ANESTHESIOLOGY

# Preoperative Vitamin D Concentration and Cardiac, Renal, and Infectious Morbidity after Noncardiac Surgery

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Low vitamin D is common in the general population
- In nonsurgical populations, low 25-hydroxyvitamin D is associated with hypertension, left ventricular hypertrophy, heart failure, and coronary artery disease
- In nonsurgical populations, low vitamin D concentrations are also associated with increased risk of some infections and renal injury

### What This Article Tells Us That Is New

- Vitamin D deficiency was common in this surgical population
- Preoperative vitamin D was not associated with a composite of postoperative 30-day cardiac outcomes
- There was an association between low vitamin D and a composite of infectious complications, and also evidence for an association with decreased kidney function

## ABSTRACT

**Background:** Low 25-hydroxyvitamin D is associated with cardiovascular, renal, and infectious risks. Postsurgical patients are susceptible to similar complications, but whether vitamin D deficiency contributes to postoperative complications remains unclear. We tested whether low preoperative vitamin D is associated with cardiovascular events within 30 days after noncardiac surgery.

**Methods:** We evaluated a subset of patients enrolled in the biobank substudy of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study, who were at least 45 yr with at least an overnight hospitalization. Blood was collected preoperatively, and 25-hydroxyvitamin D was measured in stored samples. The primary outcome was the composite of cardiovascular events (death, myocardial injury, nonfatal cardiac arrest, stroke, congestive heart failure) within 30 postoperative days. Secondary outcomes were kidney injury and infectious complications.

**Results:** A total of 3,851 participants were eligible for analysis. Preoperative 25-hydroxyvitamin D concentration was 70 ± 30 nmol/l, and 62% of patients were vitamin D deficient. Overall, 26 (0.7%) patients died, 41 (1.1%) had congestive heart failure or nonfatal cardiac arrest, 540 (14%) had myocardial injury, and 15 (0.4%) had strokes. Preoperative vitamin D concentration was not associated with the primary outcome (average relative effect odds ratio [95% CI]: 0.93 [0.85, 1.01] per 10 nmol/l increase in preoperative vitamin D, $P = 0.095$). However, it was associated with postoperative infection (average relative effect odds ratio [95% CI]: 0.94 [0.90, 0.98] per 10 nmol/l increase in preoperative vitamin D, $P$ adjusted value = 0.005) and kidney function (estimated mean change in postoperative estimated glomerular filtration rate [95% CI]: 0.29 [0.11, 0.48] ml $min^{-1}$ 1.73 $m^{-2}$ per 10 nmol/l increase in preoperative vitamin D, $P$ adjusted value = 0.004).

**Conclusions:** Preoperative vitamin D was not associated with a composite of postoperative 30-day cardiac outcomes. However, there was a significant association between vitamin D deficiency and a composite of infectious complications and decreased kidney function. While renal effects were not clinically meaningful, the effect of vitamin D supplementation on infectious complications requires further study.

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Vitamin D deficiency affects all races and age groups with different geographic distributions, and ethnic backgrounds.[1] Vitamin D plays well known roles in mineral homeostasis and skeletal health. Recently, nontraditional (pleiotropic) roles for vitamin D have been identified. For

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example, low vitamin D concentrations have been implicated in the pathogenesis of conditions including cardiovascular disease, hypertension, autoimmune syndromes, cancer, diabetes mellitus, and infections.[2,3]

Experimental studies identify several mechanisms linking vitamin D deficiency to cardiovascular disease including downregulation of the renin–angiotensin–aldosterone system, increase in inflammatory cytokines, vascular and especially coronary calcification, and increased calcium influx to myocytes.[4–6] Supporting these mechanisms, observational and epidemiologic studies in nonsurgical populations confirm an association between low vitamin D concentrations and hypertension, left ventricular hypertrophy, heart failure, and coronary artery disease.[7,8] Perioperative studies remain rare; however, one noncardiac surgical study reported an association between low vitamin D concentration and serious infections and cardiovascular events.[9]

Vitamin D stimulates innate immune responses and adaptive immunity, and directly augments T cell responses. The clinical consequence is enhanced immune defenses in the respiratory tract, skin, and gut. As might thus be expected, low vitamin D concentrations are associated with increased risk of respiratory tract infections and colitis.[10,11] For example, studies in noncardiac and bariatric surgical patients identify independent associations between low vitamin D concentrations and postoperative infections.[9,12]

Vitamin D may also provide reno-protective effects *via* an antiinflammatory action, attenuation of interstitial fibrosis, and inhibition of intrarenal renin–angiotensin system.[13] Consistent with these mechanisms, studies in the general population clearly identify associations between inadequate vitamin D deficiency and renal injury.[14]

Available data indicate that hypovitamin D is prevalent in the general population, and is associated with cardiovascular, renal, and infectious complications. Postsurgical patients are susceptible to similar complications. For example, myocardial injury is the leading attributable cause of 30-day mortality after noncardiac surgery. Infections occur in 1 to 3% of surgical patients and can cause failure of the surgical procedure, poor wound healing, longer hospital stay, sepsis, organ failure, and even death. The extent to which vitamin D deficiency might contribute to postoperative complications remains unclear. We therefore tested the primary hypothesis that low preoperative vitamin D concentrations are associated with cardiovascular events within 30 days after noncardiac surgery. Secondarily, we tested the hypotheses that low preoperative vitamin D concentrations increase the risk of acute kidney injury and a composite of infectious complications.

## Materials and Methods

With Institutional Review Board (Cleveland Clinic Review Board, Cleveland, Ohio) approval and written informed consent, we evaluated a subset of patients who were enrolled in the biobank substudy of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study—a large multicenter, international, prospective cohort study in patients having noncardiac surgery.[15] The overall purpose of VISION was to determine the incidence of major vascular events, the optimal clinical model to predict major perioperative vascular events, and the optimal clinical model to predict vascular death at 30 days.

VISION included 40,000 adults who had noncardiac surgery requiring overnight hospitalization. A total of 23 hospitals in 13 countries contributed. In each hospital, a representative sample of surgical inpatients was enrolled. Surgical and anesthetic management was entirely at the discretion of attending physicians and was not controlled by protocol. Participating patients were therefore given antibiotic prophylaxis per institutional standards.

A subset of VISION patients participated in the VISION Biobank, which included collection of blood shortly before surgery. There were eight participating sites in three countries. The Cleveland Clinic (Cleveland, Ohio) did not contribute blood samples to the current study. Blood samples were centrifuged. Serum was divided into aliquots, frozen, and thereafter transported to the Hamilton Health Sciences Center Core Research Laboratory (Hamilton, Canada) for long-term storage. The 25-hydroxyvitamin D analysis was run on an Architect i1000 using Abbott assay product 3L52 (Abbott, USA). Appropriate sensitivity and intraassay and interassay precision were confirmed. Analysis was conducted over 3 days. A total of 3,967 samples were analyzed: 2,498 were collected and processed locally, 893 were shipped on dry ice (samples from the United Kingdom and other Canadian sites), and 576 were shipped in nitrogen vapor shippers (samples from Hong Kong site). Storage conditions were as follows: Many samples received from one of the two United Kingdom sites were not in cryovials and hence could not be stored in liquid nitrogen. Vials from the remaining seven sites were all stored in liquid nitrogen. A total of 3,394 were stored in liquid nitrogen at −160°C, 208 were stored in freezers at −80°C, and 365 were stored in −70°C freezers. 25-Hydroxyvitamin D is stable; time doesn't affect the stability of the samples for 6 to 24 yr.[16]

Samples collected in Hamilton, Canada and those received on dry ice were all stored temporarily at −70°C, but those in appropriate cryovials were accessioned to Liquid Nitrogen 2 storage within 30 days of receipt. For the samples received in vapor, shippers were normally stored in liquid nitrogen; however, 136 samples were temporarily stored at −70°C, and another 87 samples were transferred from the shipper to −70°C the day after receipt. All were transferred to liquid nitrogen except 59 vials for which we have no records.

Samples were received from October 2008 to December 2014, and assays were performed between October 2015 and January 2016. The average storage duration was 4 yr. The breakdown is as follows: less than 1 yr, 108 samples; 1 to 3 yr, 1,101 samples, 3 to 5 yr, 1,376 samples, and 5 to 7 yr, 1,382 samples. The 25-hydroxyvitamin D quality control data are as

follows (mean ± SD): low quality control (50 nmol/l) 50.2 ± 2.6 5.1% coefficient of variation (n = 100), mid quality control (100 nmol/l) 98.1 ± 3.3 3.3% coefficient of variation (n = 100), high quality control (187.5 nmol/l) 193 ± 7 3.4% coefficient of variation (n = 100), and generic serum pool 72.4 ± 3.1 4.3% coefficient of variation (n = 108).

Data from VISION patients with available preoperative blood samples and nonmissing values for preoperative vitamin D were considered for analysis. All study outcomes were based on VISION case-report forms, which were completed by centers at the time of patient enrollment. Uniform definitions for outcomes were used per protocol at each site (Supplementary Digital Content 1, http://links.lww.com/ALN/C63). All case report forms were audited centrally using statistical techniques. Accuracy were also verified by on-site monitoring in selected patients.

The protocol and statistical analysis plan for this study was finalized and Institutional Review Board–approved before analysis began. A cutoff of preoperative vitamin D less than 75 nmol/l was used to define vitamin D deficiency.[17] All final models were adjusted for age, body mass index, duration of surgery, preoperative estimated glomerular filtration rate (ml $min^{-1}$ 1.73 $m^{-2}$ using the Chronic Kidney Disease Epidemiology Collaboration equation),[18] sex, race (Asian, black, white, other; see Supplementary Digital Content 2, http://links.lww.com/ALN/C64, for ethnic groups within each racial group), type of surgery (general, vascular, thoracic, major urology/gynecology, major orthopedic, major neurosurgery, unspecified low-risk surgery), level of surgical urgency (less than 24 h since precipitating event, 24 to 72 h since event, all other surgeries), history of chronic obstructive pulmonary disease, on dialysis before surgery, current atrial fibrillation, history of diabetes, history of hypertension, recent (less than 6-month) history of high-risk coronary artery disease (myocardial infarction, acute coronary syndrome, and Canadian Cardiovascular Society Angina Grading Scale III or IV), history of coronary artery disease, peripheral vascular disease, and region (Canada, Hong Kong, United Kingdom).

## Primary Outcome Measure

Our primary outcome was a composite of adverse 30-day postoperative cardiac outcomes including the five following components: (1) death; (2) myocardial injury after noncardiac surgery; (3) nonfatal cardiac arrest; (4) stroke; and (5) congestive heart failure. For analysis, we needed to collapse nonfatal cardiac arrest into congestive heart failure because there were only four (0.10%) nonfatal cardiac arrest events in the sample.

Given that incidences varied considerably (greater than 10%) across components, we tested our primary hypothesis that patients with low preoperative vitamin D levels have increased risk for postoperative cardiovascular events by assessing the average relative effect odds ratio across the four components using a multivariate distinct effects generalized estimating equations model with an unstructured working correlation.[19,20] This method also avoids the inherent problem with the collapsed composite (any *vs.* none) in which components with higher incidence receive undue weight and thus tend to drive the composite result.

We assessed heterogeneity of the relationship between vitamin D and outcome across the components by testing the vitamin D–by–component interaction at the 0.05 significance level. Results are reported as a covariate-adjusted average relative effect odds ratio summarizing the relationship between preoperative vitamin D concentration (per 10 nmol/l) across the four components at the 0.05 significance level. Individual component odds ratios are reported as well.

*Sensitivity Analysis.* We further assessed the relationship between preoperative vitamin D concentrations across the four components using the same method described in the Primary Outcome Measure section for the primary analysis, but incorporating clinical importance weights into the average relative effects generalized estimating equations model. A convenience sample of 10 attending anesthesiologists was used to estimate clinical importance weights for the four components included in the composite for the primary outcome. These physicians weighted the importance of each of the four outcomes on a scale from 1 to 100. To ensure the weights summed to one across the components, the scores were normalized within each physician by scaling their score for each component by the total sum of their scores. These normalized scores were then averaged across physicians to obtain clinical importance weights for each component to estimate a weighted average relative effect odds ratio for the primary outcome.

## Secondary Analyses

We also assessed whether preoperative vitamin D concentration was associated with two secondary outcomes—infectious morbidity and kidney function. Holm–Bonferroni step-down procedure for multiple testing adjustment[21] was utilized to adjust *P* values for testing two secondary outcomes. *P* adjusted value less than 0.05 was used to determine significance.

*Infectious Complications.* The association between preoperative vitamin D levels and 30-day postoperative infectious morbidity was assessed following the same method outlined for the primary outcome. The infectious morbidity composite included three components: (1) infection at surgical site; (2) sepsis; and/or (3) pneumonia within 30 days after surgery.

*Kidney Function.* Postoperative estimated glomerular filtration rate was used as a measure of kidney function. The highest creatinine level recorded within 30 days post-operation was used to calculate estimated glomerular filtration rate *via* the Chronic Kidney Disease Epidemiology Collaboration equation.[18] A multivariable linear regression model adjusting for baseline estimated glomerular filtration rate and other potential confounders was used to test our hypothesis that patients with low vitamin D levels would have decreased kidney function. The estimated change in mean postoperative estimated glomerular filtration rate per 10 nmol/l increase

in preoperative vitamin D concentration with corresponding 95% CI and *P* adjusted value are reported.

*Sensitivity Analysis.* We also examined the relationship between acute kidney injury and preoperative vitamin D concentration. Fold increase in serum creatinine from baseline was calculated, then classified into acute kidney injury stages as defined by the Acute Kidney Injury Network.[22] The proportional odds assumption required for ordinal logistic regression on acute kidney injury stages (Stage 0, Stage 1, Stage 2, Stage 3) was not met. Thus, multivariable logistic regression was used to test for an association between preoperative vitamin D concentration and a binary acute kidney injury outcome: "Any acute kidney injury" (Stages 1, 2, or 3) *versus* "No acute kidney injury" (Stage 0).

Post Hoc *Sensitivity Analysis.* The prognostic relevance of Stage 1 acute kidney injury may not be of importance. Therefore, a *post hoc* sensitivity analysis using multivariable logistic regression was used to test for an association between preoperative vitamin D concentration and a binary classification of acute kidney injury, comparing Stages 2 or 3 against Stages 0 or 1.

*Sample Size and Power.* In a retrospective analysis previously performed at our institution based on 3,509 adults who had noncardiac surgery 2005 to 2011, the observed mean ± SD vitamin D concentration was 26 ± 15 ng/ml, and the estimated odds ratio for a five-unit increase in vitamin D level was 0.90 (95% CI, 0.75–1.07) for mortality and was 0.92 (98.3% CI, 0.84–1.00) for cardiovascular complications. In the preliminary results of our VISION study, we observed an incidence rate of 6% at our institute and 10% overall.

Preliminary power analyses on the primary outcomes suggested that 2,240 patients would provide more than 90% power at the 0.05 significance level for detecting an odds ratio of 0.90 or stronger for a five-unit increase in vitamin D concentration, assuming a conservative incidence of 6% for the composite of mortality and adverse cardiovascular events.

## Results

### Patients

Among 3,967 patients with blood samples in the VISION biobank, data for 3,851 eligible participants were available for our analysis. N = 180 (4.7%) subjects were excluded from the cardiovascular and infectious analyses due to missing preoperative creatinine levels, while N = 797 (20.7%) subjects were excluded from the kidney analyses largely because of missing presurgical and/or postsurgical creatinine measurements (N = 759, 19.7%; fig. 1).

Eligible patients were separated into five approximately equal quantiles for the sole purpose of providing a summary of the bivariate relationships between preoperative vitamin D concentration (nmol/l) and our list of *a priori* selected confounding variables (table 1). All of the variables in table 1 were adjusted in each of the regression models examining the relationship between continuous preoperative vitamin D concentration (per 10 nmol/l) and our outcomes.

### Primary Analyses

*Cardiovascular Events Composite.* No association between vitamin D and the composite for cardiovascular events was found (average relative effect odds ratio [95% CI]: 0.93 [0.85, 1.01] per 10 nmol/l, $P = 0.095$). No heterogeneity of the effect of vitamin D across components was detected ($P = 0.388$). An odds ratio forest plot for the individual components and the unweighted average relative effect odds ratio are presented in figure 2.

*Sensitivity Analysis.* A convenience sample of 10 anesthesiologists was used to obtain clinical importance weights for the components of the cardiovascular events composite.

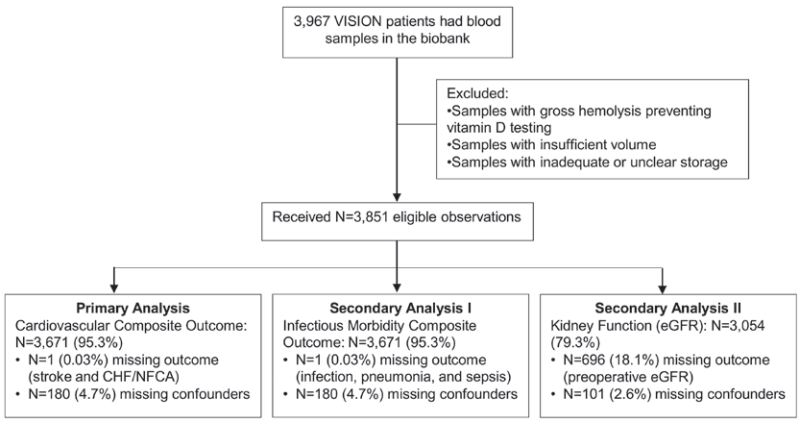


**Fig. 1.** Numbers of eligible Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) subjects for analyses. CHF/NFCA, congestive heart failure/nonfatal cardiac event; eGFR, estimated glomerular filtration rate.

**Table 1.** Patient Characteristics

| Variable | Total (N = 3,851) | Preoperative Vitamin D (nmol/l) Quantile 1st (N = 772) | 2nd (N = 764) | 3rd (N = 777) | 4th (N = 769) | 5th (N = 769) |
|---|---|---|---|---|---|---|
| Age, yr | 65 ± 11 | 63 ± 11 | 64 ± 11 | 65 ± 11 | 66 ± 11 | 68 ± 10 |
| Sex, female (%) | 1,936 (50) | 397 (51) | 380 (50) | 385 (50) | 371 (48) | 403 (52) |
| Race* (%) | | | | | | |
| –White | 3,111 (80.8) | 574 (74.4) | 525 (68.7) | 598 (77.0) | 679 (88.4) | 735 (95.6) |
| –Asian | 623 (16.2) | 152 (19.7) | 213 (27.9) | 154 (19.8) | 80 (10.4) | 24 (3.1) |
| –Black | 73 (1.9) | 33 (4.3) | 17 (2.2) | 12 (1.5) | 6 (0.8) | 5 (0.7) |
| –Other | 43 (1.1) | 13 (1.7) | 9 (1.2) | 13 (1.7) | 3 (0.4) | 5 (0.7) |
| BMI*, kg/m$^2$ | 29 ± 7 | 29 ± 7 | 29 ± 7 | 29 ± 6 | 29 ± 6 | 29 ± 6 |
| Preoperative vitamin D, nmol/l | 70 ± 30 | 35 ± 8 | 53 ± 4 | 67 ± 4 | 82 ± 5 | 114 ± 24 |
| Preoperative eGFR, ml min$^{-1}$ 1.73 m$^{-2}$* | 79 ± 20 | 82 ± 23 | 80 ± 21 | 79 ± 20 | 78 ± 19 | 76 ± 18 |
| History of | | | | | | |
| CHF* | 82 (2.1) | 21 (2.7) | 17 (2.2) | 10 (1.3) | 12 (1.6) | 22 (2.9) |
| COPD | 309 (8.0) | 70 (9.1) | 58 (7.6) | 61 (7.9) | 55 (7.2) | 65 (8.5) |
| PVD | 191 (5.0) | 53 (6.9) | 41 (5.4) | 35 (4.5) | 34 (4.4) | 28 (3.6) |
| Diabetes* | 680 (17.7) | 153 (19.8) | 155 (20.3) | 124 (16.0) | 142 (18.5) | 106 (13.8) |
| Hypertension* | 2,062 (53.6) | 384 (49.8) | 425 (55.6) | 390 (50.2) | 450 (58.5) | 413 (53.7) |
| CAD* | 532 (13.8) | 110 (14.3) | 97 (12.7) | 92 (11.8) | 112 (14.6) | 121 (15.7) |
| Recent high-risk CAD | 30 (0.78) | 6 (0.78) | 7 (0.92) | 4 (0.51) | 7 (0.91) | 6 (0.78) |
| Current atrial fibrillation* | 129 (3.4) | 25 (3.2) | 21 (2.7) | 24 (3.1) | 26 (3.4) | 33 (4.3) |
| On dialysis* | 16 (0.4) | 8 (1.0) | 3 (0.4) | 1 (0.1) | 3 (0.4) | 1 (0.1) |
| Duration of surgery, min | 131 ± 97 | 152 ± 108 | 139 ± 104 | 133 ± 95 | 120 ± 87 | 112 ± 81 |
| Surgical urgency | | | | | | |
| < 24 h since event | 38 (1.0) | 16 (2.1) | 5 (0.7) | 9 (1.2) | 5 (0.7) | 3 (0.4) |
| 24 to 72 h since event | 77 (2.0) | 34 (4.4) | 19 (2.5) | 11 (1.4) | 7 (0.9) | 6 (0.8) |
| All other surgeries | 3,736 (97.0) | 722 (93.5) | 740 (96.9) | 757 (97.4) | 757 (98.4) | 760 (98.8) |
| Primary surgery type* | | | | | | |
| General surgery | 624 (16.2) | 157 (20.4) | 139 (18.2) | 125 (16.1) | 111 (14.5) | 92 (12.0) |
| Low risk (no designation) | 829 (21.6) | 192 (24.9) | 183 (24.0) | 178 (22.9) | 147 (19.1) | 129 (16.8) |
| Major neurosurgery | 206 (5.4) | 60 (7.8) | 48 (6.3) | 49 (6.3) | 25 (3.3) | 24 (3.1) |
| Major orthopedic surgery | 1,336 (34.7) | 195 (25.3) | 209 (27.4) | 257 (33.1) | 310 (40.4) | 365 (47.5) |
| Thoracic surgery | 174 (4.5) | 29 (3.8) | 38 (5.0) | 40 (5.1) | 36 (4.7) | 31 (4.0) |
| Major urology or gynecology surgery | 516 (13.4) | 95 (12.3) | 106 (13.9) | 104 (13.4) | 108 (14.1) | 103 (13.4) |
| Vascular surgery | 161 (4.2) | 43 (5.6) | 39 (5.1) | 24 (3.1) | 31 (4.0) | 24 (3.1) |
| Site | | | | | | |
| Canada | 2,618 (68.0) | 296 (38.3) | 438 (57.3) | 549 (70.7) | 628 (81.7) | 707 (91.9) |
| Hong Kong | 555 (14.4) | 130 (16.8) | 195 (25.5) | 147 (18.9) | 71 (9.2) | 12 (1.6) |
| United Kingdom | 678 (17.6) | 346 (44.8) | 131 (17.1) | 81 (10.4) | 70 (9.1) | 50 (6.5) |

Continuous variables are summarized as mean ± SD; categorical data are summarized as N (column %).

*Data not available for all subjects. Missing values: body mass index, 30; duration of surgery, minutes, 15; preoperative eGFR, 130; race, 1; history of CHF, 3; history of diabetes, 1; history of hypertension, 1; history of CAD, 2; current atrial fibrillation, 1; patient on dialysis, 3; primary surgery type, 5.

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PVD, peripheral vascular disease.

From their responses, weights of 0.24, 0.31, 0.19, and 0.25 for the congestive heart failure/nonfatal cardiac arrest, death, myocardial injury after noncardiac surgery, and stroke components, respectively, were used to obtain a weighted estimate for the average relative effect odds ratio. No association between vitamin D and the composite outcome was found (average relative effect odds ratio [95% CI]: 0.92 [0.83, 1.02] per 10 nmol/l, $P = 0.096$).

## Secondary Analyses

*Infectious Complications.* Preoperative vitamin D concentration was significantly associated with the infectious morbidity composite (average relative effect odds ratio [95% CI]: 0.94 [0.90, 0.98] per 10 nmol/l, $P$ adjusted value = 0.005). No heterogeneity of the effect of vitamin D across components was detected ($P = 0.578$). An odds ratio forest plot for the individual components and the average relative effect odds ratio are presented in figure 3.

*Kidney Function.* An association between preoperative vitamin D concentration and postoperative estimated glomerular filtration rate was found. Mean postoperative estimated glomerular filtration rate levels increased an estimated 0.29 (0.11, 0.48) ml min$^{-1}$ 1.73 m$^{-2}$ per 10 nmol/l increase in preoperative vitamin D concentration ($P$ adjusted value =

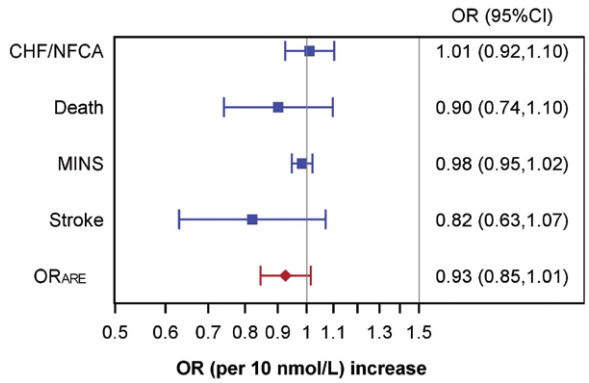


**Fig. 2.** Odds ratio plot for cardiovascular composite components. Covariable adjusted odds ratios (ORs) (95% CIs) for preoperative vitamin D concentration (per 10 nmol/l increase) and 30-day postoperative cardiovascular components (*blue*) and average relative effect OR ($OR_{ARE}$) (95% CI) for the unweighted composite outcome (*red*), after adjusting for all confounders listed in table 1. Distinct effect ORs for each component were estimated, then averaged applying equal weights, across the four components to obtain an overall estimate of the effect of preoperative vitamin D concentration on the cardiovascular composite outcome (*i.e.,* $OR_{ARE}$). CHF/NFCA, congestive heart failure within 30-days postoperation/nonfatal cardiac arrest; MINS, myocardial injury after noncardiac surgery.

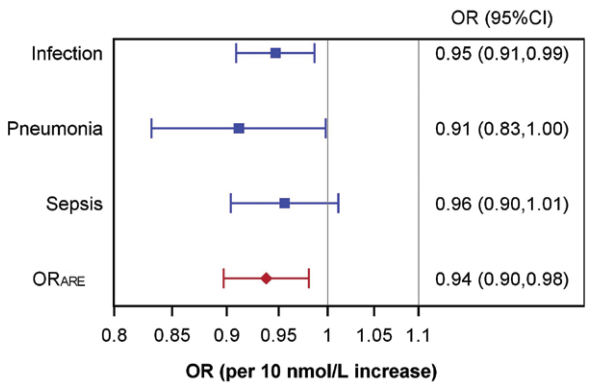


**Fig. 3.** Odds ratio plot for infectious complications composite components. Covariable adjusted odds ratios (ORs) (95% CIs) for preoperative vitamin D concentration (per 10 nmol/l increase) and 30-day postoperative infectious complications components (*blue*) and average relative effect OR ($OR_{ARE}$) (95% CI) for the unweighted composite outcome (*red*), after adjusting for all confounders listed in table 1. Distinct effect ORs for each component were estimated, then averaged applying equal weights, across the four components to obtain an overall estimate of the effect of preoperative vitamin D concentration on the cardiovascular composite outcome (*i.e.,* $OR_{ARE}$).

**Table 2.** Incidence of Postoperative Acute Kidney Injury

| Acute Kidney Injury | N (%) |
|---|---|
| No. | 2,942 (95.2) |
| Stage 1 | 94 (3.0) |
| Stage 2 | 39 (1.3) |
| Stage 3 | 17 (0.6) |

Frequencies for acute kidney injury stages, as defined by the Acute Kidney Injury Network. Acute kidney injury stage could not be assessed for N = 759 (19.71%) subjects due to missing presurgical and/or postsurgical creatinine measurements.

0.004). There were no gross deviations from multivariable linear regression model assumptions.

*Sensitivity Analysis.* Frequencies for acute kidney injury are presented in table 2. There was no association between vitamin D concentration and acute kidney injury (odds ratio [95% CI]: 0.93 [0.87, 1.00] per 10 nmol/l increase in preoperative vitamin D concentration, *P* adjusted value = 0.053).

Post Hoc *Sensitivity Analysis.* Surgical urgency and recent high-risk coronary artery disease were removed from the regression model due to the presence of zero-count cells between this parameterization of acute kidney injury and these two confounders (*i.e.*, there were no patients who had Stage 2/3 acute kidney injury and had surgery performed less than 24 h since event, nor were there any Stage 2/3 acute kidney injury patients who were diagnosed with recent high-risk coronary artery disease). Race was collapsed into a binary variable—white *versus* not white—to address collinearity between race and site. After making these adjustments to the model, there was no association between acute kidney injury and vitamin D concentration (odds ratio [95% CI]: 0.94 [0.83, 1.05] per 10 nmol/l vitamin D, *P* adjusted value = 0.269).

Results from our primary and secondary analyses are summarized in table 3.

## Discussion

Many guidelines suggest 75 nmol/l as the threshold for vitamin D deficiency, a concentration that exceeds the mean for our entire multinational population, and exceeded observed concentrations in almost 62% of our patients.[17] Our results therefore suggest that vitamin D deficiency is common in surgical patients; furthermore, it was common in patients of every age and race, and from every region. Surgical patients being vitamin D–deficient may be explained by the general frequency of vitamin D deficiency and that surgical patients are sicker than the general population.

Although laboratory and epidemiologic evidence shows that adequate vitamin D concentrations are critical to cardiovascular health, there was no association between preoperative vitamin D concentrations and a composite of cardiovascular complications in this multinational study of patients having noncardiac surgery. Our results are consistent with a previous single-center analysis in cardiac

**Table 3.** Associations between Preoperative Vitamin D Concentration and Cardiac, Infectious, and Kidney Outcomes

| Outcomes | Total (N = 3,851) | Quantile of Preoperative Vitamin D Concentration (nmol/l) 1st (N = 772) | 2nd (N = 764) | 3rd (N = 777) | 4th (N = 769) | 5th (N = 769) | Estimate (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|
| Primary outcome | | | | | | | | |
| Cardiovascular events composite | | | | | | | | |
| CHF/NFCA | 41 (1.1) | 6 (0.8) | 10 (1.3) | 7 (0.9) | 10 (1.3) | 8 (1.0) | 1.01 (0.92, 1.10) | |
| Death | 26 (0.7) | 9 (1.2) | 6 (0.8) | 3 (0.4) | 2 (0.3) | 6 (0.8) | 0.90 (0.74, 1.10) | |
| MINS | 540 (14.0) | 112 (14.5) | 91 (11.9) | 122 (15.7) | 98 (12.7) | 117 (15.2) | 0.98 (0.95, 1.02) | |
| Stroke | 15 (0.4) | 4 (0.5) | 6 (0.8) | 3 (0.4) | 1 (0.1) | 1 (0.1) | 0.82 (0.63, 1.07) | |
| Cardiac $OR_{ARE}$ | | | | | | | 0.93 (0.85, 1.01) | 0.095 |
| Secondary outcomes | | | | | | | | |
| Infectious complications composite | | | | | | | | |
| Infection | 318 (8.3) | 82 (10.6) | 63 (8.2) | 65 (8.4) | 58 (7.5) | 50 (6.5) | 0.95 (0.91, 0.99) | |
| Pneumonia | 55 (1.4) | 15 (1.9) | 17 (2.2) | 9 (1.2) | 10 (1.3) | 4 (0.52) | 0.91 (0.83, 1.00) | |
| Sepsis | 171 (4.4) | 45 (5.8) | 39 (5.1) | 29 (3.7) | 30 (3.9) | 28 (3.6) | 0.96 (0.90, 1.01) | |
| Infectious $OR_{ARE}$ | | | | | | | 0.94 (0.90, 0.98) | 0.005* |
| Kidney function | | | | | | | | |
| Postoperative eGFR, $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ | 79 ± 23 | 79 ± 26 | 78 ± 24 | 78 ± 23 | 79 ± 21 | 79 ± 21 | 0.29 (0.11, 0.78) | 0.004* |

Cardiovascular events composite: N (incidence) by quantile are presented for each component. There were only four (0.1%) NFCA events in the cohort, so they were merged with CHF to create the CHF/NFCA component. The adjusted ORs (95% CI) for risk of component or composite per 10 nmol/l increase in preoperative vitamin D concentration were estimated *via* multivariate GEE, controlling for all confounders listed in table 1. Infectious complications composite: N (incidence) by quantile are presented for each component. The adjusted ORs (95% CI) for risk of component or composite per 10 nmol/l increase in preoperative vitamin D concentration were estimated *via* multivariate GEE with Holm–Bonferroni adjusted *P* value for testing two secondary outcomes, controlling for all confounders listed in table 1. Kidney function: Mean ± SD by quantile are presented. The adjusted difference (95% CI) in postoperative eGFR corresponding to per 10 nmol/l increase in preoperative vitamin D concentration was estimated *via* multivariable linear regression estimate with Holm–Bonferroni adjusted *P* value for testing two secondary outcomes, controlling for all confounders listed in table 1.

*Holm-adjusted *P* value for testing two secondary outcomes.

CHF/NFCA, congestive heart failure/nonfatal cardiac arrest; eGFR, estimated glomerular filtration rate; MINS, myocardial injury after noncardiac surgery; OR, odds ratio; $OR_{ARE}$, average relative effect OR.

surgical patients, which also showed no association between perioperative vitamin D concentrations and cardiovascular complications.[23] However, they diverge from our previous analysis in a similarly sized group of noncardiac surgical patients in whom an association was identified.[9]

There are important differences between the two studies. In our current analysis, for example, complications were identified prospectively and from adjudicated event reports rather than from electronic records, which are less reliable. A critical distinction is that nearly all postoperative myocardial injury is clinically silent and thus only detected by routine troponin screening. All VISION patients had scheduled troponin monitoring 6 to 12 h postoperatively and the first three postoperative mornings while hospitalized, whereas monitoring was not routine in the previous study. The VISION cohort was also restricted to patients 45 yr of age or older and thus inherently at higher cardiovascular risk.[15] Consequently, 16% of patients in our current cohort experienced cardiovascular events, whereas only 5% did in our previous cohort. Presumably the incidence in the current VISION cohort better estimates the true incidence of myocardial injury and infarction.

Another important difference is that blood for vitamin D in the VISION cohort was sampled shortly before surgery, whereas in our previous analyses we included the most recent vitamin D analysis within 3 months before the procedure date to 1 month after surgery. Since vitamin D concentrations vary over time, it is possible that recorded concentrations in our previous analyses poorly reflected concentrations at the time of surgery. Because of these limitations, we assume that results from our current analysis are more reliable. Overall, available results suggest that low vitamin D concentration is an inconsistent biomarker for perioperative cardiovascular risk, and it remains unknown whether preoperative supplementation will reduce perioperative cardiovascular risk. Supporting this conclusion, vitamin D supplementation in epidemiologic and intensive care studies does not improve cardiovascular outcomes.[24,25]

Adequate preoperative vitamin D concentrations were protective against a composite of infectious complications, with an estimated 6% reduction in odds of infectious morbidity per 10 nmol/l increase in preoperative vitamin D concentration. The magnitude of this association was substantial, with the average odds of infectious morbidity in the second quantile being roughly 12% less than those in the first quantile of preoperative vitamin D concentration. More impressively, when comparing the first and fifth quantiles, the odds of infectious morbidity in the fifth quantile was about half that in the first quantile.

Our current results are consistent with our previous report that serum vitamin D concentrations are associated with infectious complications in patients having noncardiac

surgery.[9] Previous studies in kidney transplant and arthroplasty patients have reported that low vitamin D concentrations are associated with infections.[26,27] There is also a report that vitamin D is independently associated with postoperative infections after cardiac surgical patients, although we found no association in this population.[28] The bulk of available evidence suggests that there is a clinically important association between vitamin D concentration and perioperative infectious risk. A clinical trial would seem worthwhile to establish the extent to which the association might be causal, and thus amenable to vitamin D supplementation.

Vitamin D deficiency is common in patients suffering from renal dysfunction, perhaps because people with renal failure are generally relatively sick and spend little time outdoors.[29] Animal and human studies suggests a protective role for the vitamin D system in chronic renal disease and diabetic nephropathy; furthermore, vitamin D deficiency is an independent risk factor for acute kidney injury.[29,30] We nonetheless were unable to identify an association with low vitamin D concentrations and acute kidney injury. Although statistically significant changes were observed in estimated glomerular filtration rate, they were clinically unimportant, and there were no differences in kidney injury grade. The most likely explanation is that perioperative kidney injury is largely determined by hypotension, hypovolemia, drug toxicity, and obstruction.[31] However, patients without postoperative creatinine levels (20%) were generally healthier and had lower-risk surgeries compared to the patients with available creatinine measurements. Our analysis adjusted for all these factors.

Our analysis is strengthened by prospective observational design, optimized for cardiovascular outcomes, which makes our results more reliable than typical retrospective analyses based on medical records. We also used sophisticated statistical techniques, especially making average relative effect generalized estimating equations our primary analysis rather than the weaker collapsed (one or more) composite or common effect approach. Average relative effect weights each outcome equally, producing results that are not driven by the high-incidence outcomes. This is particularly important with respect to the analysis on the cardiac composite where the myocardial injury after noncardiac surgery component has a much higher incidence than the other components in the composite (table 3). A further advantage of distinct effects generalized estimating equations models are that they allowed us to assess association heterogeneity across outcome components and sites. And finally, we accounted for correlations among outcomes, which is particularly appropriate for this study because the incidence of primary components ranged from 1 to 14%.

A limitation of our analysis is that the follow-up period was only 30 days, which may be insufficient to address long-term pathway changes consequent to vitamin D inadequacy or deficiency. The nature of this study limits our findings to identifying associations; interventional trials will be necessary to establish whether the link between vitamin D concentration and postoperative infectious complications is causal and thus amenable to supplementation. Observational studies of vitamin D are inherently subject to an important source of confounding, namely that sicker people spend more time indoors and are thus likely to have lower vitamin D concentrations than healthier people in the same environment. We defined regions broadly, but the amount of sunlight varies over relatively small areas. To the extent that sunlight exposure might be correlated with other health-related factors such as wealth, our associations between vitamin D concentration and complications might be confounded.

In summary, after controlling for known and available confounding factors, we found no evidence that a composite of postoperative 30-day cardiac outcomes was associated with preoperative vitamin D concentrations. Kidney function was statistically associated, but it doesn't appear to be clinically important. However, there was a statistically significant and clinically important association between vitamin D and infectious complications. Clinical practice should not be changed until a clinical trial evaluating effect of vitamin D supplementation on infectious complications is performed, because it remains unknown whether the relationship is causal and infection risk can be reduced by supplementation.

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## Competing Interests

The authors declare no competing interests.

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# From Hartshorn to Smelling Salts: Prodding Awake the Anesthetized...with Antlers?

Whether indigenous or introduced, red deer (*Cervus elaphus*, *left*) now roam every continent except Antarctica. Females ("hinds") and males ("stags" or "harts") segregate most of the year into bachelorette and bachelor groups, respectively. In preparation for autumn battles for a harem of hinds, each hart's antlers (*right*) start growing in the spring before shedding by end of winter. Harder than bone, their antlers have been fashioned by humans into knives and other tools for thousands of years. Antler carvers learned rather quickly not to discard leftover horn into campfires because of the resulting foul odor. However, by destructively distilling antlers into "oil of hartshorn" and then dry-distilling the latter into "salt of hartshorn," pharmacists produced ammonium carbonate, the scented alcoholic solutions of which were bottled (*middle*) for use as smelling salts to treat Victorian belles' "vapours" or physicians' unconscious patients. Spontaneously releasing ammonia, such salts or "sal volatile" could be introduced nasally or orally by finger or feather in attempts to rouse unresponsive or over-anesthetized patients. So, ironically, heating ammonium *nitrate* releases nitrous oxide, which puts patients to sleep; in contrast, heating ammonium *carbonate* releases ammonia, which wakes them up. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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