D.2.1.9 Merzon 2020

Merzon, 2020

Bibliographic Reference	Merzon, Eugene; Tworowski, Dmitry; Gorohovski, Alessandro; Vinker, Shlomo; Golan Cohen, Avivit; Green, Ilan; Frenkel-Morgenstern, Milana; Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study.; The FEBS journal; 2020

Study details

Study design	Case-control study
Trial registration (if reported)	Not reported.
Study start date	01-Feb-2020
Study end date	30-Apr-2020

Aim of the study	To determine associations between low plasma 25(OH)D and the risk of COVID-19 infection and hospitalization using population-based data.
County/ Geographical location	Leumit Health Services, Israel.
Study setting	Community
Population description	14,000 people of the Leumit Health Services who were tested for COVID-19 in the study period were eligible.
Inclusion criteria	At least one previous blood test for plasma vitamin D (25(OH)D).
Exclusion criteria	Not reported.
Vitamin D status measurements	Blood was transported on ice and processed within 4 hours of collection using DiaSorin Chemiluminescence assay. 'Suboptimal' or 'low' plasma 25(OH)D level was defined as plasma 25-hydroxyvitamin D, or 25(OH)D, concentration below the level of 30 ng/ml.
Methods used to confirm COVID-19 infection	Referrals for viral tests were according to Israeli Ministry of Health guidelines by physicians based on symptoms. Tests were run using the AllplexTM 2019-nCoV Assay (Seegene Inc., Seoul, Korea).
Intervention	Not applicable
Comparator (where applicable)	Not applicable
Methods for case-matching with control	Not applicable
Methods of data analysis	Descriptive statistics compared demographic characteristics between COVID-19 positive and COVID-19 negative participants. Continuous variables were reported as means (95% CI) and compared using student's t-test for normally distributed data. Fisher's exact or chi-square test was used for categorical variables, displayed as counts and percentages. Univariate analyses were conducted to assess the association between baseline characteristics and COVID-19 infection and hospitalisation. Multivariable analyses assessed the association between 25(OH)D levels and COVID-19 infection and hospitalisation, adjusting for demographic variables, and psychiatric and somatic disorders. These were reported as odds ratios (ORs) and 95% CIs.

	Differences were considered significant at p=0.05.
	All analyses were conducted using Stata 12.
Attrition/loss to follow-up	No attrition reported.
Source of funding	The study was funded by COVID-19 Data Sciences Institute (DSI) grant (for MFM, #247017). All authors have indicated they have no financial relationships relevant to this manuscript to disclose.
Study limitations (Author)	Retrospective database design. Vitamin D levels were tested according to the presentation of symptoms, and not according to population-wide testing
Study limitations (reviewer)	Historic vitamin D measurements are unlikely to reflect actual status at time of COVID-19 test.

Study arms

COVID-19 positive (N = 782)
COVID-19 negative (N = 7025)

Characteristics

Arm-level characteristics

	COVID-19 positive (N = 782)	COVID-19 negative (N = 7025)
Age		
Mean/95% CI	35.58 (34.29 to 36.67)	47.35 (46.87 to 47.85)
Gender Male		
Sample Size	n = 385 ; % = 49.23	n = 2849 ; % = 40.56
Ethnicity		
Custom value	NA	NA
Comorbidities		

	COVID-19 positive (N = 782)	COVID-19 negative (N = 7025)
Low vitamin D level Plasma 25(OH)D <30 ng/ml		
Sample Size	n = 703 ; % = 89.9	n = 5965 ; % = 84.91
Smoking		
Sample Size	n = 127 ; % = 16.24	n = 1136 ; % = 16.17
Depression/Anxiety		
Sample Size	n = 73 ; % = 9.34	n = 817 ; % = 11.63
Schizophrenia		
Sample Size	n = 15 ; % = 1.92	n = 141 ; % = 2.01
Dementia		
Sample Size	n = 27 ; % = 3.45	n = 427 ; % = 6.08
Diabetes		
Sample Size	n = 154 ; % = 19.69	n = 1578 ; % = 22.46
Hypertension		
Sample Size	n = 174 ; % = 22.25	n = 1962 ; % = 27.93
Cardiovascular disease		
Sample Size	n = 78 ; % = 9.97	n = 1172 ; % = 16.68
Chronic lung disorders		
Sample Size	n = 66 ; % = 8.44	n = 935 ; % = 13.31
Obesity		
Sample Size	n = 235 ; % = 30.05	n = 1900 ; % = 27.05
BMI		
Mean/95% CI	27.32 (26.88 to 27.77)	27.36 (27.22 to 27.52)
Use of immune suppressing treatments		
Custom value	NA	NA
Socioeconomic status		
Low-medium		
Sample Size	n = 601 ; % = 83.7	n = 4418 ; % = 67.73

	COVID-19 positive (N = 782)	COVID-19 negative (N = 7025)
High-medium		
Sample Size	n = 117 ; % = 16.3	n = 2105 ; % = 32.27
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
Mean vitamin D *(ng/mL)*		
Mean/95% CI	19 (18.4 to 19.6)	20.6 (20.3 to 20.8)
Plasma 25(OH)D level categories		
Sufficiency >30ng/mL Odds ratio is a crude comparison between the positive and negative cohorts		
Sample Size Odds ratio	n = 79 ; % = 10.1 1	n = 106 ; % = 15.1
Insufficiency 29-20 ng/mL Odds ratio is a crude comparison between the positive and negative cohorts		
Sample Size Odds ratio/95% CI	n = 598 ; % = 76.5 1.59 (1.24 to 2.02)	n = 5050 ; % = 71.8
Deficiency <20 ng/mL Odds ratio is a crude comparison between the positive and negative cohorts		
Sample Size Odds ratio/95% CI	n = 105 ; % = 13.4 1.58 (1.13 to 2.09)	n = 915 ; % = 13.1

Outcomes

Multivariable logistic regression analysis associating low vitamin D level with COVID-19 outcomes

Controlling for multiple conditions, OR with 95% confidence interval (CI). Results are presented unadjusted and adjusted.

	COVID-19 positive vs COVID-19 negative
	N1 = 782, N2 = 7025
Infection with COVID-19 *Polarity: Lower values are better*	
Unadjusted	
Odds ratio/95% CI	1.58 (1.24 to 2.01)
Adjusted	
Odds ratio/95% CI	1.5 (1.13 to 1.98)
Hospitalisation *Polarity: Lower values are better*	
Unadjusted	
Odds ratio/95% CI	2.09 (1.01 to 4.31)
Adjusted	
Odds ratio/95% CI	1.95 (0.99 to 4.78)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Cohort of people with potentially biased vitamin D levels and not reporting ethnicity.)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Diagnosis done by verified test.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Ethnicity, immunosuppressants and vitamin D supplements not listed.)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Analyses presented adequately, no suspicion of bias)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Ethnicity, immunosuppressants and vitamin D supplements not listed. Cohort of people with potentially biased vitamin D levelsz.)*
	Directness	Partially applicable *(Historic vitamin D measurements used)*