D.2.1.11 Raisi-Estabragh 2020

Raisi-Estabragh, 2020

Bibliographic Reference	Raisi-Estabragh, Zahra; McCracken, Celeste; Bethell, Mae S; Cooper, Jackie; Cooper, Cyrus; Caulfield, Mark J; Munroe, Patricia B; Harvey, Nicholas C; Petersen, Steffen E; Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank.; Journal of public health (Oxford, England); 2020; vol. 42 (no. 3); 451-460

Study details

Study design	Case-control study
Trial registration (if reported)	Not reported.
Study start date	16-Mar-2020
Study end date	18-May-2020
COVID-19 prevalence at the time of the study	Higher prevalence (e.g. during peak of first wave)
Aim of the study	By using the UK Biobank cohort, the study aimed to test if the different rates of COVID-19 across sex and ethnicities could be explained by cardiometabolic, socioeconomic, lifestyle and behavioural factors. Vitamin D was also tested as part of these factors.
County/ Geographical location	UK
Study setting	Community
Population description	People were recruited into the UK Biobank study between 2006-2010. It aims to capture the health of a broad range of the population to track outcomes of people and assess if there are common factors causing disease of middle/old age. People were recruited by post, everyone living within 10 miles of the 22 UK Biobank assessment centres were invited to participate.
Inclusion criteria	Aged 40-69 years old, as the UKBiobank protocol specifies. Taken a COVID-19 test.
Exclusion criteria	Unable to provide consent.
Vitamin D status measurements	Measurements were taken during the 2006-2010 recruitment period. Vitamin D was measured at a central laboratory with a biochemical test, [Clinical Laboratory Improvement Amendments (CLIA) analysis on a DiaSorin Ltd. LIASON XL]. It limited results to between 10 nmol/L and 375 nmol/L. Any results above or below those thresholds were undetectable and were labelled accordingly as either 10 or 375 nmol/L.
Methods used to confirm COVID-19 infection	Data matched with Public Health England COVID-19 test results released to UK Biobank researchers.
Intervention	Not applicable.

Comparator (where applicable)	Not applicable.
Methods for population selection/allocation	People were included in this current study if they had taken a COVID-19 test. Both people with positive and negative test results were included to allow associations to be drawn. The study states that "As UK testing during this period was almost entirely restricted to hospitalized patients, researchers have been advised that COVID-19 positive status can be taken as surrogate for severe disease."
Methods for case-matching with control	Not applicable.
Methods of data analysis	Participants were grouped into COVID-19 positive and negative cohorts. 2 models relevant to the protocol were conducted in the analyses: 1) individual correlations between each of the variables and COVID infection; 2) correlations between multiple variables and COVID infection. 1) Univariate logistic regression was performed for every variable individually to assess the association between them and SARS-CoV-2 infection. Models were run for the whole cohort and then separately for men and women, and for white and non-white participants. 2) Multivariable logistic regression models were run to associated groups of variables with COVID-19 infection, one of which included vitamin D levels. The variables included in this model were: sex, age, ethnicity and vitamin D. Variables were added to the model simultaneously. Adjustments were made based on the season the vitamin D measurement was made and ethnicity. Therefore, seasonal adjustment was conducted separately for white and BAME populations and an intercept added to the adjusted variables to maintain the difference between the two groups. All analyses were conducted on R v3.6.2 and R Studio v1.2.5019
Attrition/loss to follow-up	Not applicable
Source of funding	Z.R.E. is supported by a British Heart Foundation Clinical Research Training Fellowship (FS/17/81/33318). S.E.P., P.B.M. and M.J.C. acknowledge support from the Barts Biomedical Research Centre funded by the National Institute for Health Research (NIHR). N.C.H. and C.C. acknowledge support from the UK Medical Research Council, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton and NIHR Oxford Biomedical Research Centre, University of Oxford.

Study limitations (Author)	Not possible to evaluate causal relationships. Possible changes to vitamin D concentrations between baseline measurement taken when participants were recruited over a decade before this current analysis was performed. Limited age range. Wider social, economic and behavioural factors that likely to impact on the infection rate of COVID-19 than could be studied in UK Biobank. People's occupations could be a factor in transmission. Aggregating all BAME populations overlooks differences between ethnicities.
Study limitations (Reviewer)	Other variables, apart from vitamin D status, could have changed since the participants were first recruited. Particularly if they have not updated their information, or not had to access health services, when it is most likely details are updated. This could bias results in unpredictable ways resulting in misleading conclusions. For limitations concerning using UK Biobank data, see limitations in the evidence table for Hastie 2020.

Study arms

COVID positive (N = 1326) People who tested positive with COVID-19
COVID negative (N = 3184) People who tested negative with COVID-19

Characteristics

Arm-level characteristics

	COVID positive (N = 1326)	COVID negative (N = 3184)
Age		
Standardised Mean/SD	68.11 (9.23)	68.91 (8.72)
Gender Male		
Sample Size	n = 696 ; % = 52.5	n = 1505 ; % = 47.3
Ethnicity		
White		
Sample Size	n = 1141 ; % = 86	n = 2927 ; % = 91.9
Black		
Sample Size	n = 76 ; % = 5.7	n = 91 ; % = 2.9
Chinese		
Sample Size	n = 6 ; % = 0.5	n = 3 ; % = 0.1
Mixed		
Sample Size	n = 9 ; % = 0.7	n = 24 ; % = 0.8
Other Ethnicity was missing for n = 11 test positive and n = 16 test negative participants, so were included in 'other'		
Sample Size	n = 34 ; % = 2.6	n = 61 ; % = 1.9
Comorbidities		
Diabetes		
Sample Size	n = 217 ; % = 16.4	n = 449 ; % = 14.1
Hypertension		
Sample Size	n = 624 ; % = 47.1	n = 1457 ; % = 45.8
High cholesterol		
Sample Size	n = 437 ; % = 33	n = 1034 ; % = 32.5
Prior MI		
Sample Size	n = 96 ; % = 7.2	n = 242 ; % = 7.6
BMI *(kg/m²)* Please note IQR is reported as +/- and not as a range.		

	COVID positive (N = 1326)	COVID negative (N = 3184)
MedianIQR	28.04 (21.57 to 34.51)	27.41 (21.04 to 33.78)
Use of immune suppressing treatments		
Custom value	NA	NA
Socioeconomic status		
MedianIQR	-0.91 (4.43 to -6.25)	-1.55 (-6.55 to 3.45)
Previous history of COVID-19		
Custom value	NA	NA
Other supplement use		
Custom value	NA	NA
Timing of vitamin D measurements No individual data available		
Custom value	NA	NA
Shielding status		
Custom value	NA	NA
Living in care homes		
Custom value	NA	NA
Smoking Smokers		
Sample Size	n = 683 ; % = 51.1	n = 1653 ; % = 51.9

Outcomes

Univariate logistic regression models exposures associations with COVID-19 status in whole cohort, men, and women within the tested sample

Results presented below show how likely people in the cohort were of testing positive for COVID-19 based on one characteristic at a time. An odds ratio and 95% confidence interval higher than 1 means the variable is associated with higher COVID-19 infection and vice versa.

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Sex (male)	

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Polarity: Lower values are better	
Odds ratio/95% CI	1.23 (1.08 to 1.4)
Age *Polarity: Lower values are better*	
Odds ratio/95% CI	0.99 (0.98 to 1)
Men	
Odds ratio/95% CI	0.99 (0.98 to 1)
Women	
Odds ratio/95% CI	0.98 (0.97 to 0.99)
Non-white ethnicity *Polarity: Lower values are better*	
Odds ratio/95% CI	1.85 (1.51 to 2.28)
Men	
Odds ratio/95% CI	2.09 (1.55 to 2.83)
Women	
Odds ratio/95% CI	1.69 (1.27 to 2.25)
Townsend deprivation score *Polarity: Lower values are better*	
Odds ratio/95% CI	1.04 (1.02 to 1.06)
Men	
Odds ratio/95% CI	1.04 (1.02 to 1.07)
Women	
Odds ratio/95% CI	1.05 (1.02 to 1.07)
Household size *Polarity: Lower values are better*	
Odds ratio/95% CI	1.12 (1.06 to 1.17)
Men	
Odds ratio/95% CI	1.11 (1.03 to 1.2)

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Women	
Odds ratio/95% CI	1.12 (1.05 to 1.21)
Generations in household *Polarity: Lower values are better*	
Odds ratio/95% CI	1.26 (1.11 to 1.43)
Men	
Odds ratio/95% CI	1.21 (1.01 to 1.45)
Women	
Odds ratio/95% CI	1.35 (1.14 to 1.61)
Family/friends visits *Polarity: Lower values are better*	
Odds ratio/95% CI	0.84 (0.72 to 0.98)
Men	
Odds ratio/95% CI	0.85 (0.7 to 1.04)
Women	
Odds ratio/95% CI	0.87 (0.69 to 1.11)
Socialisation habits *Polarity: Lower values are better*	
Odds ratio/95% CI	1.04 (0.91 to 1.19)
Men	
Odds ratio/95% CI	1.14 (0.94 to 1.39)
Women	
Odds ratio/95% CI	0.94 (0.77 to 1.14)
Diabetes *Polarity: Lower values are better*	
Odds ratio/95% CI	1.19 (1 to 1.42)
Men	
Odds ratio/95% CI	1.18 (0.94 to 1.49)

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Women	
Odds ratio/95% CI	1.12 (0.84 to 1.49)
Hypertension *Polarity: Lower values are better*	
Odds ratio/95% CI	1.05 (0.93 to 1.2)
Men	
Odds ratio/95% CI	0.99 (0.83 to 1.19)
Women	
Odds ratio/95% CI	1.05 (0.87 to 1.26)
BMI *(kg/m²)* *Polarity: Lower values are better*	
Odds ratio/95% CI	1.02 (1.01 to 1.04)
Men	
Odds ratio/95% CI	1.03 (1.01 to 1.05)
Women	
Odds ratio/95% CI	1.02 (1 to 1.03)
Smoking Smoker, current or previous *Polarity: Lower values are better*	
Odds ratio/95% CI	0.98 (0.87 to 1.12)
Men	
Odds ratio/95% CI	1.07 (0.89 to 1.29)
Women	
Odds ratio/95% CI	0.84 (0.7 to 1.01)
Vitamin D *(nmol/L)* *Polarity: Lower values are better*	
Odds ratio/95% CI	1 (0.99 to 1)
Men	
Odds ratio/95% CI	1 (0.99 to 1)

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Women	
Odds ratio/95% CI	1 (0.99 to 1)

Multivariable logistic regression model testing the role of vitamin D in determining risk of COVID-19

Variables added to the model were sex, age, ethnicity and vitamin D. An odds ratio and 95% confidence interval higher than 1 indicates that the variable is associated with a positive COVID-19 test when the other variables are adjusted.

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Male sex *Polarity: Lower values are better*	
Odds ratio/95% CI	1.31 (1.14 to 1.5)
Age *Polarity: Lower values are better*	
Odds ratio/95% CI	0.99 (0.98 to 1)
Men	
Odds ratio/95% CI	1 (0.99 to 1.01)
Women	
Odds ratio/95% CI	0.99 (0.97 to 1)
BAME ethnicity *Polarity: Lower values are better*	
Odds ratio/95% CI	1.77 (1.41 to 2.22)
Men	
Odds ratio/95% CI	2.02 (1.45 to 2.82)
Women	
Odds ratio/95% CI	1.6 (1.16 to 2.18)
Vitamin D *Polarity: Lower values are better*	
Odds ratio/95% CI	1 (1 to 1)

	COVID positive vs COVID negative
	N1 = 1326, N2 = 3184
Men	
Odds ratio/95% CI	1 (1 to 1.01)
Women	
Odds ratio/95% CI	1 (1 to 1.01)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(From the initial UK Biobank sampling.)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Key variable, ethnicity was missing for n = 11 test positive and n = 16 test negative participants, these participants are included as part of 'other ethnicity' in the baseline demographics table but were excluded from subsequent modelling))*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Length of time between measuring vitamin D and when it was used to associate with COVID-19 infection.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Low risk of bias due to small numbers affected.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High *(Bias in measurement of prognostic factor, vitamin D, could significantly bias results.)*
	Directness	Partially applicable *(vitamin D status and demographic data are historical)*