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Bibliographic Reference	Kaufman, Harvey W; Niles, Justin K; Kroll, Martin H; Bi, Caixia; Holick, Michael F; SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels.; PloS one; 2020; vol. 15 (no. 9); e0239252

Study details

Study design	Case-control study
Trial registration (if reported)	Not reported.
Study start date	09-Mar-2020
Study end date	19-Jun-2020
COVID-19 prevalence at the time of the study	Higher prevalence (e.g. during peak of first wave)
Aim of the study	To assess the association of circulating 25-hydroxyvitamin D [25(OH)D] levels, a measure of vitamin D status, with positivity for SARS-CoV-2.

County/ Geographical location	US, data included from all 50 states and the District of Columbia.
Study setting	Results analysed from clinical laboratory results.
Population description	The population was recruited from test results from a clinical laboratory. A Quest Diagnostics-wide unique patient identifier was used to match all results of SARS-CoV-2 testing with 25(OH)D results from the preceding 12 months.
Inclusion criteria	Had a SARS-CoV-2 test result and vitamin D measurements.
Exclusion criteria	Specimens with inconclusive results (one out of two SARS-CoV-2 targets detected) or missing residential zip code data, which are needed to assign race/ethnicity proportions and latitude.
Vitamin D status measurements	Total 25(OH)D was measured using a chemiluminescent immunoassay (DiaSorin LIAISON1XL 25-hydroxyvitamin D, total) or a laboratory-developed test based on liquid chromatograph/tandem mass spectrometry. The laboratory categorizes 25(OH)D results <20 ng/mL as deficient, 20-29 ng/mL as suboptimal, and >30 ng/mL as optimal. The laboratory assays are standardized and performed identically throughout Quest Diagnostics. When multiple 25(OH)D results were available, the most recent was used.
Methods used to confirm COVID-19 infection	All SARS-CoV-2 RNA NAATs were performed by Quest Diagnostics using one of four United States Food and Drug Administration (FDA) Emergency Use Authorized tests (Quest Diagnostics SARS-CoV-2 RNA [COVID-19], Qualitative NAAT; Hologic Panther Fusion SARS-CoV-2 assay; Roche Diagnostics cobas1SARS-CoV-2 test; or Hologic Aptima SARS-CoV-2 assay). We combined results from all four tests due to their very similar sensitivity and specificity. Analysis was limited to one SARS-CoV-2 result per patient. Patients were considered positive if at least one test result indicated positivity.
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	Comparisons of categorical and continuous variables were done by chi-square and t-test as appropriate. 25(OH)D values were binned. For most ethnic groups, 25(OH)D values were grouped into bins of two values, e.g. 20-21 ng/ml. For black non-Hispanic and Hispanic zip codes only, 25(OH)D values were put in bins of 2 values from 20-29 ng/ml and into bins of 5 values after 30 ng/ml, e.g. 30-35 ng/ml, because of the low numbers of people with values over 30ng/ml. Vitamin D was adjusted for seasonality with a model based on a previous 25(OH)D study, using Quest Diagnostics results that fit the present study, according to the authors. Age was stratified into 2 groups, under 60 years old and 60 years old and above. Participants did not have specific ethnicities linked to them - their ethnicity in the study was based on their zip code and their likelihood of being a certain ethnicity. Therefore, people were categorised into the following groups "predominately black non-Hispanic", pre-dominantly Hispanic" and "predominantly white non-Hispanic". Race/ethnicity proportions were taken as reported by the zip code in the 2018 5-year American Community Services. Zip codes with estimated proportions of black non-Hispanic population over 50% are referred to as "pre-dominantly black non-Hispanic". The same pattern was followed for "pre-dominantly Hispanic" and "predominantly white non-Hispanic" zip codes. The correlation between 25(OH)D values and infection were fitted the best by the weighted second-order polynomial regression. Multivariable logistic regression was performed using a stepwise entry criterion of $p<0.05$, after excluding participants with missing values. Analyses were performed using SAS Studio 3.6 on SAS 9.4, and R v3.6.1.
Attrition/loss to follow-up	Participants were excluded for lack of zip code data or inconclusive SARS-CoV-2 results, as specified in the exclusion criteria. No difference between included and excluded participants on infection rates, age and gender. In the multivariable model, only participants with no missing data were included (n=188,028; 98%).
Source of funding	Quest Diagnostics provide salaries to authors JKN, BC, MHK and HWK, and consulting fees for MFH who did not have any addition role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.
Study limitations (author)	Testing for SARS-CoV-2 was based on selection factors, including presence and gravity of symptoms and exposure to infected individuals. High-risk groups, such as healthcare workers and first responders, are also more likely to be tested. Another limitation is that race/ethnicity estimates were based on aggregate U.S. Census proportions by zip code.

	There may be many other potentially confounding factors that were neither identified nor controlled for in this study. The multivariable model displayed poor overall fit and correlation statistics, given SARS-CoV-2 can infect anyone.
Study limitations (reviewer)	No baseline characteristics table and baseline characteristics poorly reported. Ethnicity was only partly reported – the 3 ethnicities mentioned do not make up the whole cohort. Concerning the estimated ethnicities, there could be higher positivity in hispanic/black populations in white areas and vice versa not related to vit D status. This estimation also masks whether some ethnicities are more susceptible to COVID-19 than others.

Study arms

Entire cohort (N = 191779)

Results were presented as entire cohort.

Characteristics

Study-level characteristics

	Study (N = 191779)
Age	
MedianIQR	54 (40.4 to 64.7)
Gender Female	
Sample Size	n = 130473 ; % = 68
Ethnicity	
Predominantly black non-Hispanic	
Sample Size	n = 9529 ; % = 5
Predominantly Hispanic	
Sample Size	n = 26242 ; % = 13.7
Predominantly white non-Hispanic	
Sample Size	n = 112281 ; % = 58.5
Comorbidities	

	Study (N = 191779)
Custom value	NA
BMI	
Custom value	NA
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
Timing of vitamin D measurements	
Custom value	NA
Shielding status	
Custom value	NA
Living in care homes	
Custom value	NA

Outcomes

Association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels

Odds ratios (ORs) are presented as risk of infection per ng/ml. OR = 1 is no difference in risk per ng/ml, lower ORs indicate a lower risk of infection at a higher 25(OH)D.

	Entire cohort vs Entire cohort
	N1 = 191779
25(OH)D level *Polarity: Lower values are better*	

	Entire cohort vs Entire cohort
	N1 = 191779
Unadjusted	
Odds ratio/95% CI	0.98 (0.98 to 0.98)
Adjusted Adjusted for vitamin D seasonality. Only included 188,028 participants without missing values.	
Odds ratio/95% CI	0.98 (0.98 to 0.99)
Predominantly black non-Hispanic All other zip codes apart from predominantly black/Hispanic were used as reference. *Polarity: Lower values are better*	
Unadjusted	
Odds ratio/95% CI	2.04 (1.93 to 2.17)
Adjusted Adjusted for vitamin D seasonality.	
Odds ratio/95% CI	2.03 (1.91 to 2.15)
Predominantly Hispanic All other zip codes apart from predominantly black/Hispanic were used as reference. *Polarity: Lower values are better*	
Unadjusted	
Odds ratio/95% CI	1.61 (1.54 to 1.67)
Adjusted Adjusted for vitamin D seasonality.	
Odds ratio/95% CI	1.95 (1.87 to 2.04)

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Baseline characteristics not adequately described and not clear where data has initially come from.)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Some loss to follow-up but only 2%. Loss to follow-up in this case is participants not included in modelling due to missing data. Loss is small and random.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Measurement of 25(OH)D conducted by one company.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Very few confounders measured, only season vitamin D was measured, age, gender and ethnicity.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Presentation of data is not adequate, fundamental baseline characteristics table is missing. The number of participants in the reported ethnic groups do not add up to the total number analysed in the unadjusted nor the adjusted models. Many people would have their ethnicity incorrectly classified due to the way the study used zip code as a proxy. The only confounder that the adjusted model adjusts for is the season vitamin D was measured. 25(OH)D concentrations are binned, losing information about the linear relationship between 25(OH)D and risk of infection.)*
Overall risk of bias and directness	Risk of Bias	High *(Data planning presentation poor and missing important details, very few confounders measured, only season vitamin D was measured, age, gender and ethnicity. Baseline characteristics not adequately described and not clear where data has initially come from.)*
	Directness	Indirectly applicable *(Vitamin status data was historical (preceding 12 months) where vitamin level may have changed before SAR-CoV-2 testing. Also, the outcome is SAR-CoV-2 positive, not COVID-19)*