D.2.1.8 Meltzer 2020

Meltzer, 2020

Bibliographic Reference	Meltzer, David O; Best, Thomas J; Zhang, Hui; Vokes, Tamara; Arora, Vineet; Solway, Julian; Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.; JAMA network open; 2020; vol. 3 (no. 9); e2019722

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not reported.
Aim of the study	To assess if people would be more likely to test positive for COVID-19 if they had deficient vitamin D level measurement before COVID-19 testing.
County/ Geographical location	Chicago, US.
Study setting	University of Chicago Medicine.
Population description	Data was obtained for all 4313 patients tested for COVID-19 at the university between 3rd March 2020 and 10th April 2020. Age, sex, and race/ethnicity were also obtained from the electronic health record. The most recent data was obtained during the study period up to 14 days before COVID-19 testing to calculate body mass index and the following International Statistical Classification of

	Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)–based Elixhauser comorbidity clusters potentially related to COVID-19 and/or vitamin D metabolism: hypertension, diabetes, chronic pulmonary disease, pulmonary circulation disorders, depression, immunosuppression, liver disease, and chronic kidney disease.
Inclusion criteria	Tested for COVID-19 in the study period and had a vitamin D measurement within the past 12 months.
Exclusion criteria	People who had vitamin D testing within 14 days of COVID-19 testing in case the infection confounded the vitamin D results.
Vitamin D status measurements	Vitamin D was measured up to a year before the COVID-19 test. The authors were aware that levels may have changed, therefore they estimated whether the participants would likely be still sufficient/deficient based on their vitamin D concentration at measurement and if their vitamin D supplementation had changed since that measurement was taken. Participants were then categorised into 1 of 4 groups: : likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), and 2 groups with uncertain deficiency (last level deficient and treatment increased, and last level not deficient and treatment decreased). A more detailed explanation on how the study categorised participants is below: Patients were deemed to be vitamin D deficient if their most recent serum vitamin D levels within 1 year before their first COVID-19 tests were less than 20 ng/mL for 25-hydroxycholecalciferol (to convert to nanomoles per litre, multiply by 2.496) or less than 18 pg/ml for 1,25-dihydroxycholecalciferol (to convert to picomoles per litre, multiply by 2.4) and deemed not deficient if their most recent levels were equal to or greater than 20 ng/mL or equal to or greater than 18 pg/ml, respectively. Vitamin D treatment was defined by report in the electronic health record of vitamin D either in the patient medication list or prescription orders. Vitamin D3 dosing was defined based on most recent daily dose recorded over the past year excluding the 14 days before testing: none, 1 to 1000 IU or a multivitamin, 2000 IU, or greater than or equal to 3000 IU. Indicators for treatment with vitamin D2 and calcitriol were also included. Possible changes in patients' vitamin D treatment after the time of their last vitamin D level were accounted for by categorizing changes in treatment between the date of the last vitamin D level and 14 days before COVID-19 testing as increased, unchanged, or decreased according to the following ordering: calcitriol was considered the highest treatment category followed in decreasing order by greater than or equal to 3000 IU D_3, 2000 IU D_3, D_2, 1-1000 IU D_3 or multivitamin, and no vitamin D. The data was then combined on last vitamin D level measurements with changes in treatment after that last vitamin D level to assign each patient to 1 of 4 categories reflecting their likelihood of being vitamin D deficient at the time of COVID-19 testing: likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), and 2 groups with uncertain deficiency (last level deficient and treatment increased, and last level not deficient and treatment decreased).
Methods used to confirm COVID-19 infection	COVID-19 test status was determined by any positive COVID-19 polymerase chain reaction test result, with the Centers for Disease Control and Prevention or Viacor test used until in-house testing with the test from Roche (cobas) began on March 15, 2020. Because of test supply, testing at UCM was limited to persons presenting with potential symptoms of COVID-19 admitted to the hospital or health care workers with COVID-19 symptoms and exposure.
Intervention	Not applicable.
Comparator (where applicable)	Not applicable.

Methods for population selection/allocation	Described above.
Methods for case-matching with control	Not applicable.
Methods of data analysis	Basic descriptive statistics were reviewed for all variables. In comparing patients with last vitamin D levels that were deficient and patients with last levels that were not deficient, Fisher's exact test was used for binary variables and the t-test for continuous variables. A multivariable generalized linear model with binomial residuals and log-link function was estimated with the covariates noted above. A piecewise linear spline with a single knot at 50 improved model fit over models with unadjusted age or more complex parameterizations. Statistical significance was defined as $P < 0.05$. All tests were 2-tailed.
Source of funding	Supported by the Learning Health Care System Core of the University of Chicago/Rush University Institute for Translational Medicine (ITM) Clinical and Translational Science Award (ITM 2.0: Advancing Translational Science in Metropolitan Chicago, UL1TR002389, Solway, Contact PI) and the African American Cardiovascular Pharmacogenetic Consortium (U54-MD010723, Meltzer).
Study limitations (authors)	Vitamin D deficiency may be a consequence associated with a range of chronic health conditions or behavioural factors that plausibly increase COVID-19 risk. The authors defend the results by saying they are robust and include a broad set of demographic and comorbidity indicators that have either physiological reasons for consideration or have been suggested to influence COVID-19 outcomes. Neither patients who were deficient in vitamin D and had increased treatment nor patients who were not deficient in vitamin D who had decreased treatment were more likely than patients who were not vitamin D deficient and at least maintained their current treatment (ie, had nondeficient status) to test positive for COVID-19. If the observed association were due to confounding by behavioural or other health factors, such associations might have been expected, although our limited sample size might be inadequate to identify such effects. The data are limited to those available in the UCM electronic health record. Patterns of vitamin D screening, treatment, or COVID-19 testing at UCM or in other institutions might have somehow selected for patients who induced an association between observed vitamin D status and testing positive for COVID-19. They considered whether specific versions of this broad range of alternative hypotheses might explain our findings, including the idea that vitamin D treatment not recorded at UCM prior to COVID-19 testing might have biased our results. Analysis of medication information reported at the time of COVID-19 testing did not identify changes in vitamin D dosing. Only a few individuals received higher doses of vitamin D3 or had relative high vitamin D levels, limiting power to assess whether vitamin D dose or levels are associated with the likelihood of COVID-19. Calcitriol was also included in defining vitamin D deficiency and

	included patients treated with vitamin D2 or calcitriol, which are often used in patients with chronic kidney disease or hypoparathyroidism. Sensitivity analysis were robust at omitting these patients. The sample is overrepresented in persons with vitamin D deficiency because of the large number of African American individuals, adults with chronic illness, and health care workers, all living in a northern city and exposed to COVID-19 during winter. Vitamin D deficiency is highly prevalent in the US but could be a smaller risk factor in other populations.
Study limitations (reviewer)	Estimations of vitamin D status based on supplementation may be incorrect as it relies on medicine compliance.

Study arms

Full cohort (N = 489)

Characteristics

Study-level characteristics

	Study (N = 489)
Age	
Mean/SD	49.2 (18.4)
Vitamin D deficient <20 ng/mL	
Mean/SD	45.9 (17.6)
Vitamin D sufficient ≥20 ng/mL	
Mean/SD	51 (18.6)
Gender Female	
Sample Size	n = 366 ; % = 75
Vitamin D deficient <20 ng/mL	
Sample Size	n = 133 ; % = 77

	Study (N = 489)
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 233 ; % = 74
Ethnicity BAME	
Sample Size	n = 331 ; % = 68
Vitamin D deficient <20 ng/mL	
Sample Size	n = 142 ; % = 83
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 189 ; % = 60
Comorbidities	
BMI	
Mean	29.8
Vitamin D deficient <20 ng/mL	
Mean	30.4
Vitamin D sufficient ≥20 ng/mL	
Mean	29.4
Use of immune suppressing treatments	
Custom value	NA
Socioeconomic status	
Custom value	NA
Previous history of COVID-19	
Custom value	NA
Other supplement use	
Custom value	NA

	Study (N = 489)
Timing of vitamin D measurements Number evaluated in the past year	
Sample Size	n = 489 ; % = 100
Shielding status	
Custom value	NA
Living in care homes	
Custom value	NA
Vitamin D sufficiency Number of people who fall into each sufficiency category	
Likely deficient Answer was yes to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was stable or decreased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 124 ; % = 25
Uncertain deficiency Answer was yes to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was increased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 48 ; % = 10
Uncertain deficiency Answer was no to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was decreased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 30 ; % = 5
Likely sufficient Answer was no to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was stable or increased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 287 ; % = 59

Arm-level characteristics

	Full cohort (N = 489)
Hypertension	
Sample Size	n = 261 ; % = 53

	Full cohort (N = 489)
Vitamin D deficient <20 ng/mL	
Sample Size	n = 89 ; % = 52
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 172 ; % = 54
Diabetes	
Sample Size	n = 137 ; % = 28
Vitamin D deficient <20 ng/mL	
Sample Size	n = 51 ; % = 30
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 86 ; % = 27
Chronic pulmonary disease	
Sample Size	n = 117 ; % = 24
Vitamin D deficient <20 ng/mL	
Sample Size	n = 43 ; % = 25
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 74 ; % = 23
Pulmonary circulation disorders	
Sample Size	n = 20 ; % = 4
Vitamin D deficient <20 ng/mL	
Sample Size	n = 9 ; % = 5
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 11 ; % = 3
Depression	

	Full cohort (N = 489)
Sample Size	n = 119 ; % = 24
Vitamin D deficient <20 ng/mL	
Sample Size	n = 45 ; % = 26
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 74 ; % = 23
Chronic kidney disease	
Sample Size	n = 116 ; % = 24
Vitamin D deficient <20 ng/mL	
Sample Size	n = 36 ; % = 21
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 80 ; % = 25
Liver disease	
Sample Size	n = 56 ; % = 11
Vitamin D deficient <20 ng/mL	
Sample Size	n = 17 ; % = 10
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 39 ; % = 12
Comorbidities with immunosuppression	
Sample Size	n = 105 ; % = 21
Vitamin D deficient <20 ng/mL	
Sample Size	n = 36 ; % = 21
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 69 ; % = 22

	Full cohort (N = 489)
Most recent active vitamin D treatment before COVID-19 test Participants are listed by vitamin D treatment, and vitamin D sufficiency below	
None, vitamin D deficient	
Sample Size	n = 80 ; % = 47
None, vitamin D sufficient	
Sample Size	n = 132 ; % = 42
1-1000 IU D3/multivitamin, vitamin D deficient	
Sample Size	n = 28 ; % = 16
1-1000 IU D3/multivitamin, vitamin D sufficient	
Sample Size	n = 85 ; % = 27
2000 IU D3, vitamin D deficient	
Sample Size	n = 7 ; % = 4
2000 IU D3, vitamin D sufficient	
Sample Size	n = 53 ; % = 17
≥3000 IU D3, vitamin D deficient	
Sample Size	n = 10 ; % = 6
≥3000 IU D3, vitamin D sufficient	
Sample Size	n = 10 ; % = 3
D2, vitamin D deficient	
Sample Size	n = 44 ; % = 26
D2, vitamin D sufficient	
Sample Size	n = 32 ; % = 10
Calcitriol, vitamin D deficient The study reports <5 people in this group and to preserve confidentiality, the actual frequency counts were masked	
Sample Size	n = 5 ; % = 2
Calcitriol, vitamin D sufficient	
Sample Size	n = 5 ; % = 2
COVID-19 positive	

	Full cohort (N = 489)
Vitamin D deficient <20 ng/mL	
Sample Size	n = 32 ; % = 19
Vitamin D sufficient ≥20 ng/mL	
Sample Size	n = 39 ; % = 12

Outcomes

Multivariable Association of Vitamin D Deficiency and Treatment with Testing Positive for COVID-19

Age, sex, ethnicity, employee status, vitamin D status, comorbidity indicators and BMI were in included in this model.

	Full cohort vs Full cohort
	N1 = 489
Most recent vitamin D <20 ng/mL *Polarity: Lower values are better*	
Likely deficient Answer was yes to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was stable or decreased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 124 ; % = 25, n = 287 ; % = 59
Odds ratio/95% CI	1.77 (1.12 to 2.81)
Uncertain deficiency Answer was yes to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was increased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 48 ; % = 10, n = 287 ; % = 59
Odds ratio/95% CI	1.1 (0.49 to 2.43)
Uncertain deficiency Answer was no to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was decreased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	

	Full cohort vs Full cohort
	N1 = 489
Sample Size	n = 30 ; % = 5, n = 287 ; % = 59
Odds ratio/95% CI	1.09 (0.43 to 2.82)
Likely sufficient [reference] Answer was no to most recent vitamin D level within 1 year being deficient (<20 ng/mL); dose was stable or increased after last visit. Vitamin D dose was rank ordered as follows: calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/multivitamin > no vitamin D.	
Sample Size	n = 287 ; % = 59, n = 287 ; % = 59
Odds ratio	1
Age linear spline *Polarity: Lower values are better*	
50+	
Sample Size	n = 260 ; % = 53
Odds ratio/95% CI	1.05 (1.01 to 1.09)
50+	
Sample Size	n = 229 ; % = 47
Odds ratio/95% CI	1.02 (1 to 1.05)
Sex *Polarity: Lower values are better*	
Male [reference]	
Sample Size	n = 123 ; % = 25
Odds ratio	1
Female	
Sample Size	n = 366 ; % = 75
Odds ratio/95% CI	0.87 (0.52 to 1.44)
Race *Polarity: Lower values are better*	
White [reference]	
Sample Size	n = 158 ; % = 32

	Full cohort vs Full cohort
	N1 = 489
Odds ratio	1
Other than white	
Sample Size	n = 331 ; % = 68
Odds ratio/95% CI	2.54 (1.26 to 5.12)
Comorbidities *Polarity: Lower values are better*	
Hypertension	
Sample Size	n = 261 ; % = 53
Odds ratio/95% CI	1.08 (0.6 to 1.97)
Diabetes	
Sample Size	n = 137 ; % = 28
Odds ratio/95% CI	0.78 (0.49 to 1.26)
Chronic pulmonary disease	
Sample Size	n = 117 ; % = 24
Odds ratio/95% CI	0.91 (0.55 to 1.52)
Pulmonary circulation disorders	
Sample Size	n = 20 ; % = 4
Odds ratio/95% CI	0.64 (0.23 to 1.79)
Depression	
Sample Size	n = 119 ; % = 24
Odds ratio/95% CI	1.22 (0.74 to 2.02)
Chronic kidney disease	
Sample Size	n = 116 ; % = 24
Odds ratio/95% CI	0.8 (0.49 to 1.32)
Liver disease	
Sample Size	n = 56 ; % = 11
Odds ratio/95% CI	0.99 (0.47 to 2.08)

	Full cohort vs Full cohort
	N1 = 489
Comorbidities with immunosuppression	
Sample Size	n = 105 ; % = 21
Odds ratio/95% CI	0.39 (0.2 to 0.76)
BMI *Polarity: Lower values are better*	
Odds ratio/95% CI	1.02 (1 to 1.05)
Mean	29.8

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Adequate participation from eligible participants. People only included if they had a recent vitamin D test. People were excluded if they had had a vitamin D test 14 days before they had their COVID-19 test as positivity or reasons for presenting with symptoms may affect vitamin D levels. This may bias results.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(No attrition reported.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias Moderate risk of bias *(Vitamin D status at the time of the study was estimated depending on participant's status at time of vitamin D testing and if their supplements had changed since then. However, as sensitivity analyses showed that removing people who had less certain vitamin D status did not change the results of the multivariable analyses, preventing this domain from being classed as high risk of bias.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(COVID-19 tested by RT-PCR at the same site)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Some confounders missing from study, such as use of immune suppressing treatments. Socioeconomic status was included in some modelling but only reported as not different to the model that was reported.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Multivariable analysis allows adjustment for confounders. Model covariates was chosen based on comorbidity clusters potentially related to COVID-19 and/or vitamin D metabolism as listed in the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)–based Elixhauser.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Some confounders not reported, vitamin D status estimated but sensitivity analyses show no difference between models, only people with recent vitamin D test included which restricts the pool to people who have presented with vitamin D deficiency or symptoms of that or related conditions.)*
	Directness	Partially applicable *(Historical vitamin D measurements used)*