been given to the leading CVD risk factors, namely smoking, obesity and type 2 diabetes, other factors may also be involved in the pathogenesis and progression of CVD.

Vitamin D is a key hormone for bone health. Over the past decade, vitamin D has attracted substantial interest towards extra-skeletal roles in various disease conditions, including CVD. Emerging evidence suggests that other factors of vitamin D metabolism such as parathyroid hormone (PTH) and phosphate might also be important for calcium homeostasis. In the human body, PTH is a hormone secreted by the parathyroid glands. Both vitamin D and PTH are part of a complex metabolism aimed to maintain calcium concentrations within normal ranges. Circulating PTH plays an important role in the conversion of vitamin D to its most active form. In this thesis, disturbances in vitamin D metabolism measured by 25-hydroxyvitamin D (25(OH)D) are hypothesized to be a risk factor of CVD.

The overall objective of this thesis was to unravel potential pathways involved in vitamin D metabolism with clinical and subclinical outcomes of cardiovascular health. We examined the association of serum 25(OH)D and PTH concentrations with various aspects of cardiovascular health using different research techniques and populations.
Cardiovascular Events

Chapter 2 provides a state-of-the-art systematic literature review of available evidence of prospective studies that investigated the association of circulating PTH with CVD events and intermediate outcomes. The meta-analysis indicated that higher PTH concentrations were significantly associated with a 45-50% increased risk for total CVD, fatal CVD and non-fatal CVD events. Elevated PTH was also associated with greater systolic blood pressure and with left ventricular mass, and indicated a trend for an increased risk of incident hypertension.

Chapter 3 describes the relationship between serum PTH concentrations and all-cause and CVD mortality in the Hoorn Study. The results support that higher PTH concentrations are prospectively associated with all-cause mortality. The results for higher PTH concentrations and CVD mortality show a similar pattern, although the association was only significant in a threshold model (quartile 4 vs. quartile 1-3).

Cardiac Biomarkers, Cardiac Structure and Function

Chapter 4 evaluates the relationship of serum 25(OH)D and PTH concentrations with biochemical, electrocardiographic, echocardiographic measurements of cardiac function. Serum 25(OH)D was not associated with any of the biochemical, electrocardiographic, or echocardiographic outcomes. Circulating PTH, however, was associated with higher N-terminal pro-B-type natriuretic peptide and cardiac troponin T concentrations, and greater left ventricular mass in participants with chronic kidney disease. In subjects with normal kidney function, serum PTH concentrations were not associated with any of the outcomes.

Chapter 5 addresses the association between serum 25(OH)D and PTH concentrations with BNP levels. Serum 25(OH)D and PTH concentrations were both cross-sectionally associated with higher BNP concentrations in those subjects with impaired kidney function only. Serum PTH was associated with higher BNP levels independent of serum 25(OH)D. In longitudinal analyses, serum 25(OH)D and PTH concentrations were not associated with BNP levels after 8 years of follow-up.

Chapter 6 describes the relationship between serum 25(OH)D and PTH concentrations with cardiac structure and function after 8 years of
follow-up. Low serum 25(OH)D levels were associated with higher left ventricular mass at 8-year follow-up in participants without prior CVD and in subjects with low kidney function. The associations attenuated after adjustments for serum PTH, which was associated with higher left ventricular mass in subjects with lower kidney function.

Chapter 7 evaluates the relationships between both serum 25(OH)D and PTH concentrations with cardiac structure and function measured with magnetic resonance imaging (MRI). Serum 25(OH)D concentrations were not associated with cardiac MRI measures. Higher PTH concentrations were associated with lower ejection fraction and greater LV mass.

Hypertension

Chapter 8 addresses prospective relationships between both serum 25(OH)D and PTH concentrations with incident hypertension in a large multi-ethnic cohort after 9 years of follow-up. Lower serum 25(OH)D concentrations showed a greater risk of incident hypertension, although the relationship was not statistically significant. Higher PTH concentrations were associated with a significantly greater risk of hypertension, independent of vitamin D and kidney function.

Conclusion

Our observations indicate that vitamin D deficiency and PTH excess are common findings among older populations. The results of this thesis do not support the hypothesis that serum 25(OH)D concentrations might be beneficial for cardiovascular health. Instead, higher PTH concentrations might be harmful for cardiovascular health as was confirmed and replicated in multiple epidemiological studies using different methodologies. The totality of these results suggests that circulating PTH, and not vitamin D, may influence risk factors of CVD, including cardiac biomarkers, cardiac structure and function, and incident hypertension. These findings suggest that PTH excess may play a role in the pathogenesis of CVD.