D.2.1.1 Annweiler 2020

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Bibliographic Reference	Annweiler, Cedric; Hanotte, Berangere; de l'Eprevier, Claire Grandin; Sabatier, Jean-Marc; Lafaie, Ludovic; Celarier, Thomas; Vitamin D and survival in COVID-19 patients: A quasi-experimental study.; The Journal of steroid biochemistry and molecular biology; 2020; 105771

Study details

Trial registration number and/or trial name	Not reported.
Study type	Non-randomised controlled trial Quasi-experimental intervention study
Study location	Rhône, France
Study setting	Nursing home
Study dates	March - 15th May 2020

Sources of funding	No sources of funding declared.
Inclusion criteria	Clinically obvious or diagnosed COVID-19 with RT-PCR in March-April 2020 Data available on the treatments received, including vitamin D supplementation, since the diagnosis of COVID-19 and at least during the previous month. Data available on the vital status and COVID-19 evolution as of May 15, 2020. No objection from the resident and/or relatives to the use of anonymized clinical and biological data for research purposes.
Exclusion criteria	Not reported
Intervention(s)	Bolus vitamin D_3 supplementation during or just before COVID-19. All residents in the nursing-home receive chronic vitamin D supplementation with regular maintenance boluses (single oral dose of 80,000 IU vitamin D3 every 2–3 months), without systematically performing serum control test as recommended in French nursing-homes due to the very high prevalence of hypovitaminosis D reaching 90–100 % in this population. The "Intervention group" was defined as all COVID-19 residents who received an oral bolus of 80,000 IU vitamin D_3 either in the week following the suspicion or diagnosis of COVID-19, or during the previous month. None received D2 or intramuscular supplements. All medications were dispensed and supervised by a nurse.
Comparator	The "Comparator group" corresponded to all other COVID-19 residents who did not receive any recent vitamin D supplementation. None received D_2 or intramuscular supplements. All medications were dispensed and supervised by a nurse.
Outcome measures	COVID-19 mortality Measured during follow-up period. Follow-up started from the day of COVID-19 diagnosis for each patient, and continued until May 15, 2020, or until death if applicable. OSCI score for COVID-19 in acute phase The secondary outcome was the score on the World Health Organisation's Ordinal Scale for Clinical Improvement (OSCI) for COVID-19. The score was calculated by the geriatrician of the nursing-home during the most severe acute phase of COVID-19 for each patient. The OSCI distinguishes between several levels of COVID-19 clinical severity according to the outcomes and dedicated treatments required, with a score ranging from 0 (benign) to 8 (death). A score of 4 corresponds to the introduction of oxygen (nasal oxygen catheter or oral nasal mask), and a score of 6 to intubation and invasive ventilation.
Number of participants	N=66 Intervention group, n=57 Comparator, n=9

Duration of follow-up	From initial diagnosis in March/April to death or 15th May.
Loss to follow-up	None reported.
Methods of analysis	Participants' characteristics were summarized using means and standard deviations (SD) or frequencies and percentages, as appropriate. The study reported that the number of observations was higher than 40, comparisons were not affected by the shape of the error distribution and no transform was applied. Comparisons between participants separated into Intervention and Comparator groups were performed using Mann-Whitney U test or the Chi-square test or Fisher test, as appropriate, and then according to mortality. 3 models were conducted: 1) associations between predictor variables, such as vitamin D_3 supplements, and the likelihood of COVID-19 mortality at a specific time; 2) comparing time to death between intervention and comparator groups; 3) associations between bolus vitamin D_3 supplements and OSCI score, taking into account factors that may affect the result. 1) A full-adjusted Cox regression was used to examine the associations of mortality (dependent variable) with bolus vitamin D_3 supplements and covariables (independent variables). The model produces a survival function that provides the probability of death at a given time for the characteristics supplied for the independent variables. 2) The elapsed time to death was studied by survival curves computed according to Kaplan-Meier method and compared by log-rank test. 3) Univariate and multiple linear regressions were used to examine the association of bolus vitamin D_3 supplementation (independent variable) with OSCI score (dependent variable), while adjusting for potential confounders. P-values<0.05 were considered significant. All statistics were performed using SPSS (v23.0, IBM Corporation, Chicago, IL) and SAS® version 9.4 software (Sas Institute Inc).
Study limitations (authors)	The study cohort was restricted to a limited number of nursing-home residents who may be unrepresentative of all older adults. The study aimed to control for important characteristics that could modify the association, residual potential confounders might still be present such as the serum concentration of 25(OH)D at baseline. As this analysis was not planned, no concerted efforts were made to systematically measure the serum 25(OH)D concentration before and after supplementation. The quasi-experimental design is less robust than an RCT. Participants in the comparator group did not receive vitamin D placebo, and there was no randomization. However, the authors noted that the characteristics of the two groups did not differ at baseline, which, they suggest, links the survival difference to vitamin D3 supplementation.

Study limitations (reviewer)	Even though there were no differences in measured baseline characteristics between groups, there may be other unmeasured differences that could bias the result. It is unknown how much contact the participants had with the nurse who dispensed the medication. The nurse may have given other health protective advice that provided a short-term benefit of people who had more recent supplementation over people who did not. The timing of vitamin D supplementation relative to the timing of diagnosis meant that this study looked at both prevention and intervention, which reduces clarity on the mechanism in which vitamin D works. It is not possible to discern whether people who had supplementation before COVID-19 diagnosis experienced better outcomes and people who had supplementation after. Subgroup or sensitivity analyses would not have helped here either because of the small sample size.

Study arms

Intervention group (N = 57) Participants who received bolus vitamin D_3 supplement within a month before or up to a week after COVID-19 diagnosis or suspicion of diagnosis.
Comparator (N = 9) Participants who did not receive bolus vitamin D_3 supplement within a month before or up to a week after COVID-19 diagnosis or suspicion of diagnosis.

Characteristics

Study-level characteristics

	Study (N = 66)
Age	
Mean/SD	87.7 (9)
Intervention	

	Study (N = 66)
Mean/SD	87.7 (9.3)
Comparator	
Mean/SD	87.4 (7.2)
% Female	
Sample Size	n = 51 ; % = 77.3
Intervention	
Sample Size	n = 45 ; % = 78.9
Comparator	
Sample Size	n = 6 ; % = 66.7
Ethnicity	
Custom value	NA
Comorbidities	
Custom value	NA
BMI	
Custom value	NA
Use of immune suppressing treatments	
Custom value	NA

	Study (N = 66)
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	
Sample Size	n = 66 ; % = 100
Vitamin D status	
Custom value	na, assumed that most, if not all, of the residents were vitamin D deficient but were supplemented.
Use of corticosteroids	
Sample Size	n = 4 ; % = 6.1
Intervention	

	Study (N = 66)
Sample Size	n = 3 ; % = 5.3
Comparator	
Sample Size	n = 1 ; % = 11.1
Use of hydrocychloroquine	
Sample Size	n = 2 ; % = 3
Intervention	
Sample Size	n = 2 ; % = 3.5
Comparator	
Sample Size	n = 0 ; % = 0
Use of dedicated antibiotics	
Sample Size	n = 34 ; % = 51.5
Intervention	
Sample Size	n = 21 ; % = 54.4
Comparator	
Sample Size	n = 3 ; % = 3.33
Hospitalisation for COVID-19	
Sample Size	n = 4 ; % = 6.1

	Study (N = 66)
Intervention	
Sample Size	n = 4 ; % = 7
Comparator	
Sample Size	n = 0 ; % = 0

Outcomes

Comparison of study outcomes according to the study arm.

Includes mortality and OSCI scores for both arms.

	Intervention group	Comparator
	N = 57	N = 9
Mortality *Polarity: Lower values are better*		
Sample Size	n = 10 ; % = 17.5	n = 5 ; % = 55.6
OSCI score Measurements taken in COVID-19 acute phase *Polarity: Lower values are better*		
Zero		
Sample Size	n = 1 ; % = 1.8	n = 0 ; % = 0

	Intervention group	Comparator
	N = 57	N = 9
One		
Sample Size	n = 21 ; % = 37.5	n = 1 ; % = 11.1
Two		
Sample Size	n = 18 ; % = 32.1	n = 1 ; % = 1.11
Three		
Sample Size	n = 1 ; % = 1.8	n = 0 ; % = 0
Four		
Sample Size	n = 4 ; % = 7.1	n = 1 ; % = 11.1
Five		
Sample Size	n = 2 ; % = 3.6	n = 1 ; % = 11.1
Six		
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0
Seven		
Sample Size	n = 0 ; % = 0	n = 0 ; % = 0
Eight		
Sample Size	n = 10 ; % = 17.5	n = 5 ; % = 55.6

	Intervention group	Comparator
	N = 57	N = 9
Follow-up after COVID-19 diagnosis *Polarity: Not set*		
Mean/SD	38.9 (15.6)	20.9 (14.3)

Hazard ratio for COVID-19 mortality according to the use of bolus vitamin D_3 supplements

Values shown are adjusted for potential confounders unless stated otherwise: age, gender, number of drugs daily taken, functional abilities, nutritional status, COVID-19 treatment with corticosteroids and/or hydroxychloroquine and/or dedicated antibiotics, and hospitalization for COVID-19.

	Intervention group vs Comparator
	N1 = 57, N2 = 9
Recent bolus vitamin D_3 supplementation *Polarity: Lower values are better*	
Adjusted	
Hazard ratio/95% CI	0.11 (0.03 to 0.48)
Unadjusted	
Hazard ratio/95% CI	0.21 (0.07 to 0.63)
Age *Polarity: Lower values are better*	
Hazard ratio/95% CI	1.06 (0.98 to 1.15)

	Intervention group vs Comparator
	N1 = 57, N2 = 9
Female gender *Polarity: Lower values are better*	
Hazard ratio/95% CI	1.03 (0.3 to 3.54)
Number of drugs usually taken per day *Polarity: Lower values are better*	
Hazard ratio/95% CI	0.73 (0.52 to 1.02)
Use of corticosteroids *Polarity: Lower values are better*	
Hazard ratio/95% CI	6.64 (0.46 to 95.24)
Use of hydroxychloroquine *Polarity: Lower values are better*	
Hazard ratio/95% CI	15.07 (0.75 to 302.53)
Use of dedicated antibiotics *Polarity: Lower values are better*	
Hazard ratio/95% CI	0.36 (0.07 to 1.95)
Hospitalisation for COVID-19 *Polarity: Lower values are better*	

	Intervention group vs Comparator
	N1 = 57, N2 = 9
Hazard ratio/95% CI	0.38 (0.02 to 7.06)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias (*Important baseline characteristics, such as BMI, ethnicity, use of other supplements and socioeconomic status not included)*
Study Attrition	Study Attrition Summary	Low risk of bias (*no attrition reported*)
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias (*Two groups who had vitamin D at separate times were not split in analyses)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias (*outcomes were objective and/or a valid, recognised tool for measuring COVID-19 severity, completed by geriatrician)*
Study Confounding	Study Confounding Summary	High risk of bias (*Important confounders, such as BMI, ethnicity, use of other supplements and socioeconomic status not included)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias (*Small sample size and event rate for large number of adjustments made. Important confounders, such as BMI, ethnicity, use of other supplements and socioeconomic status not accounted for in analyses)*
Overall risk of bias and directness	Risk of Bias	High
	Directness	Partially applicable *(Analysing outcomes from people who had supplementation before and after diagnosis does not make association as clear as a study that would split these ways of supplementing people. There could be differences in the clinical decisions made before hospitalisation due to this study not being in the UK and changes over the course of the pandemic)*