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Dietary vitamin D and risk of heart failure in the Physicians' Health Study

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Abstract

Background—Experimental studies have demonstrated the role of vitamin D in key pathways related to cardiovascular health. While several studies have investigated the impact of vitamin D therapy on outcomes in subjects with prevalent heart failure, limited research exists on the relationship of dietary vitamin D consumption with the risk of heart failure. Thus, we sought to investigate whether dietary vitamin D consumption was associated with a lower risk of incident heart failure in a large prospective cohort of male physicians.

Methods and Results—We prospectively studied 19,635 males from the Physicians' Health Study. Dietary vitamin D information was obtained from a baseline food frequency questionnaire, and heart failure information was obtained by questionnaire and validated in a subsample. Mean age was 66.4 years. Median dietary vitamin D consumption was 200.4 IU and only 2.3% of the subjects used vitamin D supplements. After an average follow-up of 9.3 years, there were 858 new cases of heart failure identified. Higher intake of dietary vitamin D was not associated with incident heart failure in a multivariable adjusted model: hazard ratios (95% CI) of incident heart failure were 1.0 (reference), 1.29 (1.04 to 1.60), 1.17 (0.94 to 1.46), 1.22 (0.98 to 1.53), and 1.16 (0.92 to 1.46) from lowest to highest age- and energy-adjusted vitamin D quintile, respectively, after adjusting for age, BMI, race, exercise, alcohol use, smoking, calories, and prevalent atrial fibrillation (p for linear trend = 0.64).

Conclusions—These data are consistent with a lack of an association between dietary vitamin D and incident heart failure in this population of professionally-employed middle-aged males.

Heart failure (HF) remains a leading public health issue in the United States, with ~5.1 million Americans affected by clinically manifest disease (1). The lifetime risk of developing HF for US adults ≥ 40 years of age is approximately 20% and about 900,000

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new cases are diagnosed each year (2). Because mortality rates remain > 50% within 5 years of HF diagnosis (3), effective therapies for HF prevention are sorely needed.

Vitamin D is a fat-soluble vitamin that plays a critical role in mineral homeostasis and skeletal health. Recently, vitamin D has been implicated in the pathogenesis of non-skeletal chronic diseases, including cardiovascular disease (4-10). Experimental studies in both animals and human tissue have supported the importance of vitamin D in cardiovascular health through its effect on inflammation (11), the renin-angiotensin system (12) and cardiomyocyte structure and function (10).. Prospective studies have demonstrated an inverse association between baseline serum 25-hydroxyvitamin D (25-OH vitamin D) levels and the development of hypertension (5), diabetes mellitus (6), and coronary heart disease (7). Other investigators have reported cross-sectional associations between lower vitamin D levels and both prevalent HF as well as poor HF outcomes (8, 9).

Despite these clinical observations, results from both prospective and randomized, controlled trials (RCT) of vitamin D supplementation on cardiovascular outcomes have been inconclusive (9, 13-15). Several studies have investigated the impact of vitamin D therapy on outcomes in subjects with prevalent HF (13, 14), however limited research exists on the relationship of vitamin D supplementation and the risk of HF (15-17). These studies have been conducted in either exclusively female (15, 16) or elderly (17) populations, and examined vitamin D consumption from supplement use and not from diet. Thus, we sought to investigate whether dietary vitamin D consumption was associated with a lower risk of incident HF in a large prospective cohort of male physicians.

Methods

Study Population

The Physicians' Health Study (PHS) I was a randomized, double-blind, placebo-controlled 2 × 2 factorial trial of low-dose aspirin and beta carotene on the primary prevention of cardiovascular disease and cancer in 22,071 male physicians. The PHS II was a randomized, double-blind, placebo controlled 2 × 2 × 2 × 2 factorial trial of vitamins E, C, multivitamins, and beta-carotene on the risk of cardiovascular disease and cancer. PHS II included 7,641 subjects from PHS I and an additional 7,000 newly recruited male physicians (1997-2001). Detailed descriptions of the PHS I and II have been published previously (18, 19). Participants of PHS I and II who completed a food frequency questionnaire (FFQ) between 1997 and 2001 were eligible for inclusion in the study (n = 21,075). Each participant provided written informed consent, and the study protocol was approved by the institutional review board at Brigham and Women's Hospital, Boston, Massachusetts.

For this project, we excluded participants because of (1) prevalent HF (n = 470), and (2) missing information on dietary vitamin D consumption (n = 970). Our final sample was 19,635 subjects.

Vitamin D consumption

Information on dietary vitamin D consumption was obtained from a baseline food frequency questionnaire (FFQ) collected between 1997 and 2001. The validity and reproducibility of

FFQs have been published elsewhere (20). Nutrients were computed by using the food-composition database from the Harvard School of Public Health and manufacturer information, and this technique has been described previously (21). We used the residual method to adjust nutrients for energy intake, including dietary vitamin D (22).

Ascertainment of Incident HF

A questionnaire was mailed to participants every 6 months during the first year and annually thereafter in order to obtain information on compliance with the intervention and the occurrence of new medical diagnoses including HF. We have previously described the validation of HF in a subsample in this cohort (23).

Other variables

Demographic information was obtained through self-reported questionnaires. At baseline, each subject provided information on exercise; ("How often do you exercise vigorously enough to work up sweat?"), and exercise per week was categorized into 0, <1, 1-2, 3–4, or 5–7 d/wk; smoking history (never, former, or current smoker); and alcohol intake (daily, weekly, monthly, and rarely/almost never). Information about comorbidities – including hypertension, valvular heart disease, atrial fibrillation, coronary heart disease, and diabetes mellitus – was collected at baseline and through follow-up questionnaires. Dietary information was collected through FFQ.

Statistical analyses

We created quintiles of age-and calorie-adjusted dietary vitamin D. We used Cox proportional hazards regression to estimate the hazard ratio of HF using the lowest quintile as the reference. The multivariable models adjusted for age, body mass index (BMI), race, energy intake, alcohol consumption, exercise, smoking, and atrial fibrillation. We considered hypertension, diabetes mellitus, and coronary heart disease to be intermediate factors in the vitamin D-HF relation and did not include them in the multivariable model.

We tested the proportional hazards assumption including an interaction between logarithmic-transformed person-time and vitamin D level in the model. We further explored the possibility of a non-linear relationship using a partial likelihood ratio test by comparing a model with log-transformed vitamin D with a model that included a squared and cubic term of vitamin D. All analyses were performed using SAS (version 9.3; SAS Institute), and the alpha level was set at 0.05. All P values were 2-sided.

Results

Table 1 shows the baseline demographics of the 19,635 subjects according to age-and energy-adjusted vitamin D quintiles. Mean age of the study participants at baseline was 66.4 ± 9.2 years (range: 50 to 97 years). Median dietary vitamin D consumption was 200.4 IU (IQR: 121.4, 463.4). Only 2.3% of subjects used vitamin D supplements. Frequent dietary vitamin D consumption was associated with being Caucasian; lower frequency of current smoking and daily alcohol consumption; and higher frequency of exercise, multivitamin use,

and prevalent coronary heart disease and atrial fibrillation. During an average follow-up of 9.3 years, 858 new cases of HF occurred.

Higher intake of dietary vitamin D was not associated with incident HF in both minimally- and fully-adjusted models (**Table 2)**. We did observe a small elevated risk for HF within quintile 2 in both models. Hazard ratios (95% CI) of incident HF were 1.0 (reference), 1.29 (1.04 to 1.60), 1.17 (0.94 to 1.46), 1.22 (0.98 to 1.53) and 1.16 (0.92 to 1.46)] from lowest to highest age- and energy-adjusted vitamin D quintile, respectively, after adjusting for age, BMI, race, exercise, alcohol use, smoking, calories, atrial fibrillation (p for linear trend = 0.64). Additional adjustment for fruits and vegetables, breakfast cereal, chocolate consumption, and multivitamin use did not change the results (results not shown). Similarly, restricting the analysis to subjects who did not take additional vitamin D supplementation (n = 19,170) did not change the results: hazard ratios (95% CI) of incident HF were 1.0 (reference), 1.29 (1.04 to 1.60), 1.17 (0.94 to 1.46), 1.22 (0.98 to 1.53) and 1.16 (0.91 to 1.46) from lowest to highest age- and energy-adjusted vitamin D quintile, respectively, in the fully adjusted model (p for linear trend = 0.66).. The addition of potential intermediate variables (diabetes, hypertension, CHD) to the multivariable model did not affect the results [HRs (95% CI): 1.0 (reference), 1.27 (1.02 to 1.57), 1.13 (0.91 to 1.40), 1.15 (0.92 to 1.44), and 1.08 (0.86 to 1.36) from lowest to highest age- and energy adjusted vitamin D quintile, respectively (p for linear trend = 0.84)].

Discussion

In this prospective study of US male physicians, we found that higher intake of dietary vitamin D was not associated with the risk of HF. The observed small, yet elevated risk of HF in the second quintile of dietary vitamin D, HR 1.29 (95% CI: 1.04 to 1.60) may be due to chance given the lack of association across the remaining quintiles.

Limited data exist on the relation of vitamin D with incident HF. To our knowledge, only two randomized trials examined the effects of vitamin D supplementation on HF risk. Specifically, Hsia et al. showed that 400 IU of vitamin D3 supplementation (with concomitant calcium supplementation) did not decrease the risk for HF hospitalization compared to placebo in the Women's Health Initiative sample of over 36,000 postmenopausal women after an average of 7 years of follow-up, HR 0.95 (95% CI: 0.83 to 1.10) (15). In a secondary analysis of the Women's Health Initiative that was restricted to subjects without prevalent HF, Donneyong et al. found that vitamin D and calcium supplementation reduced the risk for incident HF by 37% (HR 0.63, 95% CI: 0.46 to 0.87) in post-menopausal women with a “low-risk” profile (defined by the absence of hypertension, diabetes mellitus, CHD, or CVD) compared to those with a “high-risk” profile. Overall, supplementation with calcium plus vitamin D was not associated with risk of HF in this cohort, HR 0.95 (95% CI: 0.82 to 1.09) (16). Our results, albeit in a prospective study and in a male population, are consistent with the main findings of Hsia et al. and Donneyong et al. and add to the limited body of research in this area. While we did not compare subjects with low and high CVD-risk profiles as Donneyong et al. have done, the addition of these risk factors to the multivariable model did not affect our results.

In an older (mean age, 77.5 years) sample of 5,292 mostly Caucasian women, Ford et al. demonstrated that supplementation with 800 IU of vitamin D3 and 1000 mg of calcium carbonate reduced the risk of incident HF by 25% (HR 0.75; 95% CI: 0.58 to 0.97) after a median follow-up period of approximately 6 years. A limitation of this study was poor adherence (43.8%) in the vitamin D group (17).

Several studies assessing the association of serum vitamin D with incident HF have reported mixed results (24-27). Using an administrative database containing young adults (mean age, 55 years), Anderson et al. reported a 31% higher risk of HF (HR = 1.31, p = 0.005) when comparing low-normal serum vitamin D (15-30 ng/mL) to normal levels (>30 ng/mL) (24). In a prospective cohort study of 1,471 post-menopausal women, Bolland et al. did not find a relationship between serum 25-OH vitamin D and incident HF (HR = 1.00, 95% CI = 0.40, 2.40) comparing levels <50 nmol/mL to ≥50 nmol/mL (25). Similarly, Kestenbaum et al. did not find an association between serum 25-OH vitamin D levels <15.0 ng/mL compared to ≥30.0 ng/mL and incident HF in 2,312 relatively healthy participants in the Cardiovascular Health Study after an average of 14 years of follow-up (HR=1.17, 95% CI = 0.78, 1.30) (26). Most recently, a large, prospective study of older (mean age >65), Caucasian men from the United Kingdom found no association between serum vitamin D level and incident HF after a mean period of 13 years of follow-up comparing highest to lowest quartiles of serum vitamin D (RR= 0.96, 95% CI= 0.71, 1.34) (27). Absence of an association between vitamin D and HF is consistent with our recent report showing no association between vitamin D binding protein (a major transporter of vitamin D) and HF risk (28).

Vitamin D status has been suggested as a possible surrogate marker for overall poor metabolic health or socio-demographic status, potentially confounding its relationship with cardiovascular disease outcomes (29). Our null findings come from a cohort comprised entirely of US male physicians with largely uniform socio-demographic status. Similarly, a recent gene association study did not find a relationship between the variation in vitamin D metabolism and risk of cardiovascular disease, raising the possibility that there may not be a causal relationship between vitamin D levels and cardiovascular disease (10, 30).

The present study has some limitations. As an observational study, it is possible that residual confounding by unmeasured factors such as sunlight exposure may partially explain our findings. Subjects may have consumed additional vitamin D from multivitamin use, however the addition of multivitamin use to the fully-adjusted model did not change our results. We analyzed a single assessment of dietary vitamin D consumption and this may not adequately reflect the long-term dietary intake of vitamin D in these patients. We lacked baseline information on serum vitamin D levels, which could influence results towards or away from the null hypothesis. Additionally, we lacked information on subjects' kidney and liver function, both of which can influence the level of bioactive vitamin D. Study participants were male physicians and it is unknown if the results are generalizable to women, other ethnic groups, and/or the general population.

The large sample size, detailed FFQ, long duration of follow-up, and high positive predictive value of self-reported HF by members of the cohort are strengths of this study.

In conclusion, higher intake of dietary vitamin D was not associated with incident HF in this population of professionally-employed middle-aged males.

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JMR and LD designed research; all authors conducted research; JMR and ABP analyzed data and performed statistical analyses; JMR and LD wrote the paper. All authors provided critical revisions for content and had responsibility for the final content. LD supervised the work and obtained funding for FFQ processing. Appreciation is expressed to the staff of the study and especially to the study participants who volunteered for the project.

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Abbreviations

HF	Heart failure
25-OH vitamin D	25-hydroxyvitamin D
CHD	coronary heart disease
CVD	cardiovascular disease

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Table 1

Baseline Characteristics of Study Population in the PHS Cohort by Vitamin D consumption

Characteristics	Age-and energy-adjusted quintile of dietary vitamin D					p for linear trend
	Q1	Q2	Q3	Q4	Q5	
Dietary Vitamin D (IU)	74.2	136.3	202.2	394.4	668.1	<0.0001
N	3924	3928	3928	3928	3927	-
Age (Y)	66.2 ± 9.1	66.3 ± 9.1	66.5 ± 9.3	66.4 ± 9.2	66.8 ± 9.1	0.28
BMI, kg/m2	25.9 ± 3.3	25.9 ± 3.3	25.8 ± 3.3	25.6 ± 3.2	25.6 ± 3.4	<0.0001
White (%)	89.1	92.6	92.6	92.9	93.3	<0.0001
Cigarette use (%)						
Never	50.6	54.6	57.2	55.3	53.8	0.005
Former	45.2	41.8	39.9	41.4	43.4	0.11
Current	4.2	3.6	2.9	3.3	2.8	0.001
Alcohol Use (%)						
Never	16.1	15.2	17.6	18.1	18.0	0.0004
Weekly	33.6	37.7	39.9	37.9	40.9	<0.0001
Daily	42.2	39.6	34.8	36.3	34.7	<0.0001
Exercise ≥1 day/week	56.9	60.5	63.7	65.5	66.2	<0.0001
Multivitamin use (%)	5.5	7.9	16.5	61.3	93.7	<0.0001
Fruit/Vegetables, servings/day	4.8	4.9	4.9	5.4	4.7	<0.0001
Chocolate, ≥1 serving/day (%)	5.9	5.1	5.2	6.1	3.1	0.62
Breakfast cereal, ≥ 1 serving/day (%)	7.9	21.0	32.8	30.7	26.9	<0.0001
Hypertension (%)	46.4	44.1	45.3	45.8	47.8	0.07
Left ventricular hypertrophy (%)	1.2	1.2	1.5	1.5	1.7	0.04
Valvular heart disease (%)	1.2	1.0	1.6	1.7	2.2	<0.0001
Coronary heart disease (%)	10.7	10.6	11.9	13.0	14.7	<0.0001
Diabetes mellitus (%)	7.1	6.6	7.2	6.8	7.9	0.2
Atrial fibrillation (%)	7.3	7.9	9.6	8.5	9.1	0.003

Values are means± SD, medians (IQR), or %

Abbreviations; SD, standard deviation; BMI, body mass index; IQR, interquartile range

Table 2

Hazard ratios (95% confidence intervals) for heart failure according to age-and energy-adjusted quintiles of vitamin D

Vitamin D Quintiles	n	Cases	Hazard Ratios (95% CI)	
			Age- and energy-adjusted model	Fully-adjusted model*
Q1	3924	153	1	1
Q2	3928	199	1.27 (1.03-1.57)	1.29 (1.04-1.60)
Q3	3928	183	1.16 (0.94-1.44)	1.17 (0.94-1.46)
Q4	3928	169	1.16 (0.93-1.45)	1.22 (0.97-1.53)
Q5 (high)	3927	154	1.10 (0.88-1.38)	1.16 (0.92-1.46)
p for linear trend			0.93	0.64

*Adjusted for: age, BMI, race, exercise, alcohol use, smoking, calories, atrial fibrillation