Relation of Vitamin D Deficiency to Cardiovascular Risk Factors, Disease Status, and Incident Events in a General Healthcare Population

Jeffrey L. Anderson, MD[a,b,*], Heidi T. May, PhD, MSPH[a], Benjamin D. Horne, PhD, MPH[a,c], Tami L. Bair, BS[a], Nathaniel L. Hall, MD[a,b], John F. Carlquist, PhD[a,b], Donald L. Lappé, MD[a], and Joseph B. Muhlestein, MD[a,b], for the Intermountain Heart Collaborative (IHC) Study Group

Vitamin D recently has been proposed to play an important role in a broad range of organ functions, including cardiovascular (CV) health; however, the CV evidence-base is limited. We prospectively analyzed a large electronic medical records database to determine the prevalence of vitamin D deficiency and the relation of vitamin D levels to prevalent and incident CV risk factors and diseases, including mortality. The database contained 41,504 patient records with at least one measured vitamin D level. The prevalence of vitamin D deficiency (≤30 ng/ml) was 63.6%, with only minor differences by gender or age. Vitamin D deficiency was associated with highly significant ($p < 0.0001$) increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Also, those without risk factors but with severe deficiency had an increased likelihood of developing diabetes, hypertension, and hyperlipidemia. The vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke (all $p < 0.0001$), as well as with incident death, heart failure, coronary artery disease/myocardial infarction (all $p < 0.0001$), stroke ($p = 0.003$), and their composite ($p < 0.0001$). In conclusion, we have confirmed a high prevalence of vitamin D deficiency in the general healthcare population and an association between vitamin D levels and prevalent and incident CV risk factors and outcomes. These observations lend strong support to the hypothesis that vitamin D might play a primary role in CV risk factors and disease. Given the ease of vitamin D measurement and replacement, prospective studies of vitamin D supplementation to prevent and treat CV disease are urgently needed. **(Am J Cardiol 2010;106:963–968)**

There is a growing epidemic of vitamin D deficiency, and its consequences beyond bone health, are still not well understood. However, early reports have linked it to such cardiovascular (CV) conditions as hypertension, diabetes mellitus, obesity and the metabolic syndrome, left ventricular hypertrophy, heart failure, coronary heart disease, renal disease, and mortality.[1–6] Because vitamin D deficiency can be readily determined by blood testing and treated by supplementation, it is crucial to solidify knowledge of its prevalence and contribution to CV disease states and outcomes. A limited evidence base has suggested a beneficial effect on clinical outcomes with replacement therapy.[2,3,7,8] We prospectively addressed the proposed relation of vitamin D deficiency to CV conditions by analyzing a large and longitudinal electronic medical record database.

Methods

We prospectively studied the electronic medical record database of the integrated Intermountain Healthcare system to address 4 objectives in a general healthcare population: (1) to determine the prevalence of vitamin D deficiency and insufficiency in subjects with measured vitamin D levels; (2) to evaluate the relation of vitamin D levels to prevalence and incidence of prespecified CV risk factors; (3) to assess the relation of vitamin D levels to prespecified CV conditions; and (4) to determine the association of baseline vitamin D levels with incident CV outcomes. The present study was approved by the Intermountain Institutional Review Board.

The Intermountain database search identified 41,497 subjects with at least one vitamin D measurement from 2000 to 2009. Vitamin D levels were drawn at the providers' discretion for clinical indications (e.g., osteoporosis risk). The study subjects averaged 55 ± 21 years old; women (74.8%) outnumbered men (25.2%). The prevalence of patients in each category was analyzed according to age, gender, and the season in which the sample was taken.

The serum vitamin D levels were measured by chemiluminescent immunoassay in Intermountain laboratories as 25(OH)D, the principal circulating form of vitamin D (generally accepted as the best measure of total body vitamin D

[a]Cardiovascular Department, Intermountain Medical Center, Murray, Utah; and Divisions of [b]Cardiology and [c]Genetic Epidemiology, University of Utah School of Medicine, Salt Lake City, Utah. Manuscript received March 17, 2010; manuscript received and accepted May 12, 2010.

This study was generously supported by the Del Loy Hansen Foundation, Logan, Utah and the Deseret Foundation, Salt Lake City, Utah.

*Corresponding author: Tel: (801) 507-4757; fax: (801) 507-4789.

E-mail address: jeffrey.anderson@imail.org (J.L. Anderson).

0002-9149/10/$ – see front matter
doi:10.1016/j.amjcard.2010.05.027

Table 1
Proportion of subjects with varying levels of serum 25(OH) vitamin D category

	Vitamin D Level (ng/ml)*		
	>30 (n = 15,121)	16–30 (n = 19,474)	≤15 (n = 6,909)
Total	36.4%	46.9%	16.6%
Men (n = 10,418)	33.9%	48.5%	17.6%
Women (n = 31,086)	37.3%	46.4%	16.3%
Age ≥50 years (n = 27,686)	36.5%	47.2%	16.3%
Age <50 years (n = 13,811)	36.2%	46.5%	17.3%
Tests in May–July	38.1%	47.7%	14.2%
Tests in December–February	35.2%	45.4%	19.4%

* On at least one measurement.

stores[3]) and stratified into 3 categories: normal, >30 ng/ml; low (insufficient), 16 to 30 ng/ml; and very low (deficient), ≤15 ng/ml.

The prevalence and incidence of CV diseases and risk factors were determined by "International Classification of Diseases," version 9, code entries documented in electronic medical records at baseline and during follow-up. The prospectively defined risk factors of interest and available to study were age, gender, hypertension, hyperlipidemia, diabetes mellitus, and peripheral vascular disease. The CV diseases of interest and available were the prevalence and incidence of coronary heart disease (i.e., clinical coronary artery disease [CAD] or myocardial infarction [MI]), heart failure (HF), cerebrovascular accident (CVA or stroke), and atrial fibrillation. Because subclassification of death was not routinely available, all-cause mortality was used as the primary survival measure. Other clinical conditions of interest for analysis included fractures, pulmonary embolism, depression, renal failure, skeletal disorder, hypothyroidism, infection requiring medical attention, and headache.

Patients were followed after the initial vitamin D determination for an average of 1.3 years (maximum 9.3). (The large numbers of shorter term follow-up periods reflect the recent interest in vitamin D status.) Deaths were determined from the hospital records and telephone queries, Utah State Health Department records (death certificates), and the national Social Security death records. Patients not listed as deceased in any registry were considered alive.

The chi-square statistic and analysis of variance test were used to characterize the categorical and continuous variables, respectively, according to vitamin D categories. Univariate and multivariate Cox regression analysis was used to determine the associations of baseline vitamin D with an incident death or "International Classification of Diseases," version 9, CV diagnosis/event (CAD/MI, HF, CVA, atrial fibrillation). The risk factors used in the multivariate modeling were those given earlier. The primary study end point was the incidence of a composite CV event of death, CAD/MI, HF, or CVA. The major secondary end points of interest were its individual components. In these analyses, the proportional hazards assumption was determined to be met by including a time-dependent covariate in a model representing the interaction between the outcome of interest's follow-up time and vitamin D level. p Values <0.05 was designated as significant; both unadjusted and (conservative) Bonferroni adjusted results are given.

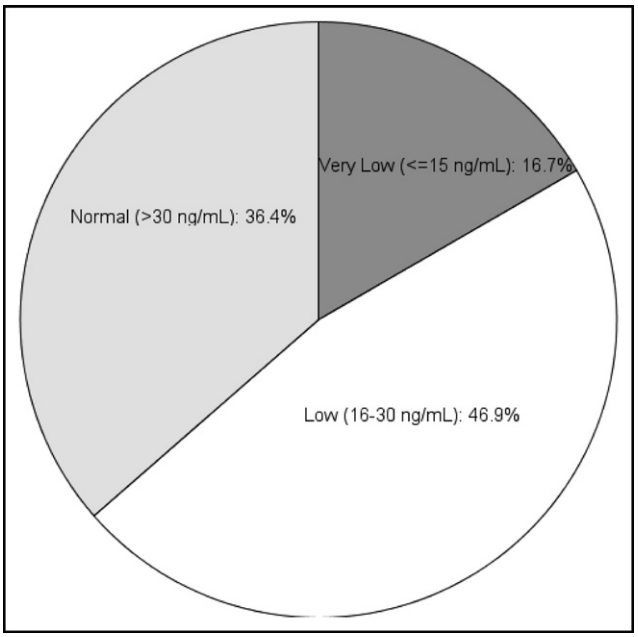

Figure 1. Distribution of vitamin D levels in Intermountain Healthcare population. Pie graph indicates percentage of vitamin D levels on first samples drawn from 41,504 subjects in Intermountain electronic medical record database that were within laboratory-reported range of normal (>30 ng/ml), low (16 to 30 ng/ml), or very low (≤15 ng/ml).

Table 2
Risk factor prevalence at initial vitamin D determination

Risk Factor	Vitamin D Level (ng/ml)			p Trend
	≤15	16–30	>30	
Hypertension	51.9%	43.8%	39.8%	<0.0001*
Hyperlipidemia	47.1%	45.9%	43.2%	<0.0001*
Diabetes mellitus	29.3%	20.0%	15.4%	<0.0001*
Peripheral vascular disease	4.6%	3.1%	3.0%	<0.0001*

* Comparisons also significant after Bonferroni correction (i.e., adjusted for 4 risk factor comparisons).

Results

In a search of the Intermountain electronic medical record database, 41,504 patients were found with at least one measured vitamin D level; 11,088 (26.7%) had 2 measurements, 3,950 (9.5%) had 3 measurements, and 1,703 (4.1%) had >3 measurements, for a total of 58,245 measured levels. The age and gender distribution is listed in Table 1.

The distribution of vitamin D levels by category is shown in Figure 1. Only minor differences among categories were noted by gender or age (Table 1). Although common, regardless of the season, vitamin D deficiency was more prevalent during winter months (p <0.0001; Table 1).

Table 3
Overall risk factor incidence and adjusted relative hazard by initial vitamin D category in subjects without previous condition

Risk Factor (Overall Incidence)	Very Low vs Normal (≤15 vs >30 ng/ml)		Low vs Normal (16–30 vs >30 ng/ml)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Hypertension (6.0%)				
Hazard ratio	1.73	1.62	1.26	1.18
95% confidence interval	1.48–2.02	1.38–1.89	1.12–1.42	1.05–1.33
p Value	<0.0001*	<0.0001*	<0.0001*	0.005*
Hyperlipidemia (5.8%)				
Hazard ratio	1.47	1.27	1.19	1.10
95% confidence interval	1.25–1.72	1.09–1.50	1.06–1.34	0.98–1.24
p Value	<0.0001*	0.003*	0.005*	0.12
Diabetes mellitus (2.2%)				
Hazard ratio	2.13	1.89	1.39	1.32
95% confidence interval	1.73–2.62	1.54–2.33	1.17–1.64	1.12–1.56
p Value	<0.0001*	<0.0001*	<0.0001*	0.001*
Peripheral vascular disease (0.8%)				
Hazard ratio	1.80	1.42	1.10	1.01
95% confidence interval	1.32–2.46	1.04–1.94	0.85–1.43	0.78–1.31
p Value	<0.0001*	0.03	0.48	0.93

Follow-up averaged 1.3 years (maximum 9.3).
* Comparisons also significant after Bonferroni correction (i.e., adjusted for 8 risk factor comparisons).

Table 4
Prevalence of cardiovascular (CV) disease diagnoses at baseline by vitamin D category in those ≥50 years old

Cardiovascular Disease	Vitamin D Level (ng/ml)			p Trend
	≤15	16–30	>30	
Coronary artery disease	25.1%	19.7%	17.5%	<0.0001*
Heart failure	19.2%	12.3%	10.1%	<0.0001*
Atrial fibrillation	11.8%	9.6%	9.2%	<0.0001*
Peripheral vascular disease	6.3%	4.2%	3.8%	<0.0001*
Previous myocardial infarction	5.8%	3.8%	3.2%	<0.0001*
Previous stroke	5.9%	4.2%	3.9%	<0.0001*
Previous transient ischemic attack	5.2%	4.5%	4.2%	0.02
Ventricular tachycardia	2.3%	1.6%	1.3%	<0.0001*

Comparisons of 27,686 subjects ≥50 years old.
* Comparisons also significant after Bonferroni correction (i.e., adjusted for 8 comparisons among prevalent CV risk factors).

Of the 41,504 patients, 36% had all measurements within the laboratory-reported range of normal (i.e., >30 ng/ml), 47% had at least one mildly to moderately reduced (insufficient) measurement (16 to 30 ng/ml), and 17% had a frankly deficient measurement (≤15 ng/ml). Thus, almost 2/3 had insufficient or deficient levels.

Highly significant and graded inverse associations were observed for the prevalence of CV risk factors among the vitamin D categories for hypertension, hyperlipidemia, diabetes, and peripheral vascular disease (all p <0.0001; Table 2). Of particular note was an increased prevalence of hypertension (30% relative and 12% absolute) and diabetes (90% relative and 14% absolute) in very low versus normal categories (p trends <0.0001).

Table 5
Prevalence of other diagnoses of interest at baseline by vitamin D category

Diagnosis	Vitamin D Level (ng/ml)			p Trend
	≤15	16–30	>30	
Recent infection	43.0%	32.5%	30.0%	<0.0001*
Renal failure	22.7%	14.6%	11.8%	<0.0001*
Previous fracture	20.9%	18.1%	18.1%	<0.0001*

* Comparisons also significant after Bonferroni correction (i.e., adjusted for 3 comparisons among other diagnoses of interest).

The overall incidence and unadjusted and adjusted relative hazards for newly appearing risk factors (i.e., first appearance after the initial vitamin D measurement) during follow-up were also determined (Table 3). Graded differences across vitamin D categories were noted for all 4 risk factors. Of particular note were the adjusted relative increases in incident hypertension (by 62%, p <0.0001) and diabetes (by 89%, p <0.0001) in very low versus normal categories.

The association of prevalent CV disease conditions with initial vitamin D status was assessed in subjects ≥50 years old (n = 27,686). In the present cohort, the age averaged 66.6 ± 10.8 years and 75.0% were women. The results are summarized in Table 4. Strong inverse associations across vitamin D categories were noted for all 8 prespecified CV disease diagnoses: CAD, HF, atrial fibrillation, MI, peripheral vascular disease, stroke, transient ischemic attack, and ventricular tachycardia. Of particular note were the increases in prevalence of HF (90% relative and 9% absolute), MI (81% relative and 2.6% absolute), and stroke (51% relative and 2% absolute) in very low versus normal vitamin D categories (all p trends <0.0001).

The association of 3 other prespecified health-related conditions of interest (i.e., recent infection, renal failure, previous fracture) with initial vitamin D status was also assessed in subjects ≥50 years old (Table 5). These results confirm the role of vitamin D in bone health and the association of vitamin D deficiency with renal failure, and they suggest a role of vitamin D in normal immune function.

The overall incidence and adjusted relative hazard for newly appearing CV disease diagnoses by vitamin D category during an average of 1.3 ± 1.2 years of follow-up (maximum 6.6 years) in those ≥50 years old is listed in Table 6. Overall, 1,193 had died (4.3%), and 763 (3.5%), 594 (2.5%), 513 (2.1%), and 197 (0.8%) patients developed CAD/MI, HF, atrial fibrillation, and CVA, respectively. Unadjusted and adjusted relative hazards showed strong inverse relationships with vitamin D levels for 5 of the 6 outcome diagnostic events—death, CAD/MI, HF, stroke, and peripheral vascular disease—but not for atrial fibrillation. Again, the relationships were graded, with greater hazard ratios in those with very low to with low levels

Table 6
Incidence and hazard ratios for cardiovascular (CV) disease diagnoses by vitamin D status among those ≥50 years old

Risk Factors (Overall Incidence)	At-Risk Subjects	Very Low vs Normal		Low vs Normal	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Death (4.3%)	27,686				
Hazard ratio		2.40	1.77	1.32	1.20
p Value		<0.0001	<0.0001	<0.0001	0.009
Coronary artery disease/myocardial infarction (3.5%)	21,853				
Hazard ratio		1.63	1.45	1.20	1.15
p Value		<0.0001	0.003	0.02	0.09
Heart failure (2.5%)	23,793				
Hazard ratio		2.19	2.01	1.33	1.31
p Value		<0.0001	<0.0001	0.002	0.005
Atrial fibrillation (2.1%)	24,565				
Hazard ratio		1.19	1.02	1.002	0.95
p Value		0.20	0.87	0.98	0.61
Stroke (0.8%)	26,025				
Hazard ratio		2.00	1.78	1.37	1.31
p Value		0.001	0.004	0.06	0.11
Peripheral vascular disease (1.0%)	26,033				
Hazard ratio		1.93	1.45	1.14	1.05
p Value		<0.0001	0.03	0.38	0.73
Composite* (6.5%)	20,069				
Hazard ratio		2.02	1.79	1.29	1.22
95% Confidence interval		1.73–2.36	1.53–2.10	1.14–1.46	1.08–1.38
p Value		<0.0001	<0.0001*	<0.0001	0.002

Low, 16–30 ng/ml; very low, ≤15 ng/ml; referent (normal), vitamin D level >30 ng/ml.
Follow-up averaged 1.3 ± 1.2 years (maximum 6.6 years).
See Figure 3 for 95% confidence intervals for individual events.
* Primary study end point (i.e., very low vs normal, adjusted) and includes death, coronary artery disease/myocardial infarction, heart failure, or cerebrovascular accident).

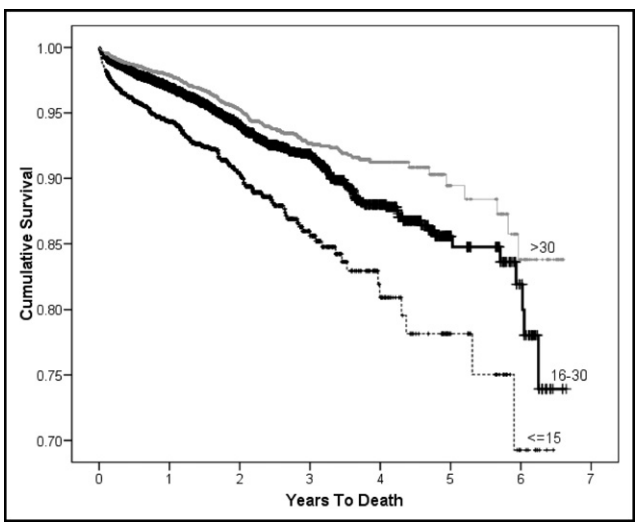

Figure 2. Kaplan-Meier survival curves according to baseline vitamin D level. Survival differed significantly by initial vitamin D level (log-rank p <0.0001). Number of patients with normal, low, and very low vitamin D levels at annual intervals was as follows: baseline, 4,509, 13,049, and 10,091; at 1 year, 1,920, 5,844, and 5,143; at 2 years, 748, 2,574, and 2,491; at 3 years, 241, 1,012, and 940; at 4 years, 80, 468, and 343; at 5 years, 31, 114, and 20l and at 6 years, 8, 44, and 41, respectively.

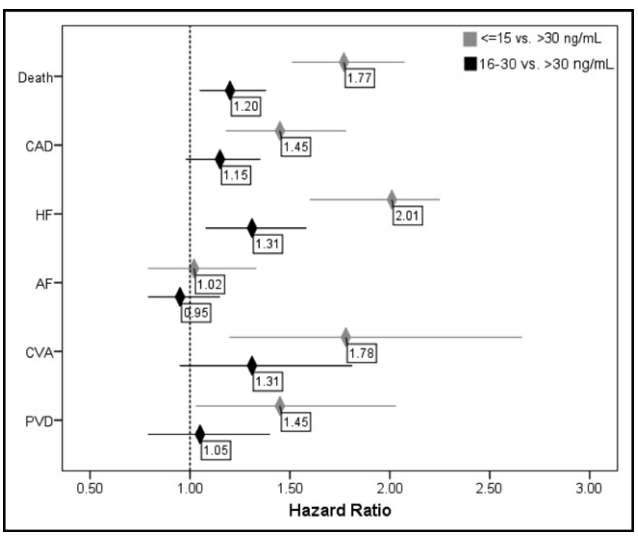

Figure 3. Multivariate-adjusted associations of incident CV diseases or death with vitamin D deficiency. Multivariate-adjusted Cox regression hazard ratios with 95% confidence intervals for patients ≥50 years old stratified by vitamin D level.

compared to normal levels. Of special note was the relation to total mortality (Figure 2 and Table 6). Adjusted relative death rates increased 20% with low vitamin D and 77% with very low vitamin D levels. Multivariate adjusted hazard ratios and 95% confidence intervals are shown graphically in Figure 3 for the 6 disease outcomes. When key CV events were combined into a primary composite event of death, CAD/MI, HF, or CVA, a very low vitamin D level was associated with an adjusted hazard ratio of 1.79 (p <0.0001). When the analysis was restricted to patients with a single

vitamin D level (to reduce confounding by treatment in vitamin D level-titrated patients), the results were similar or improved for individual adverse events (data not shown). A very low vitamin D level more than doubled the relative hazard for the composite of death, CAD/MI, HF, or CVA (hazard ratio 2.13, 95% confidence interval 1.75 to 2.58, $p < 0.0001$).

Discussion

Vitamin D has increasingly been recognized to play a role in a broad range of bodily functions beyond bone health, including CV health.[1–3] In parallel, the recognition of the presence of widespread vitamin D deficiency is increasing.[1–3] The consequences of this growing epidemic of vitamin D deficiency are still not well understood. However, recent reports of the associations of vitamin D deficiency with multiple CV conditions have been of great interest, suggesting the need for prospective validation and extended observations.

We have reported on a prospectively planned analysis of an electronic medical record database from a large integrated healthcare system to address 4 vitamin D-related issues. Of a consecutive series of 41,497 patients in a general healthcare population with at least one vitamin D measurement, vitamin D deficiency was found to be present in nearly 2/3 of the patients. This high prevalence was affected only modestly by age, gender, or season. Furthermore, patients with vitamin D deficiency had a greater prevalence of CV risk factors at baseline (i.e., hypertension, diabetes, hyperlipidemia), and, importantly, those deficient in vitamin D without previous CV risk factors were much more likely to develop them during follow-up. Beyond the CV risk factors, vitamin D deficiency was associated with an up to twofold greater prevalence of several CV disease categories, with those with severe deficiency at greatest risk. Finally, of the patients aged ≥50 years with longitudinal follow-up, moderate to severe vitamin D deficiency was strongly associated with death and the incident development of CAD/MI, HF, stroke, and peripheral arterial disease. These relationships persisted after multivariate adjustment. Because vitamin D deficiency can be readily determined by blood testing and treated by supplementation, the clinical implication of these findings, including vitamin D supplementation, should be a high priority for additional, prospective studies.

The evidence-base linking vitamin D deficiency to CV risk factors and disease is currently limited but growing, as summarized in recent reviews.[1–3] Vitamin D deficiency has been studied most thoroughly in patients with end-stage renal disease requiring dialysis,[4,7] in whom vitamin D deficiency was associated with an increased risk of death.[4] Supplementation has been reported to reduce this risk.[4,7] Recently, Giovannucci et al[5] reported that 25(OH) vitamin D deficiency was associated with an increased risk of MI in men, and Dobnig et al[6] related low vitamin D levels in a cohort of subjects scheduled for angiography to increased all-cause and CV mortality. Finally, the potential to reduce mortality with vitamin D supplementation in diverse populations was supported by a meta-analysis of 9 studies of varying size and design.[8]

A leading mechanism proposed to explain the relation between vitamin D deficiency and CV disease is that chronic vitamin D deficiency causes secondary hyperparathyroidism,[2,3] acting through ≥3 pathogenic pathways associated with parathormone excess[3]: (1) increased insulin resistance and pancreatic β-cell dysfunction, predisposing to the metabolic syndrome and diabetes; (2) activation of the renin-angiotensin system, increasing blood pressure and leading to left ventricular hypertrophy (with subsequent apoptosis and fibrosis); and (3) stimulation of systemic and vascular inflammation, augmenting atherogenesis.

Recently, Oh et al[9] reported that 1,25(OH)2 inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes, suggesting another mechanism of risk of vitamin D deficiency. A third recently proposed mechanism is an association with large high-density lipoprotein particles.[10]

The present study was a prospectively designed analysis of a retrospectively collected and observational medical records database. The incident events, except mortality, were limited to those identified within the Intermountain Healthcare system. As with all observational studies, both recognized (e.g., female gender, risk of osteoporosis) and unrecognized selection biases could exist relating to the reasons that providers performed the vitamin D measurements. Adjustment for these and other imbalances might have been incomplete; thus, the results might apply only to populations with similar characteristics. As with all medical records-based studies, our findings are dependent on their intrinsic accuracy and should be independently confirmed. The demonstration of association does not prove causality. However, the large size and independence of the findings by age and gender and the determination of an increased incidence of newly appearing CV risk factors and adverse events during longitudinal follow-up increased the likelihood of the causality of associations with vitamin D deficiency. Finally, our population base was predominantly white (i.e., ~86%); thus, relationships in populations with differing skin pigmentation, sun exposure, geography, and genetic background might differ.

Our findings, taken in the context of previous observations, suggest that vitamin D deficiency represents an important new CV risk factor and, we hypothesize, might play a causal role in the development of CV risk factors and CV diseases and adverse events, including death. Because measurement of vitamin D levels is easily done and vitamin D supplements are readily available and inexpensive, clinical trials are urgently needed to determine whether this represents a causal association and whether vitamin D replacement therapy can reduce the associated increase in CV risk.

1. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
2. Wallis DE, Penckofer S, Sizemore GW. The "sunshine deficit" and cardiovascular disease. *Circulation* 2008;118:1476–1485.
3. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008;52:1949–1956.

4. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007;72:1004–1013.
5. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men. *Arch Intern Med* 2008;168: 1174–1180.
6. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340–1349.
7. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo CA Jr, Thadhani R. Activated injectable vitamin D and hemodialysis: a historical cohort study. *J Am Soc Nephrol* 2005;16:1115–1125.
8. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167:1730–1737.
9. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, Proctor BM, Petty M, Chen Z, Schechtman KB, Bernal-Mizrachi L, Bernal-Mizrachi C. 1,25(OH)2 Vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation* 2009;120:687–698.
10. Kazlauskaite R, Powell LH, Mandapakal C, Cursio JF, Avery EF, Calvin J. Vitamin D is associated with atheroprotective high-density lipoprotein profile in postmenopausal women. *J Clin Lipidol* 2010;4: 113–119.