D.2.1.3 Hastie 2020

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Bibliographic Reference	Hastie, Claire E; Mackay, Daniel F; Ho, Frederick; Celis-Morales, Carlos A; Katikireddi, Srinivasa Vittal; Niedzwiedz, Claire L; Jani, Bhautesh D; Welsh, Paul; Mair, Frances S; Gray, Stuart R; O'Donnell, Catherine A; Gill, Jason Mr; Sattar, Naveed; Pell, Jill P; Vitamin D concentrations and COVID-19 infection in UK Biobank.; Diabetes & metabolic syndrome; 2020; vol. 14 (no. 4); 561-565

Study details

Study design	Case-control study
Trial registration (if reported)	Not applicable.
Study start date	16-Mar-2020
Study end date	14-Apr-2020
COVID-19 prevalence at the time of the study	Higher prevalence (e.g. during peak of first wave)
Aim of the study	The study hypothesised that blood 25 hydroxyvitamin D (25(OH)D) would negatively associate with COVID-19 infection, which may explain the higher incidence of COVID-19 in ethnic minority participants. The study used the data collected by the UK Biobank study which recruited 502,624 participants between 2006 and 2010, which followed up people over time to identify causes of disease in middle and old age. It matched this data with COVID-19 tests taken by participants.
County/ Geographical location	England, Scotland and Wales.
Study setting	UK Biobank and Public Health England data.
Population description	UK Biobank recruited 502,624 participants aged between 37-73 years. Complete data was available for 348,598 participants. The population studied in this correlation study was a subset of this, 1474 individuals who had undergone COVID-19 tests (2724 tests total).

Inclusion criteria	- Complete data in UK Biobank study - Taken a COVID-19 test
Exclusion criteria	None reported.
Vitamin D status measurements	Blood samples were taken when participants were first recruited into the study between 2006-2010. Biochemical assays were conducted at a central laboratory alongside other tests and assays. No detail on which tests was used to quantify 25 hydroxyvitamin D or other vitamin D concentration in the blood was reported. Minimum detectable value was imputed at 10 nmol/L if vitamin D concentration was too low to detect, and with the maximum detectable value of 375 nmol/L if the concentration was too high for detection.
Methods used to confirm COVID-19 infection	Test results data provided by Public Health England, including specimen date, origin (if the person was an inpatient or not), and if the test was positive or negative for COVID-19. A positive result was defined as at least 1 positive COVID-19 test, data available for 16th March 2020 and 14th April 2020.
Intervention	Not applicable.
Comparator (where applicable)	Not applicable.
Methods for population selection/allocation	Not applicable
Methods for case-matching with control	Not reported. Adjustment conducted in analyses.
Methods of data analysis	Three models were conducted: 1) a correlation between 25(OH)D and confirmed COVID-19 infection adjusting for covariates; 2) a correlation between ethnicity and COVID-19 infection adjusting for 25(OH)D; 3) a correlation looking for an interaction between ethnicity*25(OH)D and COVID-19 infection. 1) The association between 25(OH)D, as a continuous variable, and COVID-19 infection was explored with a univariable logistic regression analysis. The model was adjusted for sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI quintile, ethnicity, age at assessment, diabetes, systolic blood pressure, diastolic blood pressure, and long-standing illness, disability or infirmity. Sensitivity analyses were conducted with participants were categorised as vitamin D deficient (<25 nmol/L) or not deficient; and another conducted with participants categorised as vitamin D insufficient (<50 nmol/L) or sufficient. 2) The association between ethnicity and COVID-19 infection was explored with univariable logistic regression analysis. The model was first adjusted for 25(OH)D and then sex, month of assessment, Townsend deprivation quintile, household income, self-reported health

	rating, smoking status, BMI quintile, age at assessment, diabetes, systolic blood pressure, diastolic blood pressure, and long-standing illness, disability or infirmity. 3) The possible interaction between 25(OH)D and ethnicity and its association with COVID-19 infection was explored with multivariable analysis. All analyses were conducted on Stata v14.
Attrition/loss to follow-up	Not applicable.
Source of funding	CEH is funded by Health Data Research-UK (Ref. Edin-1). SVK acknowledges funding from a NRS Senior Clinical Fellowship (SCAF/15/02), the Medical Research Council (MC_UU_12017/13) and the Scottish Government Chief Scientist Office (SPHSU13). CLN is supported by the Medical Research Council (MR/R024774/1). NS receives funding from the British Heart Foundation Research Excellence Award (RE/18/6/34217).
Study limitations (Author)	Not representative of the general population: participants live in less socioeconomically deprived areas, are predominantly white, and have fewer self-reported health conditions. Baseline measures for 25(OH)D were collected over a decade before the study was conducted and it would have been preferable to have more up-to-date measurements or measurements taken immediately before development of COVID-19.
Study limitations (Reviewer)	Regarding the old 25(OH)D measurements used in the study, they defend their data by saying that concentrations vary more by season than year and generally track over time. However, this neglects other causes of vitamin D change as it also tracks health state, or covariates to health state. All other variables measured by the UK Biobank study would have been collected at the same time. Variables that can change, such as blood pressure and smoking status, may have changed over the decade since the study was conducted. There is no reason to assume that vitamin D levels from a decade ago would correlate with levels currently. The changes may be net neutral but there may be certain groups whose smoking status, for example, has changed more towards smoke-free or smoking more, but it would not be possible to deduce who this would be. This may mean that some variables that are used for adjustment do not provide accurate data for people's current state leading to misleading results. The results are reported as "COVID" and "no COVID". The COVID group rightly contains only people who have had a confirmed COVID infection. However, the "no COVID" group contains everyone else in the UK Biobank database who has not had a confirmed COVID diagnosis, but also people who have not been tested. Considering the projections that showed many more people were infected at this

	time than had been tested, including people who were symptomatic and isolating and the people who took tests may be more ill than people who did not. Therefore, this may not accurately represent the 25(OH)D levels of people with and without COVID infection. Vitamin D assay limits of 10nmol/L and 375nmol/L under- or overestimate some values that are lower or higher than thee concentrations. Many people have serum 25(OH)D <10µg/ml and therefore a linear correlation would also overestimate how low these values are, not accurately representing the data.

Study arms

No COVID (N = 348149) Number of people in the UK Biobank register who either received a negative COVID test or who were not tested.
COVID (N = 449) Number of people in the UK Biobank register who received a positive COVID test.

Characteristics

Study-level characteristics

	Study (N = 348598)
Vitamin D by ethnicity	
White	
MedianIQR	48.1 (33.8 to 63.4)
Black	
MedianIQR	29.9 (21 to 41.3)
South Asian	
MedianIQR	22.1 (14.5 to 33.7)
Other	
MedianIQR	33.7 (23.3 to 47.4)

Arm-level characteristics

	No COVID (N = 348149)	COVID (N = 449)
Age		
MedianIQR	57 (49 to 63)	58 (49 to 64)
Gender %female		
Sample Size	n = 179758 ; % = 51.63	n = 184 ; % = 40.98
Ethnicity		
White		
Sample Size	n = 331464 ; % = 95.21	n = 385 ; % = 85.75
Black		
Sample Size	n = 5022 ; % = 1.44	n = 32 ; % = 7.13
South Asian		
Sample Size	n = 5917 ; % = 1.7	n = 19 ; % = 4.23
Other		
Sample Size	n = 5746 ; % = 1.65	n = 13 ; % = 2.9
Comorbidities		
Diabetes		
Sample Size	n = 18825 ; % = 5.41	n = 49 ; % = 10.91
BMI		
Underweight		
Sample Size	n = 1759 ; % = 0.51	n = 2 ; % = 0.45
Normal weight		
Sample Size	n = 115410 ; % = 33.15	n = 95 ; % = 21.16
Overweight		
Sample Size	n = 148210 ; % = 42.57	n = 194 ; % = 43.21
Obese		
Sample Size	n = 82770 ; % = 23.77	n = 158 ; % = 35.19
Use of immune suppressing treatments		

	No COVID (N = 348149)	COVID (N = 449)
Socioeconomic status Townsend deprivation quintile - higher is more deprived		
One		
Sample Size	n = 70669 ; % = 10.37	n = 51 ; % = 11.36
Two		
Sample Size	n = 70726 ; % = 20.31	n = 76 ; % = 16.93
Three		
Sample Size	n = 70644 ; % = 20.29	n = 64 ; % = 14.25
Four		
Sample Size	n = 70270 ; % = 20.18	n = 105 ; % = 23.39
Five		
Sample Size	n = 65840 ; % = 18.91	n = 143 ; % = 31.85
Previous history of COVID-19		
Custom value	NA	NA
Other supplement use		
Custom value	NA	NA
Timing of vitamin D measurements		
Custom value	NA	NA
Shielding status		
Custom value	NA	NA
Living in care homes		
Custom value	NA	NA
Current smoker		
Sample Size	n = 36112 ; % = 10.37	n = 51 ; % = 11.36
Self-reported health rating		
Excellent		
Sample Size	n = 60508 ; % = 17.38	n = 45 ; % = 10.02

	No COVID (N = 348149)	COVID (N = 449)
Good		
Sample Size	n = 203640 ; % = 58.49	n = 227 ; % = 50.56
Fair		
Sample Size	n = 69676 ; % = 20.01	n = 133 ; % = 29.62
Poor		
Sample Size	n = 14325 ; % = 4.11	n = 44 ; % = 9.8
Long standing illness, disability or infirmity		
Sample Size	n = 110679 ; % = 31.79	n = 204 ; % = 45.43
Systolic blood pressure mmHg		
MedianIQR	138 (125 to 151)	138 (127 to 153)
Diastolic blood pressure mmHg		
MedianIQR	82 (75 to 89)	83 (76 to 90)
Vitamin D nmol/L		
MedianIQR	47.2 (32.7 to 62.7)	43.8 (28.7 to 61.6)

Outcomes

Association between vitamin D and confirmed COVID-19 infection

Multivariable results adjusted for ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and long-standing illness, disability or infirmity.

	COVID vs No COVID
	N1 = 449, N2 = 348149
Vitamin D *Polarity: Lower values are better*	
Univariate	

	COVID vs No COVID
	N1 = 449, N2 = 348149
Odds ratio/95% CI	0.99 (0.99 to 1)
Multivariable	
Odds ratio/95% CI	1 (1 to 1.01)
Vitamin D deficient (<25 nmol/L) *Polarity: Lower values are better*	
Univariable	
Odds ratio/95% CI	1.37 (1.07 to 1.76)
Multivariable	
Odds ratio/95% CI	0.92 (0.71 to 1.21)
Vitamin D insufficient (<50 nmol/L) *Polarity: Lower values are better*	
Univariable	
Odds ratio/95% CI	1.19 (0.99 to 1.44)
Multivariable	
Odds ratio/95% CI	0.88 (0.72 to 1.08)

Association between ethnicity and confirmed COVID-19 infection.

Multivariable model in this table adjusted for sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and long-standing illness, disability or infirmity.

	COVID vs No COVID
	N1 = 449, N2 = 348149
Univariable *Polarity: Lower values are better*	
White (referent)	
Odds ratio/95% CI	1 (1 to 1)
Black	
Odds ratio/95% CI	5.49 (3.82 to 7.88)

	COVID vs No COVID
	N1 = 449, N2 = 348149
South Asian	
Odds ratio/95% CI	2.76 (1.74 to 4.39)
Other	
Odds ratio/95% CI	1.95 (1.12 to 3.39)
Adjusted for vitamin D concentration *Polarity: Lower values are better*	
White (referent)	
Odds ratio/95% CI	1 (1 to 1)
Black	
Odds ratio/95% CI	5.32 (3.68 to 7.7)
South Asian	
Odds ratio/95% CI	2.65 (1.65 to 4.25)
Other	
Odds ratio/95% CI	1.9 (1.09 to 3.32)
Multivariable *Polarity: Lower values are better*	
White (referent)	
Odds ratio/95% CI	1 (1 to 1)
Black	
Odds ratio/95% CI	4.3 (2.92 to 6.31)
South Asian	
Odds ratio/95% CI	2.42 (1.5 to 3.93)
Other	
Odds ratio/95% CI	1.87 (1.07 to 3.28)

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(People in the cohort were over-represented in factors of better health, white ethnicity and less deprived compared with the general population. Outreach by UK Biobank may not be sufficient to gather data for all eligible participants.)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Difficult to assess the affect and potential bias of not including people that did not have complete data and therefore were not included in this study.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Timing of vitamin D measurement allows significant risk of bias.)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Due to lack of COVID-19 testing for all participants.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Analyses adjust for confounding but the accuracy of confounders is doubtful since they were measured over a decade before the study took place.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(All people, including people who had not taken a COVID-19 test were included. There may be selection bias between people who were tested and people who were not. To account for this potential bias, subgroup analyses could have been conducted to address this).*
Overall risk of bias and directness	Risk of Bias	High *(Based on age of vitamin D measurements and excluding participants who do not have complete outcome data.)*
	Directness	Partially applicable *(Vitamin D status taken from historical measurements, 2006-2010)*