PROGETTO ALIMENTAZIONE E VITAMINA D

Roma - Hotel Mediterraneo via Cavour 5

27 maggio 2022

Responsabile Scientifico: Professor R. Nuti

Board: I. Chiodini, A. Falchetti, B. Frediani, A. Gaudio, L. Gennari, S. Giannini, A. Giusti, S. Gonnelli, G. Iolascon, G. Letizia Mauro, M. Mazzantini, S. Migliaccio, A. Migliore, G. Minisola, S. Minisola, M. Rossini, F. Silveri, F. Vescini

11.00 Introduzione - R. Nuti

Moderazione: G. Minisola – R. Nuti

11.15 Cause di ipovitaminosi D. - M. Rossini

11.30 Carenza di Vitamina D e patologie ad essa correlate. - B. Frediani

11.45 COVID 19 e Vitamina D. - I. Chiodini

12.00 Il corretto utilizzo della Vitamina D. - S. Gonnelli

12.15 Utilità del dosaggio del 25OHD. - L.Gennari

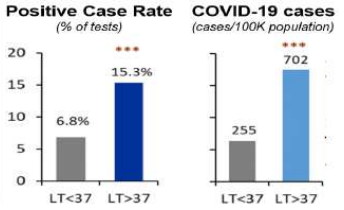
VITAMIN D and COVID-19

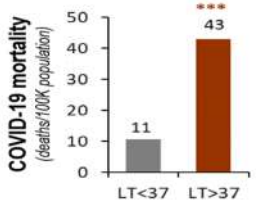
Lines of evidence that vitamin D deficiency is a risk factor for COVID-19

- **Vitamin D is important for immune function**, modulates the inflammatory response to infection, and regulates the renin-angiotensin system.
- Countries with **lower average levels of 25OHD** or lower solar ultraviolet-B radiation exposure have **higher COVID-19 mortality**
- **Demographic groups** known to be at higher risk of vitamin D deficiency (e.g. black individuals, the elderly, nursing-home residents, and those with obesity or diabetes) are **at high risk of COVID-19 hospitalization/mortality**.
- **Observational studies** (pre-COVID era):
  - Low vitamin D status is associated with increased risk of acute respiratory tract infections.
  - Vitamin D supplementation decreases risk of respiratory tract infection (especially in those with low 25OHD levels).
  - Vitamin D deficiency has been associated with increased risk of progression and death from viral infections

Courtesy of Luigi Gennari, Siena

SUNLIGHT, VITAMIN D DEFICIENCY AND COVID-19 EPIDEMIC



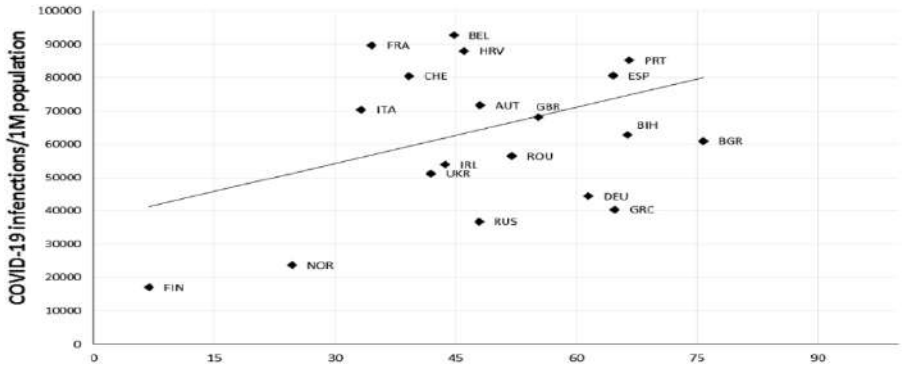


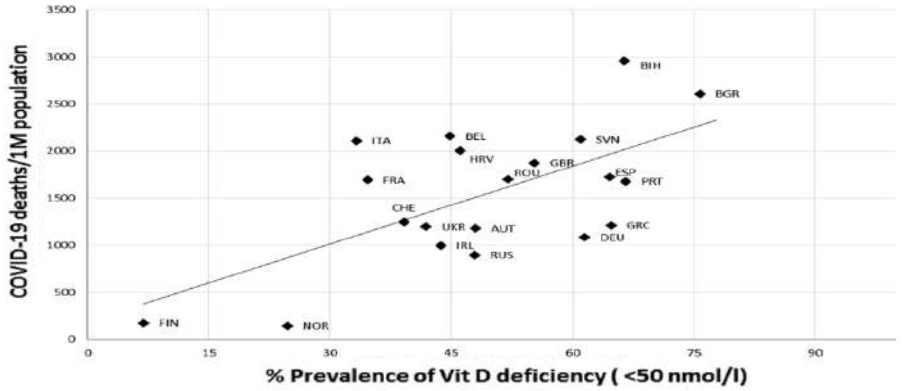
Liu Z et al. DOI:10.21203/rs.3.rs-32499/v1 Preprint

Covid-19 cases, total mortality and mortality rate as of Sept. 2020

Location	Total Confirmed Cases	Total Mortality	Percentage of Mortality to Confirmed Cases	Confirmed Cases Per Million Population	Deaths Per Million Population	Total Population
North of 23.5° N Lat	13,201,342	483,004	3.3	5378	159	3,655,796,736
23.5° N to 23.5° S	12,320,973	364,084	2.3	3295	77	3,918,475,190
South of 23.5° S Lat	1,589,874	37,423	2.1	5811	139	197,607,413

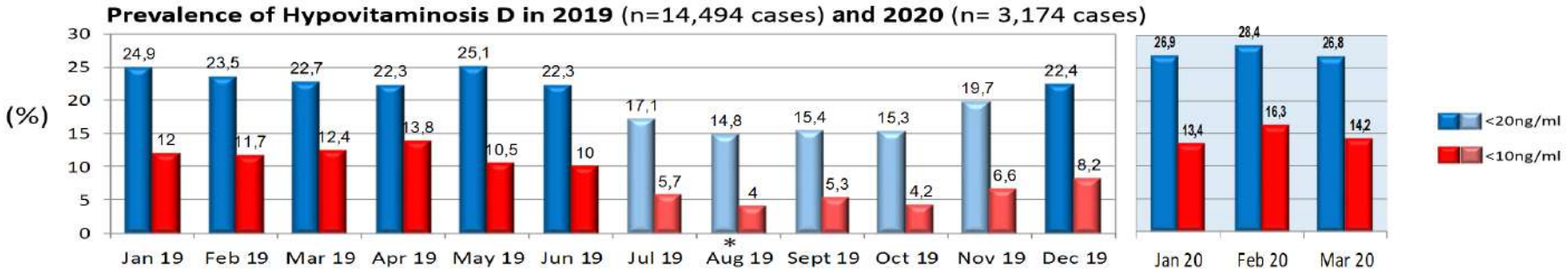
Courtesy of Luigi Gennari, Siena

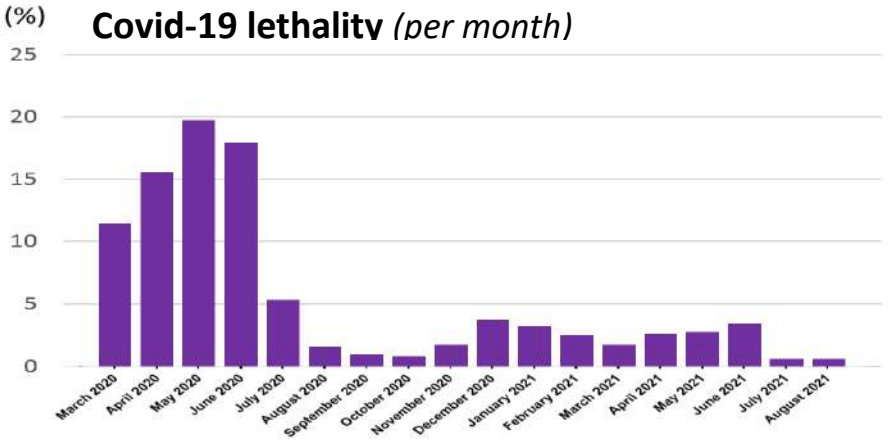


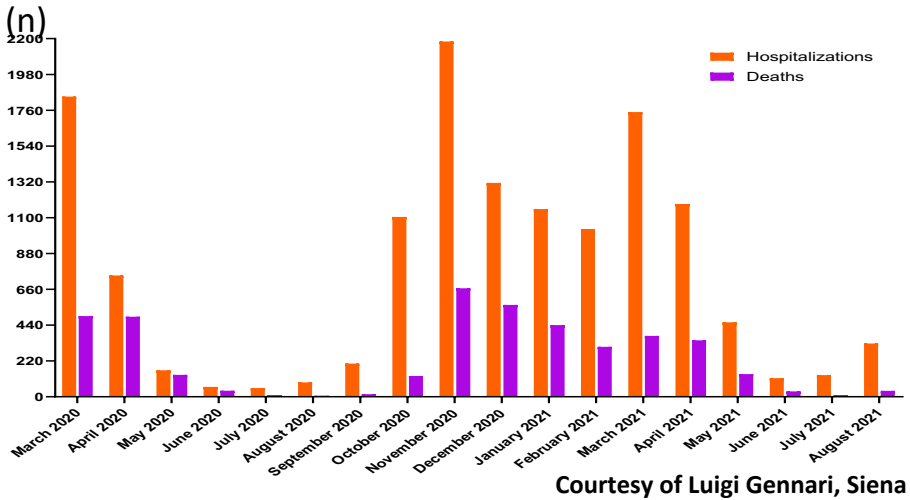


D.R. Bakaloudi and M. Chourdakis. Nutrition 2022;93:111441 [Online ahead of print]

SEASONAL VARIATION IN 25OHD AND COVID-19 MORTALITY IN ITALY

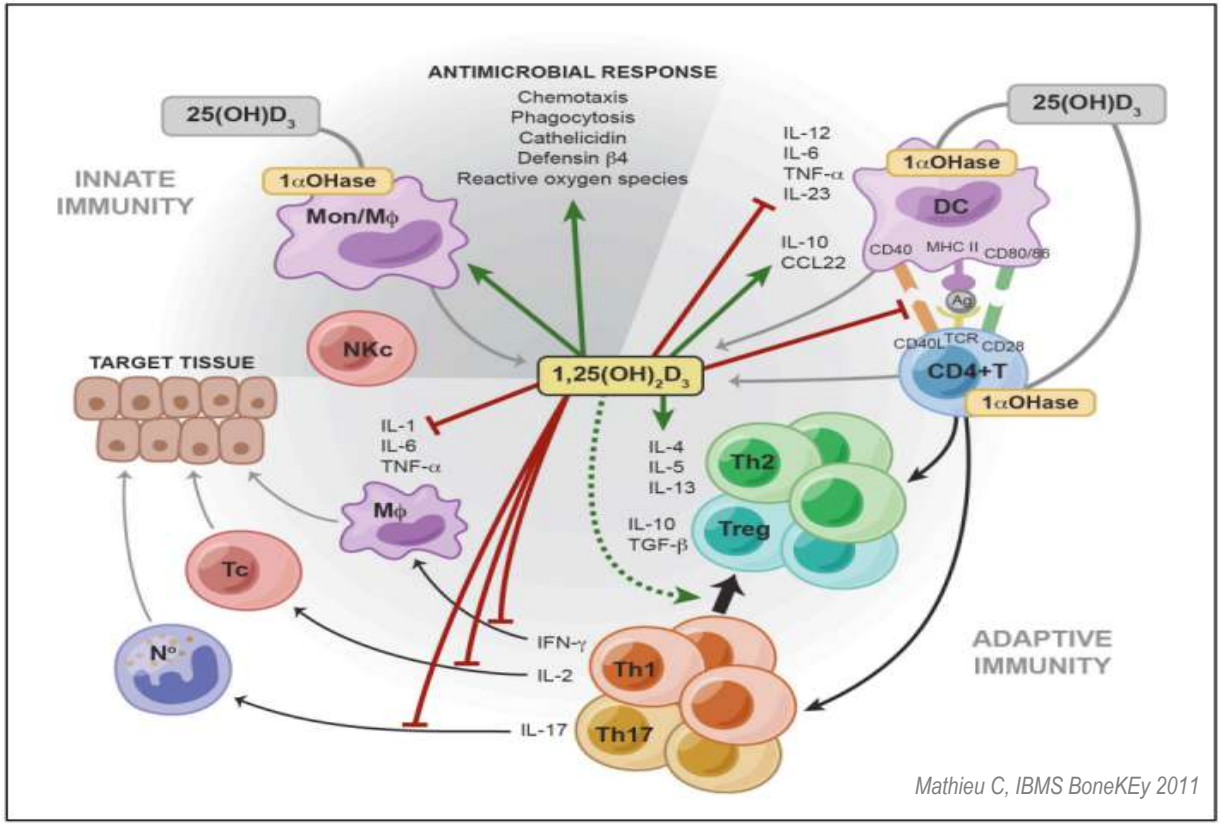




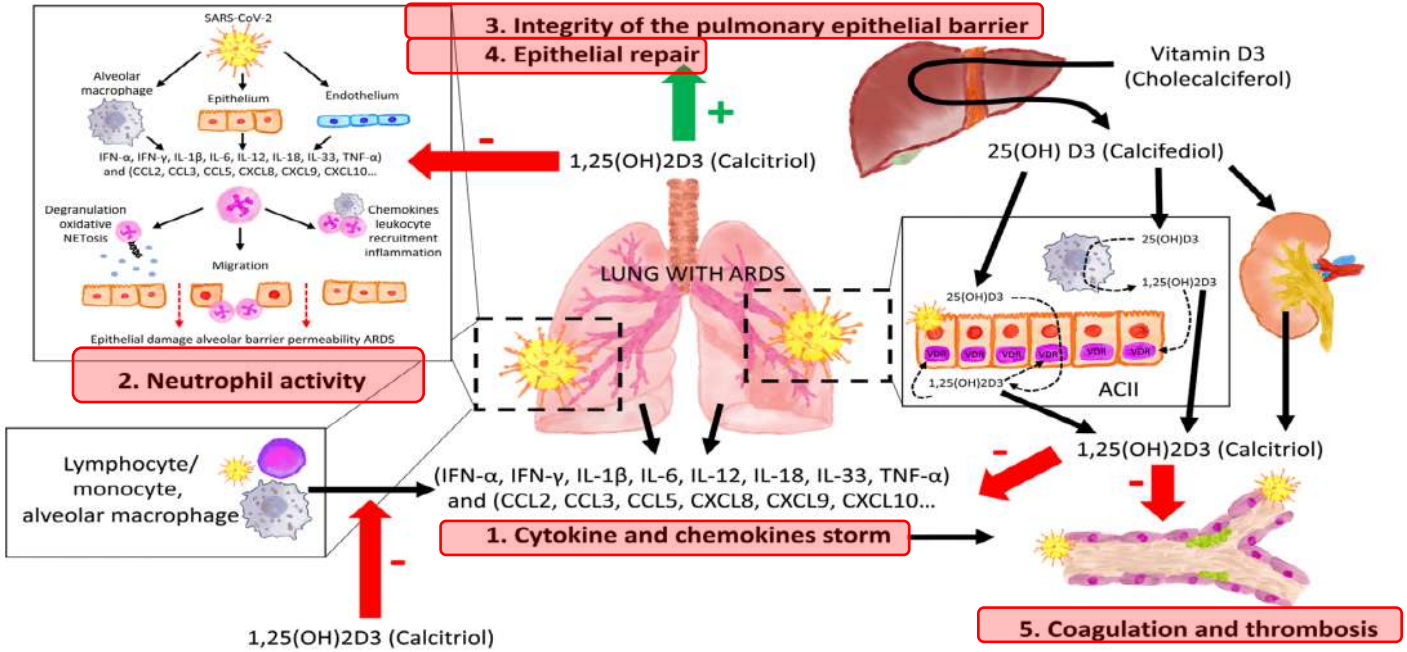


Courtesy of Luigi Gennari, Siena

Vitamin D and the Immune Function



VITAMIN D RECEPTOR STIMULATION TO REDUCE ARDS



VDRKO mice:

- experience more acute lung injury (LPS-induced)
- have increased renin-angiotensin system activity
- have increased platelet aggregation and manifest exacerbated multi- organ thrombosis after LPS-injection

I. Chiodini
Dpt of Medical Biotechnology and Translational Medicine, University of Milan. Unit for Bone Metabolism Diseases and Diabetes IRCCS Istituto Auxologico Italiano

VITAMIN D and COVID-19

Lines of evidence that vitamin D deficiency is a risk factor for COVID-19

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- Countries with **lower average levels of 25OHD** or lower solar ultraviolet-B radiation exposure have **higher COVID-19 mortality**
- **Demographic groups** known to be at higher risk of vitamin D deficiency (e.g. black individuals, the elderly, nursing-home residents, and those with obesity or diabetes) are **at high risk of COVID-19 hospitalization/mortality**.
- **Observational studies** (pre-COVID era):
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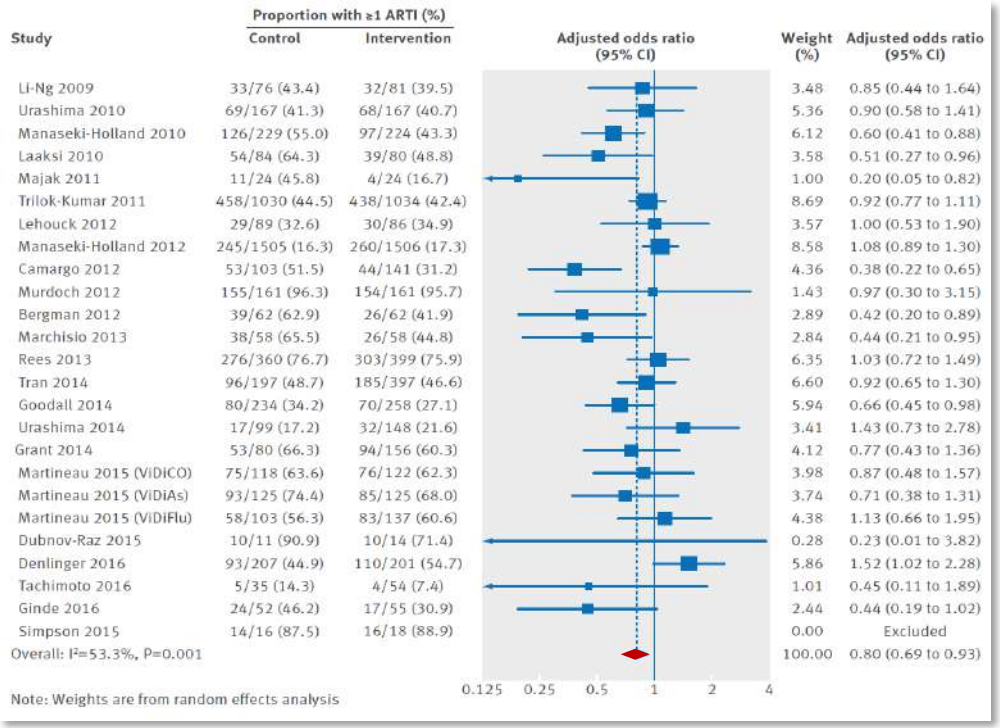
Courtesy of Luigi Gennari, Siena

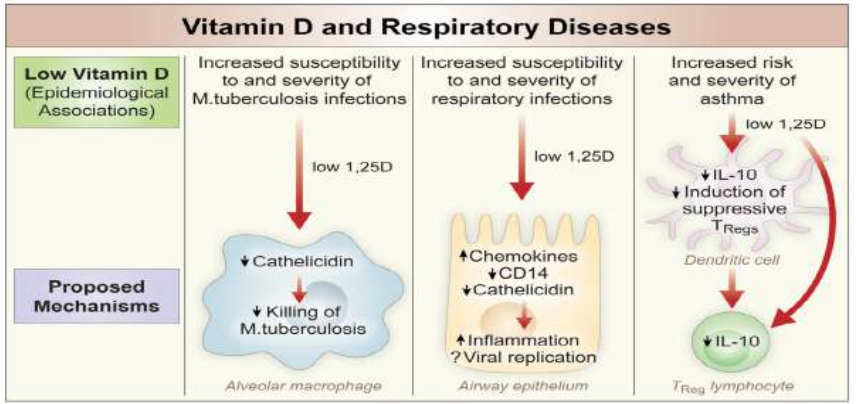
VITAMIN D AND RESPIRATORY TRACT INFECTIONS



Study	Proportion with ≥1 ARTI (%) Control	Intervention	Adjusted odds ratio (95% CI)	Weight (%)	Adjusted odds ratio (95% CI)
Li-Ng 2009	33/76 (43.4)	32/81 (39.5)		3.48	0.85 (0.44 to 1.64)
Urashima 2010	69/167 (41.3)	68/167 (40.7)		5.36	0.90 (0.58 to 1.41)
Manaseki-Holland 2010	126/229 (55.0)	97/224 (43.3)		6.12	0.60 (0.41 to 0.88)
Laaksi 2010	54/84 (64.3)	39/80 (48.8)		3.58	0.51 (0.27 to 0.96)
Majak 2011	11/24 (45.8)	4/24 (16.7)		1.00	0.20 (0.05 to 0.82)
Trilok-Kumar 2011	458/1030 (44.5)	438/1034 (42.4)		8.69	0.92 (0.77 to 1.11)
Lehouck 2012	29/89 (32.6)	30/86 (34.9)		3.57	1.00 (0.53 to 1.90)
Manaseki-Holland 2012	245/1505 (16.3)	260/1506 (17.3)		8.58	1.08 (0.89 to 1.30)
Camargo 2012	53/103 (51.5)	44/141 (31.2)		4.36	0.38 (0.22 to 0.65)
Murdoch 2012	155/161 (96.3)	154/161 (95.7)		1.43	0.97 (0.30 to 3.15)
Bergman 2012	39/62 (62.9)	26/62 (41.9)		2.89	0.42 (0.20 to 0.89)
Marchisio 2013	38/58 (65.5)	26/58 (44.8)		2.84	0.44 (0.21 to 0.95)
Rees 2013	276/360 (76.7)	303/399 (75.9)		6.35	1.03 (0.72 to 1.49)
Tran 2014	96/197 (48.7)	185/397 (46.6)		6.60	0.92 (0.65 to 1.30)
Goodall 2014	80/234 (34.2)	70/258 (27.1)		5.94	0.66 (0.45 to 0.98)
Urashima 2014	17/99 (17.2)	32/148 (21.6)		3.41	1.43 (0.73 to 2.78)
Grant 2014	53/80 (66.3)	94/156 (60.3)		4.12	0.77 (0.43 to 1.36)
Martineau 2015 (ViDiCO)	75/118 (63.6)	76/122 (62.3)		3.98	0.87 (0.48 to 1.57)
Martineau 2015 (ViDiAs)	93/125 (74.4)	85/125 (68.0)		3.74	0.71 (0.38 to 1.31)
Martineau 2015 (ViDiFlu)	58/103 (56.3)	83/137 (60.6)		4.38	1.13 (0.66 to 1.95)
Dubnov-Raz 2015	10/11 (90.9)	10/14 (71.4)		0.28	0.23 (0.01 to 3.82)
Denlinger 2016	93/207 (44.9)	110/201 (54.7)		5.86	1.52 (1.02 to 2.28)
Tachimoto 2016	5/35 (14.3)	4/54 (7.4)		1.01	0.45 (0.11 to 1.89)
Ginde 2016	24/52 (46.2)	17/55 (30.9)		2.44	0.44 (0.19 to 1.02)
Simpson 2015	14/16 (87.5)	16/18 (88.9)		0.00	Excluded
Overall: I²=53.3%, P=0.001				100.00	0.80 (0.69 to 0.93)

Note: Weights are from random effects analysis

Martineau AR et al, BMJ 2017;356:i6583



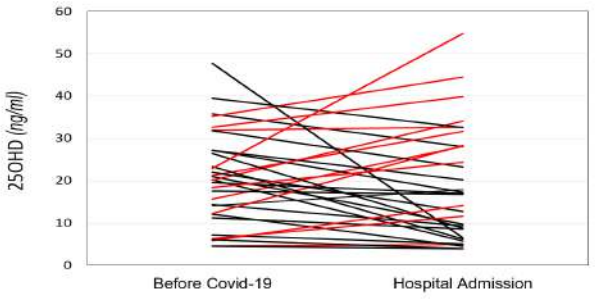
Cell type	Conversion of 25D → 1,25D	1.25D Effects
Airway Epithelium	Constitutive	Increases CD14 and cathelicidin. Dampens IFN-β and chemokine response during viral infection
Alveolar Macrophages	Upon activation	Increases the antimicrobial peptide cathelicidin
Dendritic Cells	Increases with differentiation	Inhibits dendritic cell differentiation, maturation and function, decreases IL-12 and increases IL-10, alters T cell activation
T lymphocytes	At least when activated	Inhibits proliferation, modulates cytokine production - inhibits Th1 and Th17 cytokines but induces Tregs
B lymphocytes	Unclear	Inhibits proliferation of activated B cells and generation of plasma cells

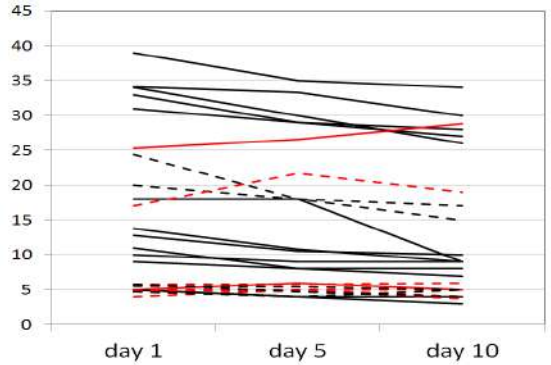
Hansdottir S et al. Vitam Horm. 2011 ; 86:217–37

VITAMIN D AND COVID-19: POTENTIAL IMPLICATIONS

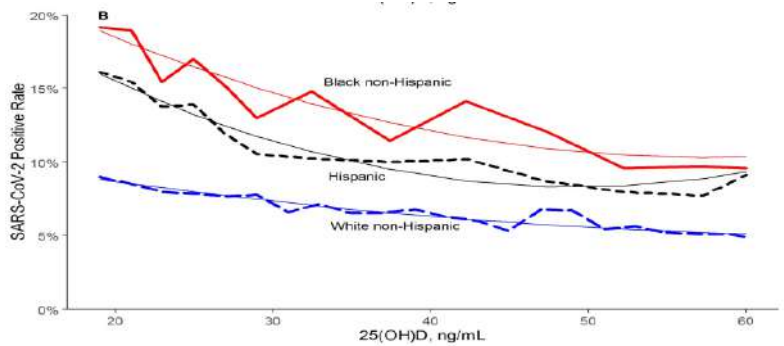
- Vitamin D deficiency may increase the risk of Covid-19 infection
- Vitamin D deficiency may worsen Covid-19 severity
- Vitamin D supplementation may improve the clinical outcome of Covid-19
- Optimal vitamin D status as a potential adjuvant for COVID-19 vaccines

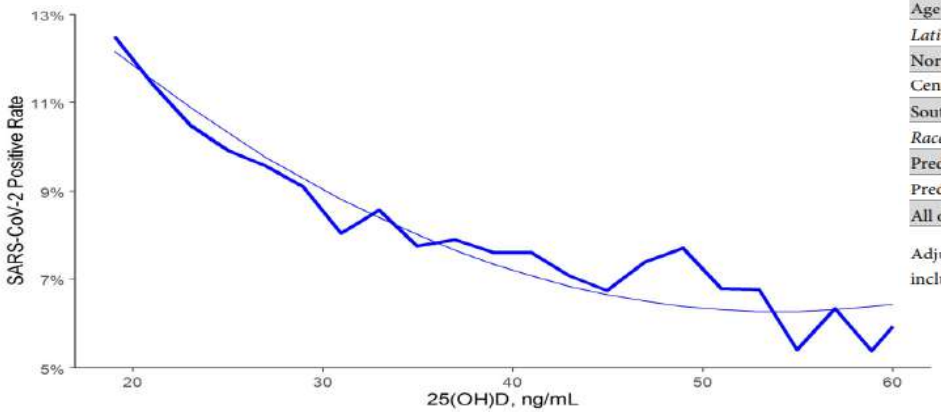
- High heterogeneity
  (design, setting, methodology)
- Confoundings
  (ethnicity, adiposity, comorbidities)
- Reverse causation
  (25OHD as acute phase reactant)





VITAMIN D STATUS AND THE RISK OF COVID-19 INFECTION





- N=191,779 US patients with SARS-CoV-2 results performed March through June 2020 and matching 25OHD results from the preceding 12 months

Table 1. Associations with SARS-CoV-2 positivity.

	Unadjusted Odds Ratio (95% C.I.)	Adjusted Odds Ratio (95% C.I.)
25(OH)D (per ng/mL increment)	0.979 (0.977–0.980)	0.984 (0.983–0.986)
Male	1.26 (1.22–1.31)	1.24 (1.20–1.28)
Female	reference	reference
Age ≥60 years	0.74 (0.71–0.76)	0.84 (0.81–0.87)
Age <60 years	reference	reference
Latitudes		
Northern (>40 degrees)	2.43 (2.32–2.54)	2.66 (2.54–2.79)
Central (32–40 degrees)	1.17 (1.12–1.23)	1.22 (1.16–1.28)
Southern (<32 degrees)	reference	reference
Race/Ethnicity zip codes		
Predominately black non-Hispanic	2.04 (1.93–2.17)	2.03 (1.91–2.15)
Predominately Hispanic	1.61 (1.54–1.67)	1.95 (1.87–2.04)
All other zip codes	reference	reference

Adjusted model H-L Fit: $p = 0.003$; $R^2 = 0.024$. SI conversion factor: 1 ng/mL = 0.400641 nmol/L. Adjusted model included 188,028 patients with no missing values (98% of included patients).

Kaufman HV et al. PLoS One. 2020 Sep 17;15(9):e0239252

Vitamin D Deficiency Is Associated With Higher Hospitalization Risk From COVID-19: A Retrospective Case-Control Study

Participant characteristics	Lancashire Teaching Hospitals NHS Foundation Trust (n = 58 368)	Tameside and Glossop Integrated Care NHS Foundation Trust (n = 21 234)
Age (years), median [IQR]	53.2 [36.6-69.1]	55.1 [39.8-70.4]
Female sex, n (%)	38 472 (65.9)	14 527 (68.4)
Hospitalized patients, n (%)	1036 (1.8)	772 (3.6)
Inpatient deaths, n (%)	375 (36.9)	295 (38.2)
Serum 25(OH)D (nmol/L), median [IQR]	50.0 [34.0-66.6]	46.7 [31.3-64.4]
Time (days) between 25(OH)D measurement and admission to hospital (hospitalized participants only), median [IQR]	148 [22-265]	51 [12-187]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range.

Variable of interest	*Primary cohort*		*Validation cohort*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Serum 25(OH)D < 50 nmol/L	2.22 (1.93-2.53)	<0.005	2.16 (1.83-2.54)	<0.005
Serum 25(OH)D < 50 nmol/L, adjusted	2.40 (2.10-2.74)	<0.005	2.33 (1.98-2.74)	<0.005
Serum 25(OH)D < 25 nmol/L	3.77 (3.30-4.30)	<0.005	3.36 (2.89-3.92)	<0.005
Serum 25(OH)D < 25 nmol/L, adjusted	3.57 (3.12-4.08)	<0.005	2.98 (2.55-3.49)	<0.005

Where odds ratios have been adjusted, these have been adjusted for age, sex, and whether serum 25(OH)D measurement was carried out in UK spring/summer months (March through August).
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

A.Primary cohort subanalysis

Serum 25(OH)D < 50 nmol/L and association with hospitalization

Subgroup	OR (95% CI)	*P* value
Female	2.15 (1.78-2.61)	<0.005
Male	2.10 (1.75-2.52)	<0.005
Age ≥ 60 years	2.46 (2.12-2.86)	<0.005
Age < 60 years	2.68 (2.02-3.55)	<0.005
25(OH)D measured in spring/summer	2.14 (1.69-2.72)	<0.005
25(OH)D measured in autumn/winter	2.19 (1.87-2.57)	<0.005

Serum 25(OH)D < 25 nmol/L and association with hospitalization

Subgroup	OR (95% CI)	*P* value
Female	3.56 (2.91-4.35)	<0.005
Male	3.59 (3.00-4.28)	<0.005
Age ≥ 60 years	3.68 (3.15-4.31)	<0.005
Age < 60 years	4.11 (3.17-5.32)	<0.005
25(OH)D measured in spring/summer	4.54 (3.58-5.75)	<0.005
25(OH)D measured in autumn/winter	3.42 (2.91-4.01)	<0.005

B.Validation cohort subanalysis

Serum 25(OH)D < 50 nmol/L and association with hospitalization

Subgroup	OR (95% CI)	*P* value
Female	2.15 (1.70-2.72)	<0.005
Male	1.92 (1.54-2.40)	<0.005
Age ≥ 60 years	2.47 (2.06-2.97)	<0.005
Age < 60 years	2.39 (1.71-3.36)	<0.005
25(OH)D measured in spring/summer	2.30 (1.71-3.10)	<0.005
25(OH)D measured in autumn/winter	2.05 (1.69-2.48)	<0.005

Serum 25(OH)D < 25 nmol/L and association with hospitalization

Subgroup	OR (95% CI)	*P* value
Female	3.30 (2.62-4.16)	<0.005
Male	2.93 (2.38-3.59)	<0.005
Age ≥ 60 years	3.19 (2.67-3.82)	<0.005
Age < 60 years	3.43 (2.53-4.64)	<0.005
25(OH)D measured in spring/summer	4.28 (3.25-5.64)	<0.005
25(OH)D measured in autumn/winter	3.00 (2.50-3.61)	<0.005

Jude EB et al. J Clin Endocrinol Metab. 2021 Jun 17:dgab439

VITAMIN D AND COVID-19 SEVERITY AND RELATED MORTALITY: A PROSPECTIVE STUDY IN ITALY

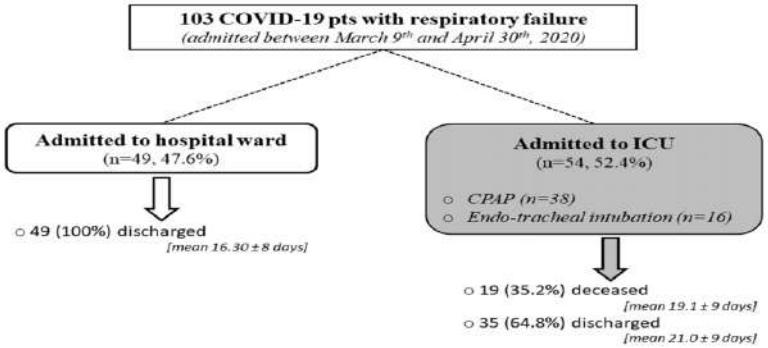


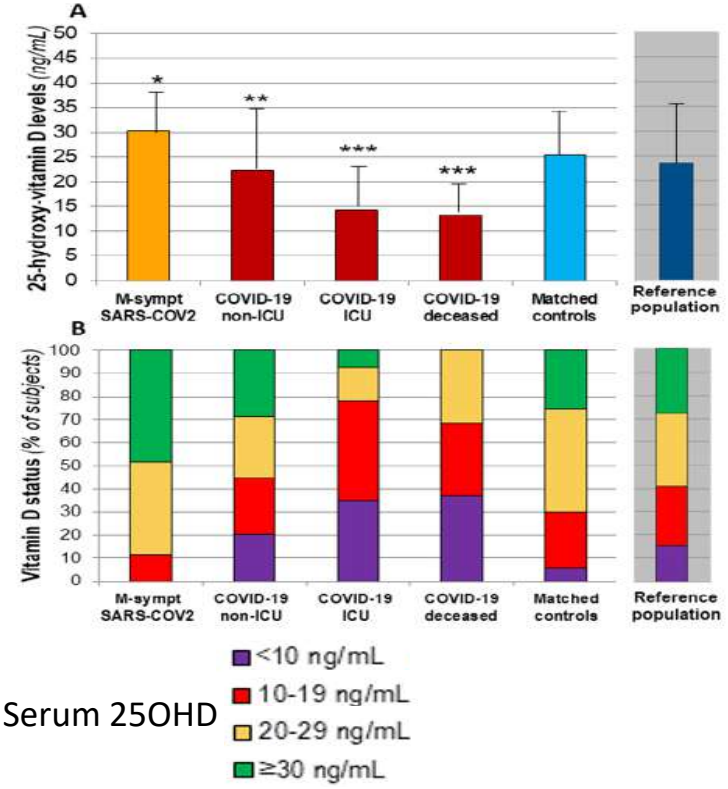
Table 3 Factors independently associated with admission to intensive care Unit in severely-symptomatic COVID-19 patients

	RR (95% CI)	*P*-value
Age	0.993 (0.980 to 1.007)	0.325
Gender		
Female	Ref	
Male	1.222 (0.793 to 1.882)	0.363
At least 1 comorbidity [a]		
No	Ref.	
Yes	1.556 (1.079 to 2.244)	0.018
Creatinine	0.503 (0.268 to 0.944)	0.032
IL-6	1.000 (0.997 to 1.004)	0.907
Lactate dehydrogenase	1.000 (1.000 to 1.001)	0.459
Neutrophil cells count	1.076 (1.018 to 1.136)	0.009
Lymphocytes count	0.860 (0.651 to 1.137)	0.289
Platelets count	0.998 (0.996 to 1.000)	0.089
25OHD	0.989 (0.981 to 0.997)	0.011

Patients in Intensive Care Unit: patients with respiratory distress requiring continuous positive airway pressure and/or endo-tracheal intubation. *25OHD* 25hydroxyvitamin D; *IL-6* interleukin-6;
[a] at least 1 comorbidity among obesity, diabetes, arterial hypertension

Table 5 Factors independently associated with in-hospital mortality in severely-symptomatic COVID-19 patients

	RR (95% CI)	*P*-value
Age	1.070 (1.029 to 1.114)	0.0008
Gender		
Female	Ref	0.369
Male	1.672 (0.545 to 5.126)	
Diabetes		
No	Ref.	< 0.0001
Yes	3.446 (1.900 to 6.248)	
IL-6	1.009 (1.002 to 1.017)	0.019
C-reactive Protein	1.035 (1.001 to 1.069)	0.042
Lactate dehydrogenase	1.004 (1.001 to 1.006)	0.006
Neutrophil cells count	1.064 (0.936 to 1.209)	0.344
Lymphocytes count	0.437 (0.204 to 0.938)	0.034
Platelets count	1.002 (0.997 to 1.006)	0.487
25OHD	0.961 (0.937 to 0.985)	0.002



Serum 25OHD

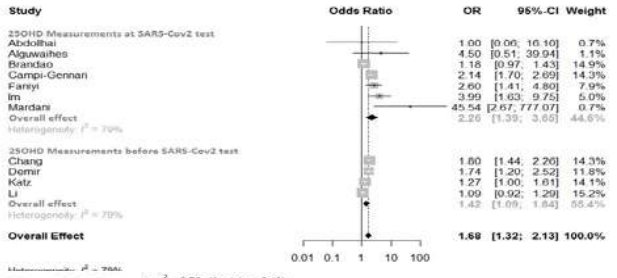
Campi *et al. BMC Infectious Diseases* (2021) 21:566

VITAMIN D AND SARS-COV2 CLINICAL OUTCOMES: REVIEW AND META-ANALYSIS

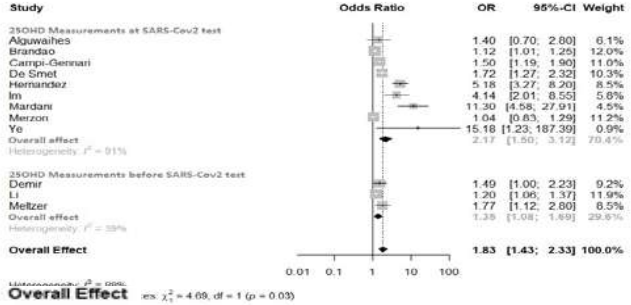
Infection

Hospital Admiss.

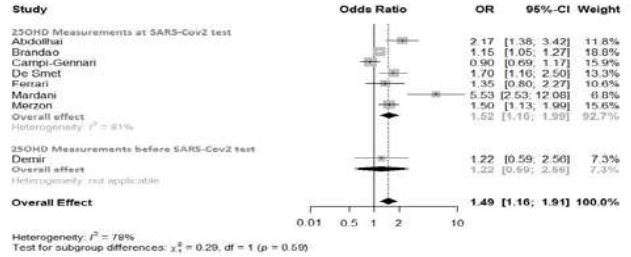
25OHD <25 nmol/L



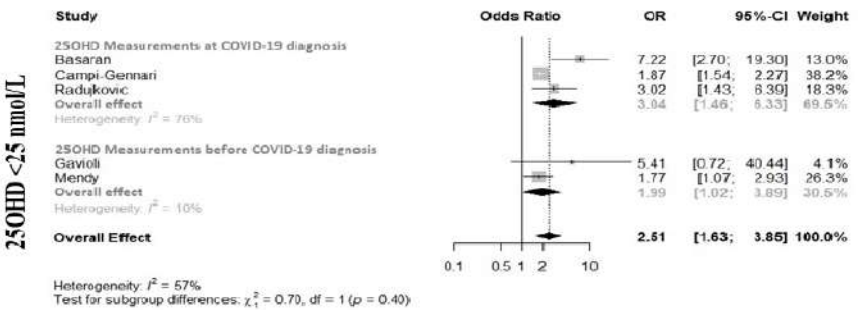
25OD <50 nmol/L



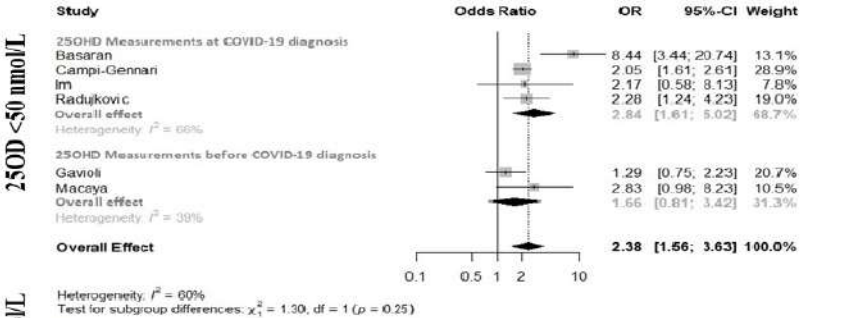
25OHD < 75 nmol/L



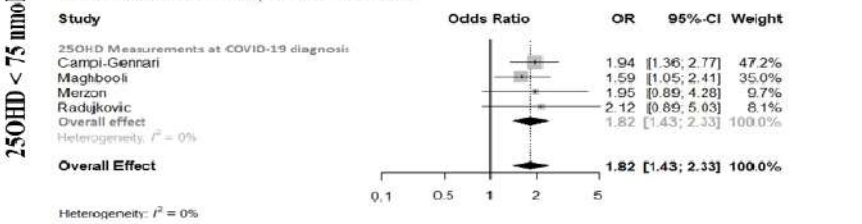
25OHD <25 nmol/L



25OD <50 nmol/L



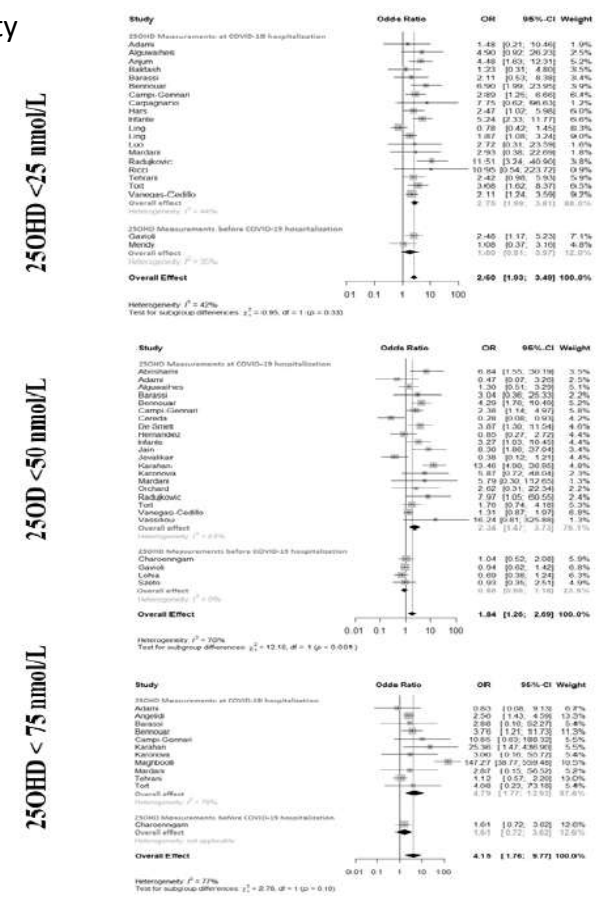
25OHD < 75 nmol/L



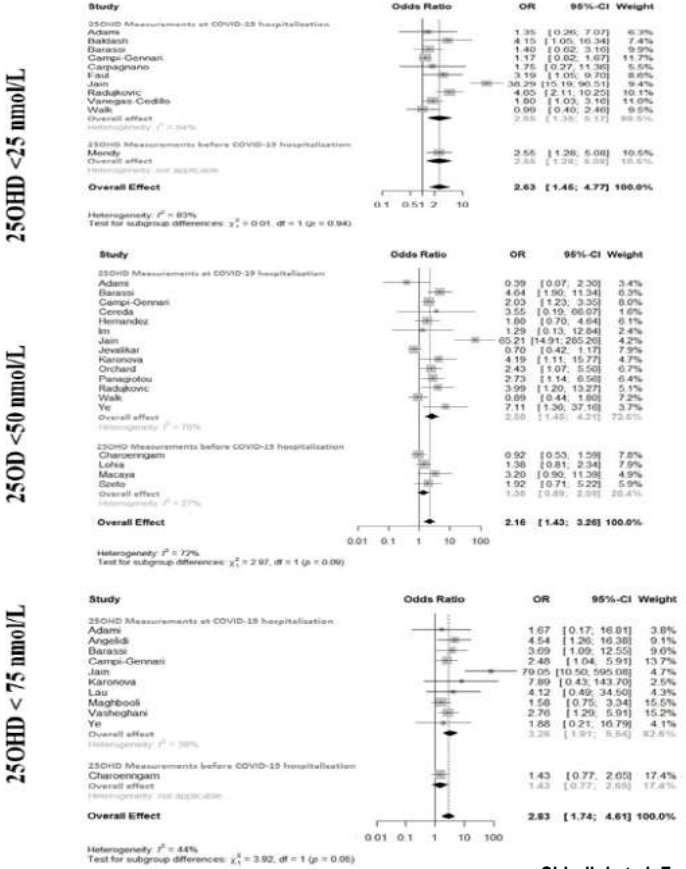
Chiodini et al, Front. Public Health 2021

VITAMIN D AND SARS-COV2 CLINICAL OUTCOMES: REVIEW AND META-ANALYSIS

Mortality



ICU Admiss.



Chiodini et al, Front. Public Health 2021

I. Chiodini

Dpt of Medical Biotechnology and Translational Medicine, University of Milan. Unit for Bone Metabolism Diseases and Diabetes IRCCS Istituto Auxologico Italiano

VITAMIN D AND COVID-19: POTENTIAL IMPLICATIONS

- Vitamin D deficiency may increase the risk of Covid-19 infection
- Vitamin D deficiency may worsen Covid-19 severity
- Vitamin D supplementation may improve the clinical outcome of Covid-19
- Optimal vitamin D status as a potential adjuvant for COVID-19 vaccines

www.aging-us.com AGING 2020, Vol. 12, No. 24

Research Paper

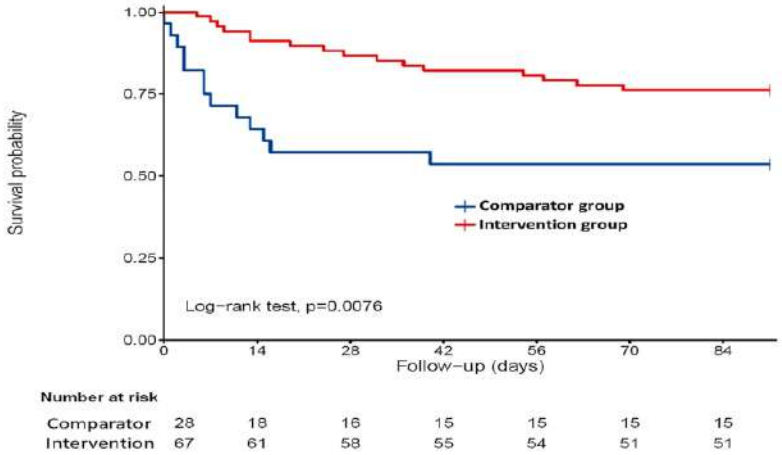
Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests

Biagio Cangiano[1,2,3,*], Letizia Maria Fatti[1,*], Leila Danesi[1], Giacomo Gazzano[4], Marina Croci[1], Giovanni Vitale[1,3,5], Luisa Gilardini[1], Stefania Bonadonna[1], Iacopo Chiodini[1,2], Chiara Francesca Caparello[6], Antonio Conti[1], Luca Persani[1,2,3], Marco Stramba-Badiale[7], Marco Bonomi[1,2,3] on behalf of the "Mons G. Bicchierai" nursing home group[#]

Design: In this observational study, we described the two-month mortality among the 157 residents (age 60-100) of a nursing home after Sars-CoV-2 spreading, reporting the factors associated with the outcome. We also compared the diagnostic tests for Sars-CoV-2.

Conclusion: Our data confirms a higher geriatric mortality due to COVID-19. Negative residents also had higher mortality, which we suspect is secondary to preanalytical error and a low sensitivity of the swab test in poorly compliant subjects. Male gender, older age and low scores on ADL scales (probably due to immobility) are risk factors for COVID-19 related mortality. Finally, mortality was inversely associated with vitamin D supplementation.

Vitamin D supplementation prior to or during COVID-19 associated with better 3-month survival in geriatric patients: Extension phase of the GERIA-COVID study

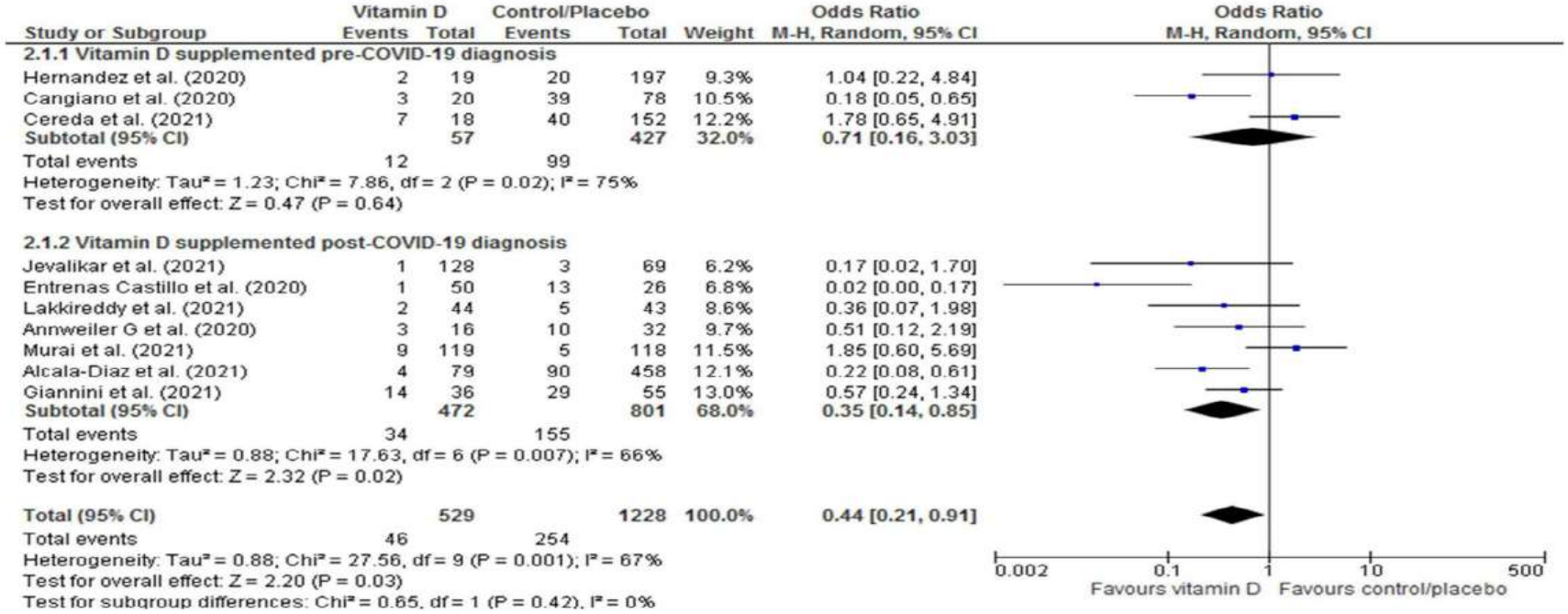


	3-month mortality					
	Unadjusted model		Partially-adjusted model*		Fully-adjusted model	
	HR [95 % CI]	P-value	HR [95 % CI]	P-value	HR [95 % CI]	P-value
Vitamin D supplementation	0.38 [0.18;0.80]	**0.010**	0.30 [0.13;0.70]	**0.005**	0.23 [0.09;0.58]	**0.002**
Age	1.02 [0.95;1.09]	0.651	1.01 [0.94;1.08]	0.848	1.04 [0.95;1.13]	0.436
Female gender	0.53 [0.25;1.15]	0.109	0.82 [0.35;1.96]	0.656	0.65 [0.23;1.84]	0.417
GIR score	0.70 [0.53;0.92]	**0.010**	0.66 [0.50;0.86]	**0.003**	0.71 [0.52;0.97]	**0.029**
Serum 25(OH)D concentration	1.00 [0.99;1.01]	0.394	0.99 [0.98;1.00]	**0.049**	0.99 [0.97;1.00[	**0.035**
Severe undernutrition†	1.78 [0.84;3.78]	0.131	–	–	1.36 [0.57;3.26]	0.489
History of malignancies	3.11 [1.49;6.47]	**0.003**	–	–	2.99 [1.35;6.60]	**0.007**
History of cardiomyopathy	1.14 [0.55;2.37]	0.724	–	–	0.85 [0.37;1.97]	0.699
Number of acute health issues	1.30 [1.04;1.63]	**0.024**	–	–	1.34 [1.05;1.72]	**0.018**
Use of antibiotics‡	2.58 [0.98;6.76]	0.054	–	–	2.32 [0.78;6.94]	0.132
Use of systemic corticosteroids	0.78 [0.76;4.17]	0.184	–	–	2.39 [0.82;7.00]	0.111

25(OH)D: 25-hydroxyvitamin D; CI: confidence interval; COVID-19: coronavirus disease 2019; GIR: Iso Resource Groups; HR: hazard ratio; *: adjusted for age, sex, GIR score and 25(OH)D concentration; †: serum albumin concentration < 30 g/L; ‡: quinolones, beta-lactams, sulfonamides, macrolides, lincosamides, aminoglycosides, among others.

Annweiler C et al, J Steroid Biochem Mol Biol. 2021

VITAMIN D SUPPLEMENTATION AND CLINICAL OUTCOMES IN COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

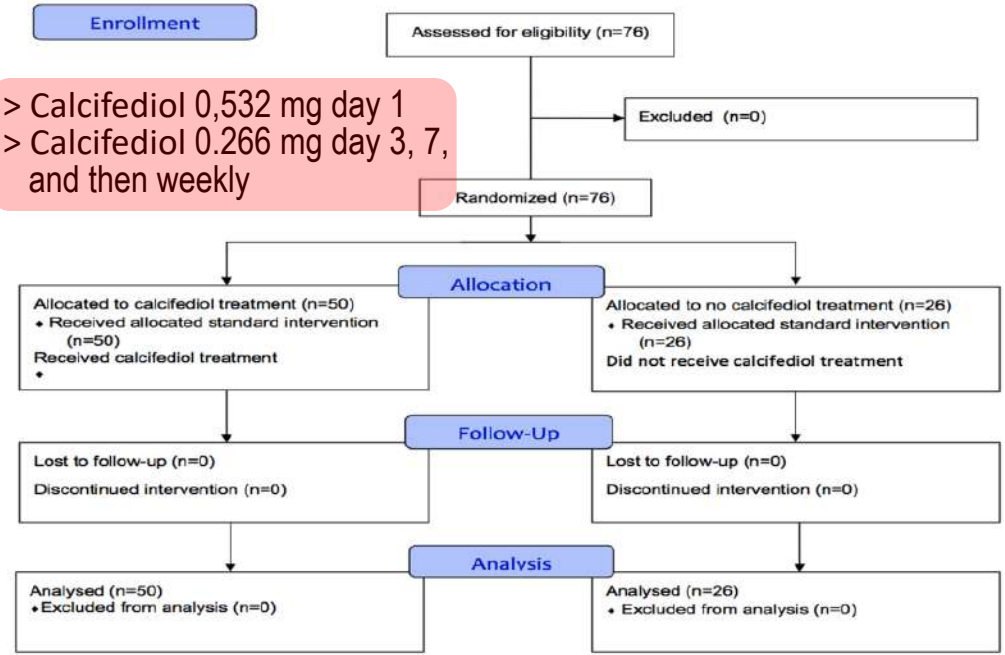


- none of the studies fulfilled the criteria required for the inclusion of clinical studies examining nutrient effects in systematic reviews and meta-analysis

Pal R et al. J Endocrinol Invest 2021 Jun 24:1-16

"Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study"

> Calcifediol 0,532 mg day 1
> Calcifediol 0.266 mg day 3, 7, and then weekly



Prognostic factors for COVID-19 at baseline.

Poor prognosis risk factor	Group receiving Calcifediol (n = 50)	Group without Calcifediol (n = 26)	IC 95 %	P
≥ 60 years	14 (28 %)	5 (19.23 %)	−0.11 – 0.28	0.40
Previous lung disease	4 (8%)	2 (7.69 %)	−0.12 – 0.13	0.96
Previous Chronic kidney disease	0	0	–	–
Previous Diabetes mellitus	3 (6%)	5 (19.23 %)	−0.30 – 0.03	0.08
Previous High blood pressure	11 (24.19 %)	15 (57.69 %)	−0.58 – −0.13	0.002
Previous Cardiovascular disease	2 (4%)	1 (3.85 %)	−0.09 – 0.09	0.97
Immunosuppressed & transplanted	6 (12 %)	1 (3.85 %)	−0.03 – 0.20	0.24
At least one prognostic bad risk factor	24 (48 %)	16 (61.54 %)	−0.37 – 010	0.26

Requirements for admission to the Intensive Care Unit, in patients hospitalized with COVID-19 (treated or not with calcifediol).

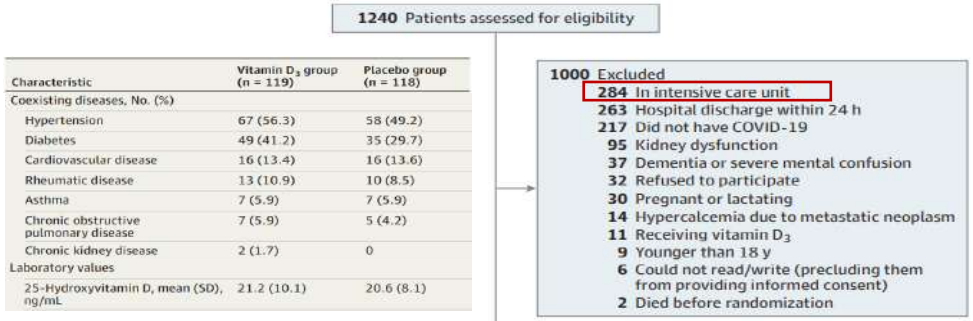
	Without Calcifediol Treatment (n = 26)	With Calcifediol Treatment (n = 50)	p value (1d712;2), Fischer Test
Need for ICU			<0.001
Not requiring ICU, n (%)	13 (50)	49 (98)	
Requiring ICU, n (%)	13 (50)	1 (2)	

* Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment: 0.02 (95 %CI 0.002−0.17).
** Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003−0.25).

Entrenas Castillo M et al. J Steroid Biochem Mol Biol 2020;203:105751

Effect of a Single High Dose of Vitamin D_3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19

a multicenter, double-blind, parallel-group, randomized, placebo-controlled trial



Characteristic	Vitamin D_3 group (n = 119)	Placebo group (n = 118)
Coexisting diseases, No. (%)		
Hypertension	67 (56.3)	58 (49.2)
Diabetes	49 (41.2)	35 (29.7)
Cardiovascular disease	16 (13.4)	16 (13.6)
Rheumatic disease	13 (10.9)	10 (8.5)
Asthma	7 (5.9)	7 (5.9)
Chronic obstructive pulmonary disease	7 (5.9)	5 (4.2)
Chronic kidney disease	2 (1.7)	0
Laboratory values		
25-Hydroxyvitamin D, mean (SD), ng/mL	21.2 (10.1)	20.6 (8.1)

All patients had COVID-19 diagnosis confirmed by polymerase chain reaction (PCR) testing at the time of enrollment or by serology assay (ELISA) to detect IgG against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) throughout the study.

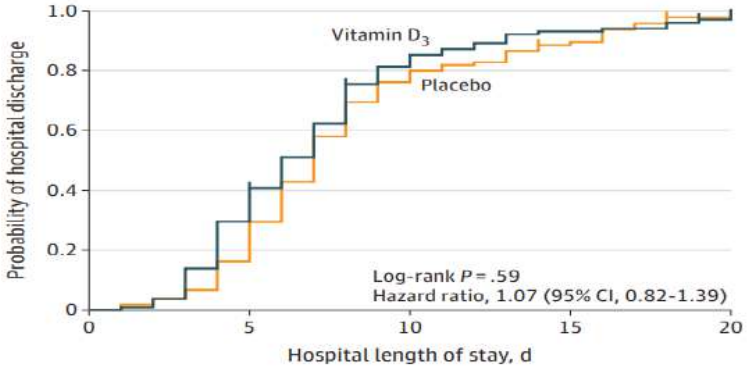


Table 2. Secondary Outcomes in a Study of the Effect of a High Dose of Vitamin D_3 on Patients With Modera to Severe Coronavirus Disease 2019

Outcome	Patients (95% CI), %		Between-group difference (95% CI), %	*P* value
	Vitamin D_3 group	Placebo group		
All patients	n = 119	n = 118		
In-hospital mortality	7.6 (3.5 to 13.9)	5.1 (1.9 to 10.7)	2.5 (-4.1 to 9.2)	.43
Admission to intensive care unit	16.0 (9.9 to 22.5)	21.2 (14.2 to 29.7)	-5.2 (-15.1 to 4.7)	.30
Mechanical ventilation requirement	7.6 (3.5 to 13.9)	14.4 (8.6 to 22.1)	-6.8 (-15.1 to 1.2)	.09
Patients with 25-hydroxyvitamin D deficiency (<20 ng/mL)	n = 57	n = 58		
In-hospital mortality	7.0 (1.9 to 17.0)	1.7 (0.04 to 9.2)	5.3 (-3.3 to 15.1)	.21
Admission to intensive care unit	19.3 (10.0 to 31.9)	15.5 (7.4 to 27.4)	3.8 (-10.3 to 17.8)	.59
Mechanical ventilation requirement	7.0 (1.9 to 17.0)	8.6 (2.9 to 19.0)	-1.6 (-12.5 to 9.2)	>.99

Murray IH et al. JAMA. 2021;325(11):1053-1060.

Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank

TABLE 2 Association between vitamin D supplement use and risk of coronavirus disease 2019 infection

	Nonusers, $n = 7934$	Vitamin D users, $n = 363$	P value
Cases, n (%)	1329 (16.8%)	49 (13.5%)	
Unadjusted	1 (reference)	0.78 (0.57–1.05)	0.105
Model 1	1 (reference)	0.67 (0.46–0.98)	0.038
Model 2	1 (reference)	0.67 (0.46–0.98)	0.040
Model 2 + baseline circulating vitamin D levels	1 (reference)	0.66 (0.45–0.97)	0.034

Logistic regression models were used to calculate the ORs and 95% CIs ($n = 8297$). Model 1 was adjusted for age group, sex, race, research centers, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, Townsend deprivation index, smoking, moderate drinking, physical activity, healthy diet score, and any other supplements. Model 2 was further adjusted for obesity, diabetes, hypertension, high cholesterol, cardiovascular diseases, cancer, asthma, and chronic obstructive pulmonary disease on the basis of Model 1.

Ma H et al. Am J Clin Nutr 2021;113:1275–1281

Vitamin D supplementation and COVID-19 risk: a population-based, cohort study

All individuals ≥18 years old living in Barcelona-Central Catalonia (**n=4.6 million**) supplemented with cholecalciferol or calcifediol from April 2019 to February 2020 were compared with **propensity score-matched** untreated controls

	Cholecalciferol treated and serum 25OHD ≥ 30 ng/ml (n = 9474)	Untreated controls with serum 25OHD < 20 ng/ml (n = 7616)	Univariate analysis[3]		Multivariate analysis[4]	
			HR (CI 95%)	p	HR (CI 95%)	p
SARS-CoV2 infection[1], n (%)	309 (3.3%)	430 (5.6%)	0.57 (0.50–0.66)	<0.001	0.66 (0.57–0.77)	<0.001
Severe COVID-19[2], n (%)	65 (0.7%)	99 (1.3%)	0.53 (0.39–0.72)	<0.001	0.72 (0.52–1.00)	0.050
COVID-19 mortality, n (%)	56 (0.6%)	96 (1.3%)	0.47 (0.34–0.65)	<0.001	0.66 (0.46–0.93)	0.018

	Calcifediol treated and serum 25OHD ≥ 30 ng/ml (n = 16,276)	Untreated controls with serum 25OHD < 20 ng/ml (n = 7616)	Univariate analysis[3]		Multivariate analysis[4]	
			HR (CI 95%)	p	HR (CI 95%)	p
SARS-CoV2 infection[1], n (%)	535 (3.3%)	430 (5.6%)	0.58 (0.51–0.66)	<0.001	0.69 (0.61–0.79)	<0.001
Severe COVID-19[2], n (%)	100 (0.6%)	99 (1.3%)	0.47 (0.36–0.62)	<0.001	0.61 (0.46–0.81)	0.001
COVID-19 mortality, n (%)	88 (0.5%)	96 (1.3%)	0.43 (0.32–0.57)	<0.001	0.56 (0.42–0.76)	<0.001

- Patients supplemented with cholecalciferol or calcifediol achieving serum 25OHD levels ≥30 ng/ml were associated with better COVID-19 outcomes.

Oristrell J et al. J Endocrinol Invest. 2021 Jul 17:1–13

VITAMIN D AND COVID-19: CONCLUSIVE REMARKS

- Vitamin D has a recognized immunomodulatory activity and may be a biologically plausible target in the prevention/treatment of Covid-19
- Most of the clinical evidence suggest that low 25OHD levels are predictive of Covid-19 severity and related mortality
- Further evidence is required to fully support the role of vitamin D supplementation for the prevention and treatment of Covid-19

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GRAZIE PER L'ATTENZIONE