Systematic Review and Meta-Analysis Evaluating the Impact of Vitamin D on the Risk of Heart Failure: New Evidence from Population-based Studies

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Abstract
We examined the effect of vitamin D on heart failure (HF) prevalence, incidence, and mortality, as well as all-cause mortality in HF patients, using data from peer-reviewed published population-based studies. Relevant studies (n=8766) were identified by systematically searching MEDLINE and EMBASE from 1966 to October 2013. Reported hazard ratio (HR), relative risk (RR), or odds ratio (OR) were extracted for the highest versus lowest categories of blood level of vitamin D or vitamin D supplement. Of 90 studies reviewed in full, 12 eligible studies were selected. The pooled analysis revealed that increased serum vitamin D concentration failed to prevent general population from developing incident HF (RR, 95%CI: 0.927, 0.821 to 1.045), though it appeared to be significantly associated with HF prevalence. Moreover, vitamin D may not affect the risk of death due to HF, but significantly reduces the risk of all-cause death in patient with HF (RR, 95%CI: 0.652, 0.557 to 0.764). Our findings indicate higher levels of vitamin D may not decrease the risk of HF incidence and mortality, but HF patients who are deficient in vitamin D tend to suffer from higher risk of all-cause death.

Keywords — cardiovascular disease, heart failure, meta-analysis, systematic review, vitamin D.


I. INTRODUCTION
In the past several decades, the association between vitamin D and cardiovascular health has been widely reported by epidemiological and animal studies. One of key issues is whether vitamin D deficiency plays a vital role in the development of heart failure (HF), an end stage of several major forms of cardiovascular diseases (CVD). Current guidelines and scientific statements neither formally considered vitamin D deficiency as a risk factor for HF nor recommend routine vitamin D supplement as a preventive measure. As the rapid accumulation of epidemiological data in the recent decade, there is a need to review what has been done on the association between vitamin D and HF, which may provide important evidence to HF prevention and clinical practice and new insights into further studies. In the present study, we aimed to perform a systematic review and meta-analysis to evaluate the effect of vitamin D on HF-related outcomes.

II. METHODS
Data Sources and Search Strategy
A standardized protocol was developed and used in this systematic review, according to the consensus of reporting meta-analysis. We performed a systematic and comprehensive literature search on vitamin D and HF by using MEDLINE and EMBASE databases from 1966 to October 2013. Search terms were determined in accordance with Medical Subject Heading terms and relevant text words from previously identified key articles. Terms selected for HF included heart failure, cardiac failure, cardiovascular disease, cardiovascular events, heart disease, coronary artery disease, and myocardial infarction. Terms selected for vitamin D included vitamin D, calcifediol, calcitriol, cholecalciferol, and ergocalciferol. In addition to literature search, we also manually reviewed the reference lists of retrieved studies, review articles, as well as clinical guidelines. Any citation that appeared relevant would be further inspected in the full-text.
Eligibility Criteria and Study Selection

The procedure of study selection was conducted in adherence to three key eligibility criteria: (1) the exposure of interest was vitamin D supplement or blood levels (plasma or serum) of vitamin D and the exposure variable should be categorical; (2) the outcome of interest was one of the following HF-related outcomes, including HF incidence, HF prevalence, HF mortality, and all-cause mortality in patients with HF; (3) hazard ratio (HR), relative risk (RR), or odds ratio (OR) estimates with 95% confidence intervals (CIs) were reported or data to calculate these estimates were available. We excluded case reports, review articles, guidelines, letters to editors, editorials, comments, animal studies, and articles published in non-English. Then two investigators independently applied a full-text review in those articles that passed initial screening. If different published articles were duplicate deriving from the same study population, the one with the longest follow-up or having the most recent information would be chosen. Finally, 12 articles were identified for the pooled analysis. Figure 1 shows the flowchart of literature search and study selection.

Data Extraction

One investigator extracted the following information from selected studies, including the abbreviation of study’s name and/or the first author’s last name, publication year, country where the study was performed, study design, study population (sample size and population features), age and gender of participants, time of follow-up, measure of vitamin D, outcome definition, variables adjusted in the analysis, and the main finding. The extracted estimates of HR, RR, or OR were based on the comparison of HF-related outcomes between the highest and lowest categories of blood level of vitamin D or vitamin D supplement, reflecting the greatest degree of controlling for potential confounders. The other investigator then verified these extracted data for completeness and accuracy; the disagreements between researchers would be resolved by consensus. The extracted data was summarized in Table 1-4. One prospective cohort study simultaneously provided data of HF prevalence and mortality \(^{[10]}\) and these data were separately sifted out.

Study Quality Assessment

We used a three-category grading system, which is applicable to all types of study design, to demonstrate the overall methodological quality of selected articles in evaluating the effect of vitamin D on risk of HF. \(^{[11]}\) A high quality study is defined on the basis of these with (1) a prospective design, (2) no obvious selection bias, (3) exposure assessment, (4) outcome ascertainment, (5) completeness of follow-up, (6) appropriate analytic methods and results report. Using these aforementioned criteria, selected studies were categorized as good, fair, or poor. If a study largely adhered to the criteria for a high quality study, it would be graded as good; if a study failed to meet parts of the criteria but the possible bias was not adequate to invalidate the results, it would be graded as fair; if a study was found having severe defects in study design, data collection, analyses, or reporting, it would be graded as poor.

Statistical Analysis

We applied random-effect models, which consider both within-study and between-study variation, \(^{[12]}\) to estimate the pooled effects of vitamin D on the risk of developing HF-related outcomes. Four random-effect models were built to examine the associations of vitamin D with HF incidence, prevalence, and mortality, as well as all-cause mortality in HF patients, respectively; Statistical heterogeneity among these studies was tested using Cochrane Q and \(I^2\) statistic. We also assessed potential publication bias using Kendall’s tau and Egger’s regression intercept test. \(^{[13]}\) All statistical analyses were performed using Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ, USA) and SAS (version 9.2; SAS Institute, Cary, NC) software packages. A two-sided \(P\) value < 0.05 was considered statistically significant.

III. RESULTS

General Study Characteristics

Of 90 articles that were qualified for a full text review, we finally identified 12 eligible articles in which 10 tested the association between vitamin D and HF as their primary study outcomes, and the other 2 as their secondary outcomes. Four studies were conducted in the United States, 4 in Germany, and the other 4 in New Zealand, Denmark, Netherland, and Israel, respectively. On the basis of study quality assessment, 8 studies were graded as fair and 4 as good. Table 1-4 shows the results of the study quality assessment.

Twelve studies involved a total of 80,826 participants and 63,762 of them were included in the final meta-analysis, because only those in the highest and lowest categories of blood level of vitamin D or vitamin D supplement will enter into random-effect models. Nine studies were prospective cohort studies, 2 were randomized clinical trials (RCT), and 1 was cross-sectional study. All of cohort and cross-sectional studies measured serum vitamin D level, while 2 RCTs have vitamin D supplement as the intervention versus matching placebo as the control. General features of studies were summarized in Table 1-4 according to the diverse HF-related outcomes. Table 1, 2, and 3 showed studies evaluating the effect of vitamin D on the HF incidence, prevalence, and mortality, respectively; Table 4 presented studies that explored the association between vitamin D and all-cause mortality in patients with HF.

Vitamin D and Heart Failure Incidence

Two prospective cohort studies compared the risk of incident HF among different serum vitamin D levels, \(^{[14, 15]}\) while 1 RCT compared that between calcium/vitamin D supplement and placebo \(^{[16]}\) (Table 1). Both cohort studies showed that lower serum vitamin D concentration neither increased nor decreased
the HF incidence in the population free of CVD at baseline.\textsuperscript{[14, 15]} The RCT from the Women’s Health Initiative also suggested that there was no significant association between calcium/vitamin D supplement and risk of hospitalized HF incidence in the healthy postmenopausal women.\textsuperscript{[16]} though the possible confounding effect of calcium was not controlled. The pooled analysis that combined the data from these three studies demonstrated that vitamin D is not an independent predictor for incident HF in the generally healthy population (Figure 2-A, RR, 95%CI: 0.927, 0.821-1.045). Neither statistically significant heterogeneity (Q = 1.461, I\(^2\) = 0.0%, P = 0.482) nor publication bias (Kendall’s tau test, P = 0.602; Egger’s test, P = 0.550) was observed.

**Vitamin D and Heart Failure Prevalence**

Two prospective cohort studies\textsuperscript{[10, 17]} and 1 cross-sectional study\textsuperscript{[18]} reported HF prevalence and examined its association with serum vitamin D concentration (Table 2). The cross-sectional study derived from National Health and Nutrition Examination Survey (NHANES)\textsuperscript{[18]} the cohort study using a large-scale electronic medical record database\textsuperscript{[17]} indicated a statistically significant, inverse association between serum vitamin D level and HF prevalence, while the other cohort study, German Diabetes Dialysis Study (4D study),\textsuperscript{[10]} showed a non-significant association between serum vitamin D concentration and HF prevalence. The pooled OR (95%CI) from these three studies was 0.640 (0.412-0.995), indicating that individuals within the highest category of serum vitamin D level had a 36% lower risk of prevent HF as compared to those who were within the lowest category of serum vitamin D level (Figure 2-B). Statistical tests showed no publication bias (Kendall’s tau test, P = 0.117; Egger’s test, P = 0.281) but significant heterogeneity (Q = 12.388, I\(^2\) = 83.9%, P = 0.002).

**Vitamin D and Heart Failure Mortality**

Currently, only 2 published studies were available exploring the effect of vitamin D on the risk of death due to HF (Table 3).\textsuperscript{[10, 19]} One prospective study of 3299 Caucasian patients referred for coronary angiography concluded severe vitamin D deficiency might cause an increased risk of HF mortality,\textsuperscript{[19]} but the other study (n=1108) conducted among the patients with type-2 diabetes mellitus did not observed a significantly inverse association between serum vitamin D level and risk of mortality from HF .\textsuperscript{[10]} The pooled RR of subjects within the highest categories of serum vitamin D level did not show a statistically lower risk of HF mortality as compared to those who were in the lowest categories of serum vitamin D concentration (Figure 2-C, RR, 95%CI: 0.573, 0.143-2.303). Since at least three studies are needed to assess potential publication bias, we are unable to analyze whether a publication bias exists in this pooled analysis. For study heterogeneity, a significant result was observed (Q = 5.555, I\(^2\) = 82.0%, P = 0.018).

**Vitamin D and All-cause Mortality in Patients with Heart Failure**

There were 5 studies (4 prospective cohort studies and 1 RCT) assessing the association between vitamin D and all-cause mortality in patients with HF (Table 4).\textsuperscript{[20-24]} Of these studies, two used a composite outcome; the COACH study used re-hospitalization due to worsening HF and all-cause death as a combined outcome,\textsuperscript{[23]} while the other study defined the combined outcome as if a patient died or received a cardiac transplantation.\textsuperscript{[21]} All 4 cohort studies showed a significant difference of survival time between the highest and lowest categories of serum vitamin D concentration in favor of the protective effect of higher vitamin D level;\textsuperscript{[20, 22-24]} however, the only RCT did not observe a significant difference in all-cause mortality between patients with vitamin D supplement and the matching placebo group.\textsuperscript{[21]} Using the meta-analysis approach, the pooled RR (95%CI) of the five studies was 0.652 (0.557-0.764) for all-cause mortality in HF patients in the highest category of serum vitamin D (include patients receiving vitamin D supplement) as compared to their counterparts in the lowest category of serum vitamin D (include patients receiving placebo), (Figure 2-D). All tests indicated non-significant study heterogeneity (Q = 5.948, I\(^2\) = 32.75%, P = 0.203) and publication bias (Kendall’s tau test, P = 0.624; Egger’s test, P = 0.874).

IV. DISCUSSION

**Key Findings**

In the present meta-analysis, higher levels of serum vitamin D fail to prevent generally healthy people from developing incident HF during follow-ups, though the analysis derived from cross-sectional studies showed a statistically significant protective effect for vitamin D. We also found that higher levels of serum vitamin D do not reduce the risk of dying from HF; however, a pooled, preventive effect of vitamin D on all-cause death was observed in patients with HF. These findings of the current paper, combined with that from other epidemiological and experimental studies, can add new insights to the longstanding issue about the role of vitamin D in cardiovascular health.

**Vitamin D and Cardiovascular Health**

Human beings can obtain vitamin D through dietary intake (e.g. oily fish, dairy products, and fortified foods) as well as cutaneous synthesis from 7-dehydrocholesterol by ultraviolet (UV) irradiation.\textsuperscript{[1, 2, 5]} The latter endogenous production of vitamin D is predominant, accounting for approximate 80-90% of total supply,\textsuperscript{[25]} and is dependent on the seasonal changes and distance from equator and altitude.\textsuperscript{[2]} Owing to insufficient UV light, levels of vitamin D tend to decline over the winter, especially in regions at high latitudes. The observation that cardiovascular events are also more common in winter therefore caused the widespread interest linking vitamin D to cardiovascular health.\textsuperscript{[3]}
Laboratory research has shown that vitamin D may have a protective effect on circulation systems, as it affects the function of cardiomyocytes [26-29] and vascular endothelial cells [30-34]. Lower levels of vitamin D receptor (VDR) expression in endothelial cells and impaired electromechanical coupling; treatment of vitamin D analogues attenuated cardiac abnormalities that were induced under different conditions [28, 29]. In addition, vitamin D binds to VDR expressed in endothelial cells to stimulate the development of immature cells through modulating response elements in the vascular endothelial growth factor (VEGF) promotors [32, 33]. The up-regulation of VEGF activated by vitamin D is thought to be critical for the maintenance of myocardial blood supply and function, especially diastolic function [34]. In human coronary artery smooth muscle cells, vitamin D metabolites exert effects on regulating VDR target gene expression [35]. These metabolites can also decrease endothelium-dependent vascular smooth muscle contractions and vascular tone in hypertensive rat models. Moreover, it was found that vitamin D blunts the deleterious effect of advanced glycation end product in endothelial cells [31].

In spite of encouraging results from basic research, these findings do not completely parallel that from clinical and epidemiologic studies. Findings about the relationship between vitamin D status and various cardiovascular disorders are somewhat divergent, from different study populations to different study designs. Inverse associations of vitamin D with well-established cardiovascular risk factors, such as age, obesity, diabetes, and hypertension, have been widely reported. Of these associations, that between vitamin D sufficiency and lowered blood pressure (BP) level was believed to be the most convincing evidence of confirming the role of vitamin D in the pathogenesis of CVD. A meta-analysis involving 8 RCT, however, exhibited a non-significant reduction in systolic BP (-3.6 mmHg, 95% CI -0.8 to 0.7) and a statistically significant but small effect in diastolic BP (3.1 mmHg, 95% CI -5.5 to -0.6), comparing vitamin D supplements to placebo [38].

Other meta-analyses on a similar topic even have discrepant conclusions. One utilizing the data from 19 independent prospective studies, 17 cohort and 2 nested case-control, demonstrated significant, generally linear, and inverse associations between circulating 25(OH)D and risk of various CVD endpoints, including total CVD mortality, coronary heart disease (CHD), and stroke. Two other meta-analyses had closed conclusions; lower levels of vitamin D appears to be harmful for stroke having a pooled OR (95% CI) of 1.54 (1.43 to 1.65) and a corresponding RR of 1.46 (1.35-1.58) in prospective general population studies, comparing lowest with highest quartile of vitamin D concentration [40]. Similarly, higher levels vitamin D was found to have 21% (95% CI, 13-28%) lower vascular mortality. Nevertheless, meta-analyses of RCT provided opposed outcomes, one based on 8 RCT revealed that a slight decline in risk of having cardiovascular events was not statistically significant for vitamin D supplements versus placebo (pooled RR, 95% CI: 0.90, 0.77 to 1.05), where cardiovascular events were defined as CVD death, nonfatal CHD or myocardial infarction (MI), or nonfatal stroke [11]. It is worth mentioning that most randomized vitamin D therapy trials were not specifically designed to assess its effect on cardiovascular health [2-11]. The non-significant outcome was either confirmed by a meta-analysis that summarized 51 randomized trials and did not find significant associations of vitamin D with patient-important outcomes of death (pooled RR, 95% CI: 0.96, 0.93 to 1.00), MI (pooled RR, 95% CI: 1.02, 0.93 to 1.13), and stroke (pooled RR, 95% CI: 1.05, 0.88 to 1.25). In addition, meta-analyses focusing on all-cause mortality provided evidence favoring the preventive benefits of vitamin D [13, 41]. A study included 12 prospective, population-based cohort studies and showed a 20 nmol/L increase of 25(OH)D was significantly associated with an 8% lower overall mortality in general elderly population [13] while the other one indicated a 28% reduced all-cause mortality, comparing top versus bottom quarter of vitamin concentration [41]. So far available clinical and epidemiologic evidence for vitamin D and cardiovascular health appears dissonant, to some extent. It is the reason why vitamin D was neither formally considered as a risk factor for heart failure nor recommended as routine replenishment in the scientific statement [7] and clinical guideline [8].

Findings of the Present Study

The present meta-analysis concentrates on vitamin D and HF, adding new evidence to this academic debate. We found a strong association between vitamin D and HF prevalence from 3 cross-sectional investigations (pooled OR, 95% CI: 0.640, 0.412 to 0.995); however, such an association fails to remain significant when turning to incident HF from other 3 prospective cohort studies (pooled RR, 95% CI: 0.927, 0.821 to 1.045). Given the advantage of studies designed prospectively that can assure the temporality in causal inference, the result showing a non-significant relationship of vitamin D to HF incidence may be more credible. But, to interpret the non-significant result from prospective studies, we still need to be careful. Incident HF, as the end-stage of several major forms of CVD, is probably affected by its precursors, which means CVD patients may die before developing HF and these competing deaths can confound the potential association between HF and vitamin D. Another possible explanation is patients with precursors of HF may be deficient in vitamin D and receive vitamin D treatment, leading to higher levels vitamin D when he or she diagnosed with HF. Our findings also indicate that vitamin D may not affect the risk of death due to HF (pooled RR, 95% CI: 0.573, 0.143 to 2.303); however, this result should also be treated
conservatively, since it is synthesized from merely 2 studies and study population may not be representative. One of the studies with a non-significant result is derived from 1108 diabetic haemodialysis patients,[10] so the significant result of LURIC study with 3299 patients referred for coronary angiography may have better external validity. In contrast, vitamin D was found to significantly reduce the risk of all-cause death in patient with HF (pooled RR, 95%CI: 0.652, 0.557 to 0.764). This confirms the finding of another previously published meta-analysis which was derived from 12 prospective cohort studies in geriatric population.[13] The effect of vitamin D on decreasing the risk of all-cause mortality in HF patients as well as in general aged population may be explained by the fact that vitamin D exerts diverse impacts on different biological systems. This fact also is the reason why there is no consensus regarding the optimum level of circulating 25(OH)D for human health, implying different thresholds may apply to different biological systems.[10] Additionally, it should be noted that the pooled RR of 0.652 for the risk of all-cause death was estimated on basis of 5 studies, where all 4 prospective cohort studies had statistically significant RRs, but the only RCT exhibited a non-significant one. Nonetheless, the power of the RCT seems inadequate, considering a relative small sample size of 118 eligible participants.

Aside from those studies included in the meta-analysis, there are other studies exploring the association of vitamin D supplements with functional capacity and quality of life in patients living with HF. Two cross-sectional studies used 6-minute walk[44] and peak oxygen uptake (Vo2)[45] as substitutes of functional capacity, respectively, and both demonstrated a significant decline of physical function related to vitamin D intake. These findings, however, was contradicted by a RCT in which functional capacity and quality of life were not improved by vitamin D interventions relative to placebo.[46] All three studies have no more than 105 study subjects.

In sum, findings about the association between vitamin D status and HF varied across different study designs and populations. Therefore, the corresponding causal inference remains tough.

**Difficulties in Causal Inference**

Inconsistencies from different studies undoubtedly weaken the causality between vitamin D and cardiovascular health. Lack of consistency, however, does not rule out the causal relationship, since some effects produced by one cause may change under different conditions.[43] Even if it is supposed the cause-effect relationship was unaffected by inconsistencies of findings, the independent statistical association is complicated by the possible reverse causality that lower circulating vitamin D levels may be the result of cardiovascular disorders instead of the cause of diseases.[2, 3] Since ambient sunlight exposure maintains physiological production of vitamin D, it is possible that cardiovascular abnormalities limit outdoor physical activities for people having CVD and thus this population tends to have vitamin D insufficiency, compared with ambulatory individuals who are more physically active.[2] This plausible explanation has been supported by the finding that vitamin D levels are associated with exercise capacity in healthy humans.[47] In addition, obesity, an important risk factor leading to CVD and subsequent poor outcomes, may also lower circulating vitamin D levels for the reason that excessive adipose tissue can act as a reservoir of hydrophobic molecule to absorb fat-soluble vitamins.[3] Hence, current limited evidence cannot exclude the doubt about the epiphenomenon that vitamin D deficiency in patients with CVD or HF may only reflect the burden of preexisting disease and risk factors. To remove this doubt, we need more well-designed RCTs with large sample sizes to examine the causality.

However, RCTs are only able to prove whether supplements of vitamin D improve cardiovascular health; the difference between supplements and natural, cutaneous synthesis of vitamin D ought to be further evaluated. Currently, cutaneous synthesis of vitamin D that consumes 7-dehydrocholesterol, a precursor of cholesterol, is considered to probably influence lipid levels.[2] It has been observed that plasma lipid levels, as vitamin D levels, experience a seasonal variation having higher levels in winter and reaching the nadir in summer; this finding remains unchanged even after controlling for diet and physical activity.[48] On the other hand, a RCT found short-term oral vitamin supplements fail to significantly alter the lipid levels.[49] Also, other photoproducts during the process of synthesizing vitamin D in the human epidermis may affect cardiovascular health.

Additionally, a recent systematic review that compared the discrepancy between observational and experimental studies may be able to provide beneficial insights; most of prospective studies reported moderate to strong inverse association between vitamin D and diverse diseases, including CVD; however, intervention studies did not show an effect of vitamin D supplement on disease occurrence except for slight decrease in all-cause mortality. To explain the discrepancy, this systematic review raised a possibility that ageing and inflammation involved in disease occurrence resulted in lower vitamin D concentration in the wide range of disorders. The slight gain in survival via vitamin D supplement in elderly people could be attributable to the benefit of restoring vitamin D deficits due to ageing and lifestyle changes.[50]

**Strengths and Limitations**

Due to the effective blood pressure and CVD management in past decades, more and more CVD patients proceed to HF, the end-stage of several forms of CVD. Thus, to evaluate the effect of vitamin D on HF has important public health implication. To the best of our knowledge, it is the first meta-analysis exploring the association between vitamin D and HF. Also, this study systematically covers diverse HF-related outcomes, involving HF prevalence, incidence, mortality, and all-cause mortality in HF patients. Some limitations have to be considered when
interpreting the result of the present meta-analysis. First of all, our findings are limited by a small number of qualified studies. Population-based studies about vitamin D and HF are still very limited at present. Because of limited qualified studies, we did not differentiate study designs between cohort study and RCT when estimating the pooled effect of vitamin D on the risk of incident HF and all-cause death in HF patients. Limited quantity of eligible studies further made sensitivity analyses which evaluate the impacts of each selected study on the final results unfeasible. Also, of twelve selected studies, only two were RCT; the very limited RCT may result in inadequate causal inference. Second, possible variability in selected studies’ quality may be another non-ignorable limitation. The definition of HF slightly differs among studies; the categorization of blood level of vitamin D was not standardized and so was the dose of vitamin D supplement. Also, though most of selected studies have controlled diverse confounders in their analyses, we cannot guarantee that possible biases and residual confounding have been fully ruled out. Third, study heterogeneity may affect the quality of the current study. Statistically significant heterogeneity was shown when evaluating the combined association of vitamin D with HF prevalence and mortality. Despite this limitation, random effect models incorporating heterogeneity could fix the flaw to some extent. Fourth, publication bias should be a concern. Kendall’s tau and Egger’s tests found no significant publication bias in this study; however, the small number of selected studies may lower the power of statistical tests to detect potential publication bias and thus possible publication bias cannot be totally excluded. Last but not least, although we have meticulously developed and conducted the strategy of literature search and study selection, it is still possible that a few related studies, published or unpublished, were not included. The search strategy based on English may also exclude studies published in other languages.

V. CONCLUSIONS

Results from the present meta-analysis indicate that higher levels of vitamin D may not decrease the risk of HF incidence and mortality, but HF patients who have deficient levels of vitamin D tend to suffer from higher risk of all-cause death. Given the aforementioned limitations of data from observational studies and very limited clinical trials, future large-scale epidemiological studies and high-quality clinical trials are needed and may provide advanced evidence to determine the causal associations between vitamin D deficiency and risk of HF and outcomes.

References


[50.] Autier P, Boniol M, Pizot C and Mullie P. Vitamin D status and ill health: a systematic review. *The Lancet Diabetes & Endocrinology* 2014;2(1):76-8
### Table 1.
CHARACTERISTIC OF STUDIES ON VITAMIN D AND HEART FAILURE INCIDENCE

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Country</th>
<th>Study design*</th>
<th>Study population</th>
<th>Age (mean)</th>
<th>Sex</th>
<th>Follow-up</th>
<th>Exposure (range of vitamin D)</th>
<th>Outcome definition</th>
<th>Factors adjusted in analysis</th>
<th>Main finding</th>
</tr>
</thead>
</table>
| **Bolland et al,** (2010)  
[14]               | Fair    | New Zealand      | prospective cohort (secondary) | 1471 healthy community-dwelling women who were free from major medical conditions, had normal lumbar spine bone mineral density for their age, were not taking agents for osteoporosis (e.g. hormone replacement therapy or vitamin D supplements >1000 IU/d), and had a serum 25(OH)D>= 25 nmol/L. | 74 y       | F   | 5 y       | seasonally adjusted serum 25(OH)D:<50.0 (insufficiency), >=50.0, nmol/L | Self reported HF were independently verified by using medical records and adjudicated by a cardiologist. | Treatment allocation (calcium or placebo), baseline age, body weight, smoking status, SBP, and history of ischemic heart disease, stroke or transient ischemic attack, dyslipidemia, and diabetes. | Women with a seasonally adjusted 25(OH)D concentration <50 nmol/L were not at increased risk of HF. HR (95% CI): 1.00 (0.40-2.40) |
| **CHS; Kestenbaum et al,** (2011)  
[15]               | Good    | the United States | prospective cohort (primary) | 2312 participants who were free of cardiovascular disease at baseline                | 73.9 y     | F&M | 14 y      | serum 25(OH)D: <15.0 (deficiency), >30.0 (sufficiency) ng/mL, according to previously published categories | The study define HF by a physician diagnosis of HF plus documentation of symptoms and signs of HF; pulmonary edema on chest x-ray, Echocardiographic results, or specific medical treatment for HF. | PTH, age, race, sex, season of the year, clinic site, diabetes, AM, smoking, education, kilocalories of physical activity, BMI, SBP, CRP, TC, HDL cholesterol, calcium, phosphorus, and eGFR,<sub>cystatin C</sub>. | Serum 25(OH)D concentrations < 15 ng/ml were not associated with the risk of incident HF (HR 1.17, 95% CI 0.83-1.67), compared to 25(OH)D > 30 ng/ml. |
| **WHI; Hsia et al,** (2007)  
[16]               | Good    | the United States | randomized, double-blind, placebo-controlled trial (secondary) | 36282 generally healthy postmenopausal women 50 to 79 years of age                  | 62.4 y     | F   | 70±14 y mean | calcium and vitamin D supplement (containing calcium carbonate, 500 mg as elemental calcium, with vitamin D3 200 IU twice daily) vs. matching placebo | Hospitalized HF                                                                                      | Stratified by age, prevalent CVD at baseline, and randomization status in the hormone and dietary modification trials. | Calcium/vitamin D supplementation neither increased nor decreased hospitalized HF risk. HR (95% CI): 0.95 (0.83–1.10) |

CHS, Cardiovascular Health Study; WHI, Women's Health Initiative; PTH, parathyroid hormone; AM, antihypertensive medications; BMI, body mass index; SBP, systolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

* Of 12 selected studies, 10 tested the association between vitamin D and HF as their primary study outcomes, and the other 2 as their secondary outcomes.

* Range of vitamin D indicated the cut-off points for the highest and lowest categories of serum vitamin D level or vitamin D intake.

* The intervention of WHI study is combined supplements of calcium and vitamin D.
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Quality</th>
<th>Country</th>
<th>Study design</th>
<th>Study population</th>
<th>Age (mean)</th>
<th>Sex</th>
<th>Follow-up</th>
<th>Exposure (range of vitamin D)</th>
<th>Outcome definition</th>
<th>Factors adjusted in analysis</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES; Kim et al,  (2008)¹¹</td>
<td>Fair</td>
<td>the United States</td>
<td>Cross-sectional (primary)</td>
<td>8351 non-institutionalized population (&gt;20 yrs) from NHANES</td>
<td>NA</td>
<td>F/M</td>
<td>NA</td>
<td>serum 25(OH)D: &lt;50.0, &gt;75.0, nmol/L</td>
<td>HF was self-reported as a response to the question 'Has a doctor or other health professional ever told you that you had heart failure?'</td>
<td>age, race, gender, current smoking, leisure-time physical activity, vitamin D supplement use, and regular milk drink</td>
<td>People having serum 25(OH)D &lt; 50.0 nmol/L may have a higher risk of developing HF (OR 1.73, 95% CI 1.03-2.91) than those with serum 25(OH)D &gt; 75.0 nmol/L</td>
</tr>
<tr>
<td>Anderson et al,²   (2010)¹²</td>
<td>Fair</td>
<td>the United States</td>
<td>prospective cohort (primary)</td>
<td>23792 general healthcare population (&gt; 50 years) data from electronic medical record database</td>
<td>66.6 y</td>
<td>F/M</td>
<td>NA</td>
<td>serum 25(OH)D: &lt;=15.0 (very low), &gt;30.0 (normal) ng/mL, according to previously published categories</td>
<td>HF diagnoses derived from electronic medical record system</td>
<td>NA</td>
<td>Strong inverse association across vitamin D categories were noted for prevalent heart failure</td>
</tr>
<tr>
<td>4D study; Drechsler et al,³ (2010)¹³</td>
<td>Fair</td>
<td>Germany</td>
<td>prospective cohort (primary)</td>
<td>1108 patients with type 2 diabetes mellitus, aged 18-80 years, and on haemodialysis for &lt;2 years</td>
<td>66 y</td>
<td>F/M</td>
<td>NA</td>
<td>serum 25(OH)D: &lt;=25.0 (severe deficiency), &gt;75.0 (sufficiency) nmol/L, according to widely used cut-off values</td>
<td>No detailed HF definition was provided</td>
<td>NA</td>
<td>There was no significant association between HF prevalence and vitamin D levels</td>
</tr>
</tbody>
</table>

NHANES, National Health and Nutrition Examination Survey; 4D study, German Diabetes Dialysis Study; NA, not available HR, hazard ratio; CI, confidence interval.

¹ Anderson’s paper provided the information of HF prevalence at baseline and HF incidence during the follow-up, but data about incident HF were not extractable.

² 4D study simultaneously reported data of HF prevalence and mortality and these data were separately sifted out. Information about HF mortality was summarized in Table 3.
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Quality</th>
<th>Country</th>
<th>Study design</th>
<th>Study population</th>
<th>Age</th>
<th>Sex</th>
<th>Follow-up</th>
<th>Exposure (range of vitamin D)</th>
<th>Outcome definition</th>
<th>Factors adjusted in analysis</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>LURIC Study; Pilz et al, (2008)¹⁹</td>
<td>Good</td>
<td>Germany</td>
<td>prospective cohort (primary)</td>
<td>3299 Caucasian patients referred for coronary angiography</td>
<td>Severe deficiency: 66.0 y; Moderate deficiency: 64.0 y; Insufficiency: 61.8 y; Optimal range: 61.0 y; Median</td>
<td>F/M 7.7 y median</td>
<td>Serum 25(OH)D: &lt;25.0 (severe deficiency), &gt;75.0 (optimal) nmol/L, according to widely used cut-off values</td>
<td>Death due to HF according to death certificates</td>
<td>The month of blood sampling, age, sex, BMI, active smokers, DM, arterial hypertension, GFR, LDL- and HDL-cholesterol, triglycerides, CRP, CAD, ACE inhibitors, diuretics, and β-blockers.</td>
<td>Multivariate HR (with 95% CI) for death due to HF was 2.84 (1.20 – 6.74), when comparing patients with severe vitamin D deficiency with persons in the optimal range.</td>
<td></td>
</tr>
<tr>
<td>4D study; Drechsler et al, (2010)¹⁰</td>
<td>Fair</td>
<td>Germany</td>
<td>prospective cohort (primary)</td>
<td>1108 patients with type 2 diabetes mellitus, aged 18–80 years, and on haemodialysis for &lt;2 years</td>
<td>66 y, mean</td>
<td>F/M 4 y, median</td>
<td>Serum 25(OH)D: ≤25.0 (severe deficiency), &gt;75.0 (sufficiency) nmol/L, according to widely used cut-off values</td>
<td>Details were not provided</td>
<td>Age, sex, atorvastatin treatment, season, CAD, congestive HF, SBP, smoking, duration of dialysis, ultrafiltration volume, BMI, LDL- and HDL-cholesterol, CRP, HbA1c, use of β-blockers, ACE inhibitors, diuretics, PTH, calcium, and phosphate.</td>
<td>There was no significant association between death due to HF and vitamin D levels. 25(OH)D: ≤25.0 vs. &gt;75.0 (reference), HR (95% CI) for death due to HF was 0.96 (0.27–3.41).</td>
<td></td>
</tr>
</tbody>
</table>

LURIC Study, Ludwigshafen RIsk and Cardiovascular Health Study; 4D study, German Diabetes Dialysis Study; BMI, body mass index; DM, diabetes mellitus; GFR, glomerular filtration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; CAD, coronary artery disease; ACE, angiotensin converting enzymes; SBP, systolic blood pressure; HbA1c, hemoglobin A1c; PTH, parathyroid hormone; HR, hazard ratio; CI, confidence interval.
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Quality</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Age</th>
<th>Sex</th>
<th>Follow-up</th>
<th>Exposure (Range of Vitamin D)</th>
<th>Outcome Definition</th>
<th>Factors Adjusted in Analysis</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schierbeck et al, (2011)²⁰</td>
<td>Fair</td>
<td>Denmark</td>
<td>prospective cohort (primary)</td>
<td>148 HF outpatients</td>
<td>68 y median</td>
<td>fM</td>
<td>3.5 y</td>
<td>serum 25(OH)D: &lt;=50.0 (insufficiency), &gt;50.0 (sufficiency) nmol/L</td>
<td>all cause mortality</td>
<td>continuous PTH, categorical PTH status, continuous 25-OHD, age, eGFR, LVEF, and NT-proBNP</td>
<td>A strong and independent significant association of vitamin D insufficiency to all-cause mortality was found (HR 1.9 95% CI 1.1–3.4).</td>
</tr>
<tr>
<td>Schleithoff et al, (2006)²¹</td>
<td>Fair</td>
<td>Germany</td>
<td>double-blind, randomized, placebo-controlled trial (primary)</td>
<td>123 patients with congestive HF (NYHA functional class II); 5 were excluded because of lack of compliance</td>
<td>D(+) 57 y; D(-) 54 y; median</td>
<td>fM</td>
<td>15 mo</td>
<td>D(+): 50 µg vitamin D3/d plus 500 mg Ca/d; D(-): placebo plus 500 mg Ca/d for 9 mo.</td>
<td>all cause mortality</td>
<td>NA</td>
<td>KM estimates showed no significant differences in survival rates in the D(+) and D(−) groups during the 15 mo follow-up (85.7% and 88.2%, respectively; P=0.836).</td>
</tr>
<tr>
<td>Zittermann et al, (2008)²²</td>
<td>Fair</td>
<td>Germany</td>
<td>prospective cohort (primary)</td>
<td>383 end-stage chronic HF patients on a waiting list of cardiac transplantation. Patients &lt;18 y with cardiac re-transplantation were excluded survivors: 54.9 y; non-survivors: 56.9 y; mean</td>
<td>fM</td>
<td>1 y</td>
<td>serum calcitriol: &lt;43 (T1), &gt;73 (T3) pmol/L</td>
<td>Event incidence: an event was considered if a patient died or had to be transplanted (non-survivor) during follow-up.</td>
<td>serum creatinine, CRP, TNF-α, interleukin 6, magnesium, sodium, NT-proBNP, TIMP-1</td>
<td>Patients in the highest calcitriol tertile had a HR (95% CI) for an event of 0.51 (0.33–0.77) compared with patients in the lowest calcitriol tertile (P&lt;0.01).</td>
<td></td>
</tr>
<tr>
<td>COACH study; Liu et al, (2011)²³</td>
<td>Fair</td>
<td>Netherlands</td>
<td>prospective cohort (primary)</td>
<td>548 patients with HF (NYHA functional class II-IV)</td>
<td>74 y median</td>
<td>fM</td>
<td>18 mo mean</td>
<td>25(OH)D: &lt;29.6 (T1), &gt;43.9 (T3) nmol/L</td>
<td>A composite outcome: rehospitalization due to worsening HF and all-cause death. Rehospitalized HF, defined as an unplanned overnight stay in a hospital due to progression of HF or as a direct result of HF.</td>
<td>age, DM type II, eGFR, and NT-proBNP</td>
<td>Multivariable Cox Model showed low 25(OH)D was independently associated with an increased risk for the combined endpoint (HR 1.09 per 10 nmol/L decrease; 95% CI 1.00–1.16; P=0.040).</td>
</tr>
<tr>
<td>Gotsman et al, (2012)²⁴</td>
<td>Good</td>
<td>Israel</td>
<td>prospective cohort (primary)</td>
<td>3009 patients with HF, 45 years or older</td>
<td>75.9 y mean</td>
<td>fM</td>
<td>518 d median</td>
<td>serum 25(OH)D: &lt;25.0 (deficiency), &gt;25.0 nmol/L</td>
<td>all cause mortality</td>
<td>age, gender, DM, hyperlipidaemia, IHD, AF, BMI, SBP, ura, eGFR, pulse, haemoglobin, sodium, albumin, and calcium</td>
<td>Vitamin D deficiency was an independent predictor of increased mortality in patients with HF (HR 1.52, 95% CI 1.21–1.92; P&lt;0.001).</td>
</tr>
</tbody>
</table>

COACH, Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure; NYHA, New York Heart Association; T, tertile; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; TNF-α, tumor necrosis factor; TIMP-1, tissue inhibitor of metalloproteinases 1; IHD, ischemic heart disease; AF, atrial fibrillation BMI, body mass index; SBP, systolic blood pressure; DM, diabetes mellitus; KM, Kaplan-Meier; HR, hazard ratio; CI, confidence interval; NA, not available.

* These two studies used a combined outcome
Figure 1 Literature Search and Study Selection in Meta-analysis

Search terms for vitamin D included vitamin D, calcifediol, calcitriol, cholecalciferol, and ergocalciferol; search terms for heart failure included heart failure, cardiac failure, cardiovascular disease, cardiovascular events, heart disease, coronary artery disease, and myocardial infarction.

* A prospective cohort study simultaneously published data of HF prevalence and mortality\(^{10}\).

RCT, randomized clinical trial;
A: vitamin D and HF incidence

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>HF / Total</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolland (2010)</td>
<td>0.834 (0.363, 1.919)</td>
<td>0.670</td>
<td>10 / 735</td>
<td>2.10</td>
</tr>
<tr>
<td>CHS; Kestenbaum (2011)</td>
<td>0.804 (0.616, 1.051)</td>
<td>0.111</td>
<td>107 / 681</td>
<td>20.36</td>
</tr>
<tr>
<td>WHI; HSIA (2006)</td>
<td>0.964 (0.841, 1.106)</td>
<td>0.803</td>
<td>394 / 18176</td>
<td>77.54</td>
</tr>
<tr>
<td>Overall</td>
<td>0.927 (0.821, 1.045)</td>
<td>0.215</td>
<td>107 / 681</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q=1.461; P=0.482; I^2=0.0\%$

B: vitamin D and HF prevalence

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>HF / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Relative weight [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES; Kim (2008)</td>
<td>0.583 (0.406, 0.838)</td>
<td>0.004</td>
<td>39 / 1659</td>
<td>32.18</td>
</tr>
<tr>
<td>Anderson (2010)</td>
<td>0.473 (0.429, 0.522)</td>
<td>0.000</td>
<td>1021 / 10105</td>
<td>40.27</td>
</tr>
<tr>
<td>4D study; Drechsler (2010)</td>
<td>1.111 (0.868, 1.798)</td>
<td>0.670</td>
<td>46 / 114</td>
<td>27.55</td>
</tr>
<tr>
<td>Overall</td>
<td>0.640 (0.412, 0.995)</td>
<td>0.047</td>
<td>1021 / 10105</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q=12.388; P=0.002; I^2=83.9\%$

C: vitamin D and HF mortality

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Death / Total</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LURIC Study; Pilz (2008)</td>
<td>0.282 (0.122, 0.651)</td>
<td>0.003</td>
<td>6 / 336</td>
<td>49.94</td>
</tr>
<tr>
<td>4D study; Drechsler (2010)</td>
<td>1.164 (0.507, 2.675)</td>
<td>0.720</td>
<td>9 / 114</td>
<td>50.06</td>
</tr>
<tr>
<td>Overall</td>
<td>0.573 (0.143, 2.303)</td>
<td>0.433</td>
<td>9 / 114</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q=5.555; P=0.018; I^2=82.0\%$
D: vitamin D and all-cause mortality in patients with HF

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>High_Vd</th>
<th>Low_Vd</th>
<th>Risk ratio and 95% CI</th>
<th>Relative weight [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schierbeck (2011)</td>
<td>0.480</td>
<td>0.296</td>
<td>0.716</td>
<td>0.001</td>
<td>21 / 87</td>
<td>32 / 61</td>
<td></td>
<td>10.61</td>
</tr>
<tr>
<td>Schleithoff (2006)</td>
<td>1.249</td>
<td>0.446</td>
<td>3.483</td>
<td>0.672</td>
<td>7 / 57</td>
<td>6 / 61</td>
<td></td>
<td>2.27</td>
</tr>
<tr>
<td>Zittermann (2008)</td>
<td>0.595</td>
<td>0.479</td>
<td>0.740</td>
<td>0.000</td>
<td>57 / 128</td>
<td>95 / 127</td>
<td></td>
<td>28.61</td>
</tr>
<tr>
<td>COACH; Liu (2011)</td>
<td>0.746</td>
<td>0.564</td>
<td>0.952</td>
<td>0.019</td>
<td>66 / 183</td>
<td>88 / 182</td>
<td></td>
<td>25.25</td>
</tr>
<tr>
<td>Gotsman (2012)</td>
<td>0.682</td>
<td>0.563</td>
<td>0.825</td>
<td>0.000</td>
<td>247 / 2168</td>
<td>141 / 843</td>
<td></td>
<td>33.06</td>
</tr>
<tr>
<td>Overall</td>
<td>0.652</td>
<td>0.557</td>
<td>0.784</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q=5.948; P=0.203; I²=32.7%

**Figure 2 (A-D)** Meta-analysis of the risk of HF-related adverse outcomes for the highest versus lowest categories of serum vitamin D concentration or vitamin D intake. The size of each square is proportional to weight of the study (inverse of variance). **A:** vitamin D and HF incidence; **B:** vitamin D and HF prevalence; **C:** vitamin D and HF mortality; **D:** vitamin D and all-cause mortality in patients with HF. Vd, vitamin D