The Role of Vitamin D in Treating COVID-19: Current Scientific Evidence

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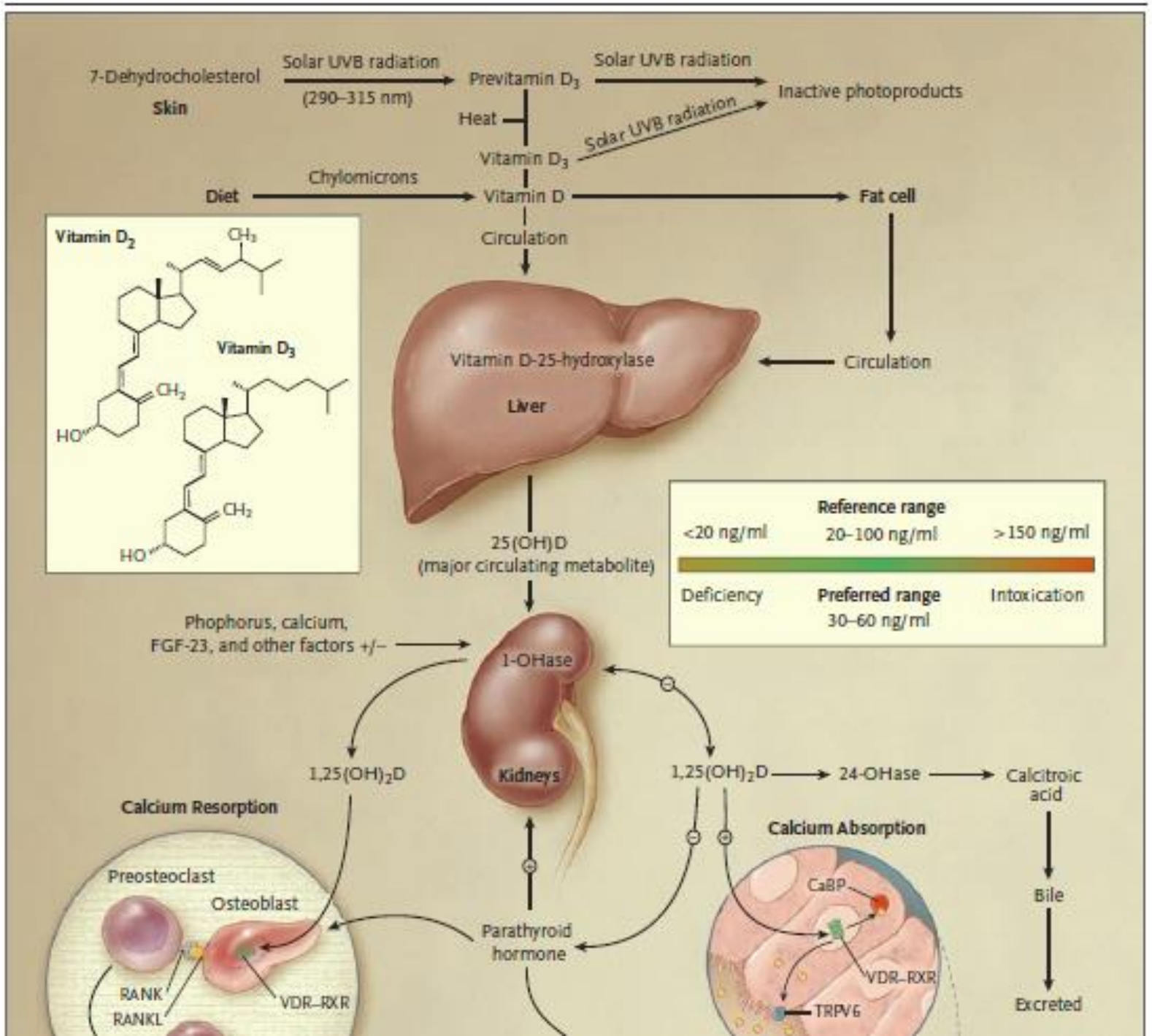
Disclosures

- The presenter has no conflict of interest
- She is a volunteer member of the following groups but is not speaking on behalf of any group:
  - Vitamin D Society
  - Vitamin D Workshop board
  - Grassrootshealth

Outline

1. Overview of Vitamin D metabolism
   - Why vitamin D deficiency is common
   - Vitamin D deficiency in Africa; in Ethiopia
2. Functions of vitamin D in inflammation and immune response
   - Innate (eg Cathelicidin) & Acquired (cytokines) Immunity
   - Lower respiratory infection prevention meta-analysis
3. How can vitamin D status prevent or mitigate covid severity?
4. What are options for ICU treatment?
5. Registered RCTs
6. Discussion



VITAMIN D:

- Make in skin (UVB)
- Can ingest as D3 or D2
  - Natural sources
  - Supplement/fortified

STORAGE:

- In fat cells
- As serum 25(OH)D
  - Transport form
  - Reflects both diet+sun
  - Half-life of 3 weeks
  - 1 ng/mL = 2.5 nmol/L

ACTIVE FORM = CALCITRIOL (1,25)

- Made in Kidney in ENDOCRINE PATHWAY
- This circulates as a “hormone”
- Most actions are as transcription factor with VDR

Holick MF (2007). Vitamin D deficiency. The New England Journal of Medicine 357(3): 266–281. PMID: 17634462

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,108,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D,[2,3,86,87] inadequate sun exposure[2,3,4,7] or supplementation[2,3,4,7])	Adequate exposure to sun or ultraviolet radiation,[7,113] 50,000 IU of vitamin D_2 every day, every other day, or every wk,† up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU of vitamin D_2 every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp),[111-114] 50,000 IU of vitamin D_2 every day or every other day‡

- **VITAMIN D Deficiency**

1. Unable to make in skin

- **Lack UVB (wrong time of day; winter)**
- **Lack sun (indoors, clothing, clouds, pollution …)**

AND

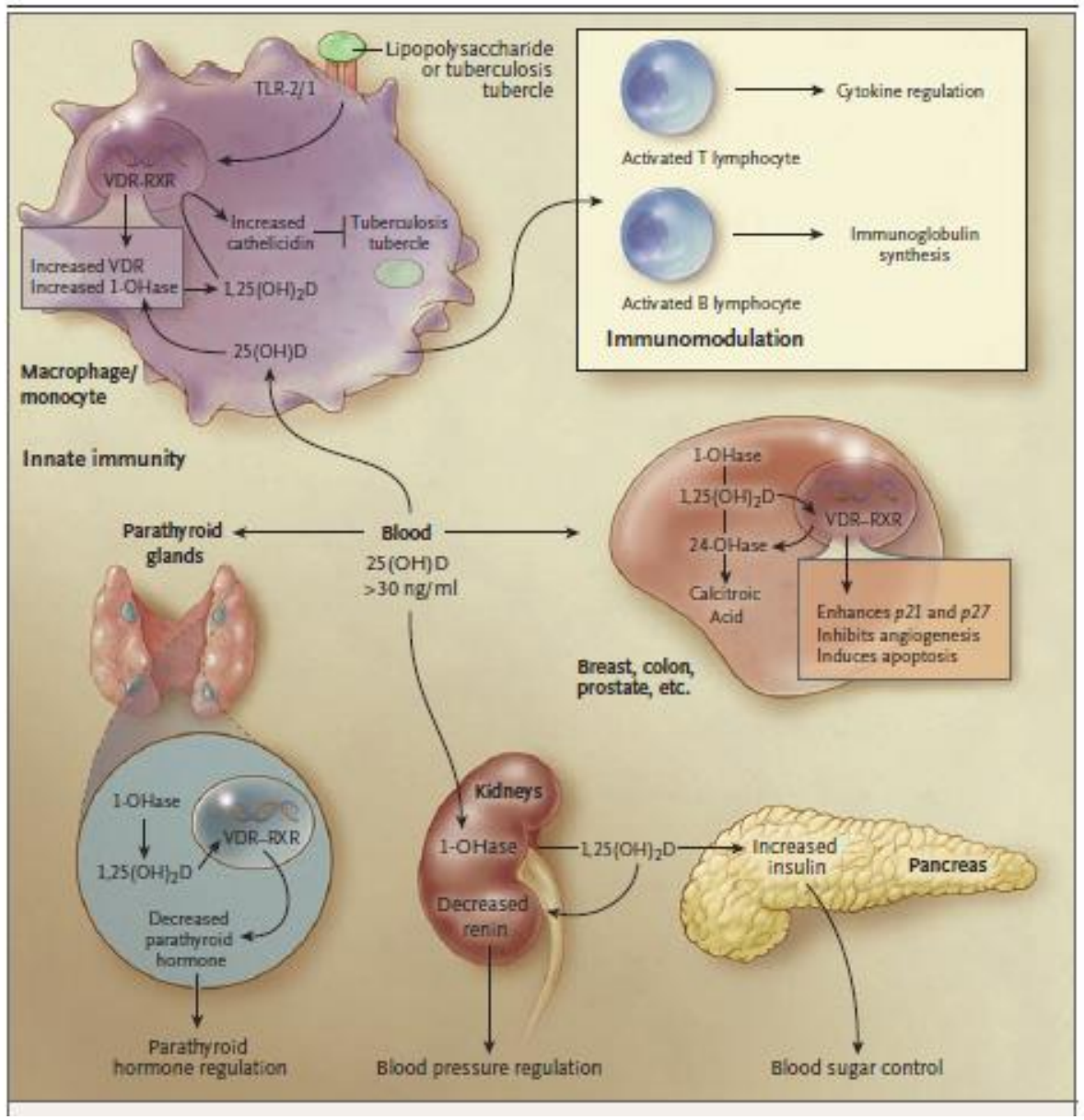
2. No dietary source

OTHER CONSIDERATIONS

e.g., malabsorption

Holick MF (2007). Vitamin D deficiency. The New England Journal of Medicine 357(3): 266–281. PMID: 17634462

PARACRINE/AUTOCRINE Pathway of vitamin D



ACTIVE FORM = CALCITRIOL (1,25)

- **Made locally in many tissues**
- **Does NOT circulates as a "hormone" - acts locally**
- **Actions are as transcription factor with VDR**
- **Here both INNATE and ACQUIRED Immunity are illustrated.**
- **Innate: synthesis of peptides (defensins) such as cathelecidin**
- **Acquired: regulation of cytokines though T Helper cells (↓ pro-Inflammatory; ↑anti-Inf**

Holick MF (2007). Vitamin D deficiency. The New England Journal of Medicine 357(3): 266–281. PMID: 17634462

Examples of Recent Discoveries Relating to Vitamin D and Immunity

References:

Martinez-Moreno J, Hernandez JC, Urcuqui-Inchima S. Effect of high doses of vitamin D supplementation on dengue virus replication, Toll-like receptor expression, and cytokine profiles on dendritic cells. *Mol Cell Biochem* 2020; 464(1-2): 169-80.

Clark K, Goldstein RL, Hart JE, et al. Plasma vitamin D, past chest illness, and risk of future chest illness in chronic spinal cord injury (SCI): a longitudinal observational study. *Spinal cord* 2020; 58(4): 504-12.

Zheng S, Yang J, Hu X, et al. Vitamin D attenuates lung injury via stimulating epithelial repair, reducing epithelial cell apoptosis and inhibits TGF-beta induced epithelial to mesenchymal transition. *Biochem Pharmacol* 2020: 113955.

Zhou Y, Dong B, Kim KH, et al. Vitamin D Receptor Activation in Liver Macrophages Protects Against Hepatic Endoplasmic Reticulum Stress in Mice. *Hepatology* 2020; 71(4): 1453-66.

Assessment of Vitamin D Status

Organization/ Country	25(OH)D nmol/L [ng/ml]	RDA or equivalent µg/d [*IU/d*]	
Public Health Focus		***20-50 y***	***>75 y***
WHO (2003)	27.5 [11]	5 [*200*]	15
IOM (2011)	50 [20]	15 [*600*]	20
Nordic (2012)	50 [20]	10[*400*]	20
DACH (2012)	50 [20]	20 [*800*]	20
Netherlands (2012)	30 [12]	10 [*400*]	20
Australia–NZ (2013)	50 [20]	15 [*600*]	20
UK (SACN 2016)	25 [10]	10 [*400*]	10
EFSA (2016)	50 [20]	15 [*600*]	15
Clinical Health Focus		***Healthy***	*At-Risk*
IOF (2010)	75 [30]	20 [*800*]	50 [*2000*]
Endocrine Soc (2011)	75 [30]	n.a.	37.5-50

Modified from Bouillon R. (2017). Comparative analysis of nutritional guidelines for vitamin D. Nature Rev Endocrinology 13(8):466-479.

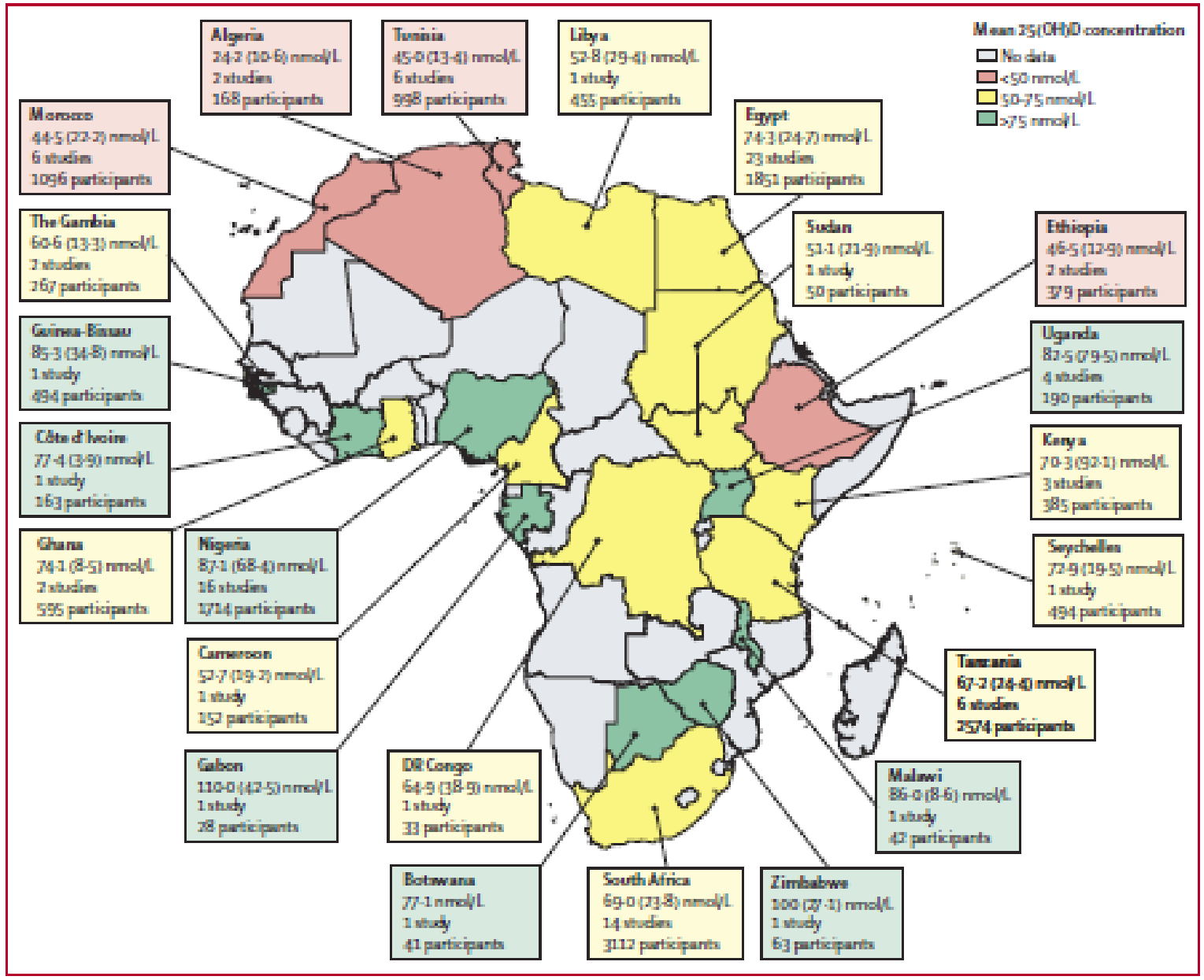


Figure 2: Mean 25(OH)D concentrations in African countries

Data are the mean (SD) 25(OH)D concentrations reported in studies done in each country. Pooled means were calculated if the country had more than one study, and were computed only from studies that stated mean (SD) 25(OH)D concentrations. Studies that reported only median concentrations are not included in this map, with the exception of Botswana, which had a single study that reported only median levels. 25(OH)D=25-hydroxy vitamin D.

VITAMIN D IN AFRICA :

Overall 20% below 50 nmol/L

- Mean levels
- RED 25(OH)D < 50 nmol/L
- Yellow 25(OH)D 50-75 nmol/L
- Green 25(OH)D >75 nmol/L

AT-RISK GROUPS

- Newborns
- Women
- Urban

Mogire RM, Mutua A, Kimita W, Kamau A, Bejon P, Pettifor JM, Adeyemo A,Williams TN and SH Atkinson Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. *Lancet Global Hlth 2020*;**8:**e134-e142.

Vitamin D status in Ethiopia

- Wayako et al. PlosOne 2015 10(3): e0120963.doi:10.1371/journal.pone.0120963
  - 25(OH)D <50 nmol/L in 42% of youth in Adama. Prevalence higher among students in **urban** setting(**62%**) compared to rural (21%) p<0.001
- Gebreegziabher & Stoecker. Food Nutr Bull. 2013;34(4):429-433.
  - Women in SNNPR with BMI = 20.0 ± 2.2. 84% of the participants < 50 nmol/L with **most < 30 nmol/L**
- Ahmed et al. Nutrients 2019, 11, 289; doi:10.3390/nu11020289
  - % female breast cancer patients in a study in TASH Addis < 50 nmol/L 86%
  - % of severe vitamin D deficiency (<25 nmol/L) **41.1**%

Review

Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections

Recommendations for Immunity

Philip C. Calder [1], Anitra C. Carr [2], Adrian F. Gombart [3] and Manfred Eggersdorfer [4,*]

Table 1. Recommended intakes of selected nutrients to support optimal immune function.

Nutrient	Rationale	Recommendation
Vitamins and trace elements	These micronutrients play important roles in supporting the cells and tissues of the immune system. Deficiencies or suboptimal status in these micronutrients negatively affect immune function and can decrease resistance to infections.	A multivitamin and trace element supplement that supplies the nutrient requirements (e.g., 100% US RDA for age and gender) [78] for vitamins and trace elements including vitamins A, B_6, B_{12}, C, D, E, and folate, and trace elements including zinc, iron, selenium, magnesium and copper. This is in addition to the consumption of a well-balanced diet.
Vitamin C	Doses of ≥200 mg/day provide saturating levels in the blood, and support reduction in the risk, severity and duration of upper and lower respiratory tract infections. Requirements for vitamin C increase during infection.	Daily intake of at least 200 mg/day for healthy individuals. In individuals who are sick, 1–2 g/day is recommended.
Vitamin D	Daily supplementation of vitamin D reduces the risk of acute respiratory tract infections.	Daily intake of 2000 IU/day (50 µg/day).
Zinc	Marginal zinc deficiency can impact immunity. Those deficient in zinc, particularly children, are prone to increased diarrheal and respiratory morbidity.	Daily intake in the range of 8–11 mg/day.
Omega-3 fatty acids (EPA + DHA)	Omega-3 fatty acids support an effective immune system, including by helping to resolve inflammation.	Daily intake of 250 mg/day of EPA + DHA.

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

- 25 eligible RCTs (total 11321 participants, aged 0 - 95 y)
- The primary outcome of the meta-analysis was incidence of acute respiratory tract infection: upper, lower and acute respiratory tract infection of unclassified location
- MAIN finding: significant reduction in proportion of participants experiencing at least one **acute respiratory tract infection** (adjusted odds ratio 0.88, 95% CI 0.81 to 0.96, P=0.003; NNT=33).
- Daily and weekly D >> than bolus
- Baseline 25(OH)D is important modifier: NNT = 8 for baseline < 25 nmol/L

Martineau et al., 2017. the bmj | BMJ 2017;356:i6583 | doi: 10.1136/bmj.i6583

Review

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

Table 1. Results of vitamin D randomized controlled trials (RCTs) on risk of influenza.

Country	Population	Baseline 25(OH)D (ng/mL)	Vitamin D Dose (IU/d)	Influenza Cases in Vitamin D, Placebo Arms	Outcome	Ref
Japan	Schoolchildren aged 6–15 yrs	N/A	0, 1200	Type A: 18/167; 31/167. If not taking vitamin D before enrollment: 8/140; 22/140. Type B: 39/167; 28/167	Type A: RR = 0.58 (95% CI, 0.34 to 0.99); if not taking vitamin D before enrollment, RR = 0.36 (95% CI, 0.17 to 0.79); no effect for Type B	[52]
Japan	High school students, including many vaccinated against influenza	N/A	0, 2000	20/148; 12/99	Type A, RR = 1.11 (95% CI, 0.57 to 2.18)	[54]
China	Infants, 3–12 mos	17	400, 1200		Diff. in influenza A viral load, high vs. low vitamin D on day 4 of illness: 1.3 ± 0.5 vs. $4.5 \pm 1.4 \times 10^6$ copies/mL	[53]
Japan	223 patients with IBD, mean age 45 yrs	23–24	0, 500	8/115; 6/108	RR = 1.25 (95% CI, 0.45 to 3.49)	[55]
Vietnam	Children aged 3–17 yrs	26	0, 14,000 /wk	50/650; 43/650	HR = 1.18 (95% CI, 0.79 to 1.78)	[56]

Note: 95% confidence interval (95% CI); day (d); hazard ratio (HR); inflammatory bowel disease (IBD); months (mos); not available (N/A); relative risk (RR); upper respiratory tract infection (URTI); week (wk); years (yrs).

PRE-COVID

RCTs with vitamin D have been conducted

- **Doses vary**
- **1200 IU (30 µg/d)**
- **Below UL (100 µg = 4000 IU)**
- **Baseline may predict outcome**

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JA, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020, *12*, 988. doi: 10.3390/nu12040988. Review. PubMed PMID: 32252338.

Mechanisms for Covid-19 and immunity

- **COVID-19** rapidly replicates efficiently in the upper respiratory tract, and has clinical features of cough, sore throat, fatigue, GI symptoms and potential for coagulation (stroke)
- **Viral infections** are first blocked by **innate** immunity through induction by calcitriol of peptides (defensins) such as Cathelicidin – natural antivirals capable of preventing the virus from replicating and entering a cell. Also there may be induction of autophagy and synthesis of reactive N or O intermediates
- **Viral infections** are purged by **acquired** immunity with activation of cytotoxic T cells
  - The pro-inflammatory cytokines IL-6 and IL-10 are elevated and there are lower levels of CD4+T and CD8+T parallel to severity of COVID-19
  - Vitamin D suppresses pro-inflammatory cytokines: **Cytokine storm** is rapidly produced in innate response and continues by T Helper cells contributing to acute respiratory distress syndrome (ARDS) and organ dysfunction syndrome (MODS).
- Unusual for covid-19 is **coagulopathy**. Calcitriol exerts anticoagulant effects by upregulating the expression of thrombomodulin and downregulating the expression of tissue factor (a critical coagulation factor) in monocytes and human aortic smooth muscle cells

Hypponen E. Does vitamin D protect against coronavirus? The Conversation. May 21, 2020. + Lau et al Preprint

Prevention Studies

- Investigator-initiated studies by clinicians
- Most are preprints of covid; others look at corona virus such as SARS
- Relate severity of covid-19 outcomes to 25(OH)D. Most do not adjust for confounders
- Samples are small.
- YET – many relate to known published mechanisms of vitamin D and immunity
- ALL articles available from EPHI

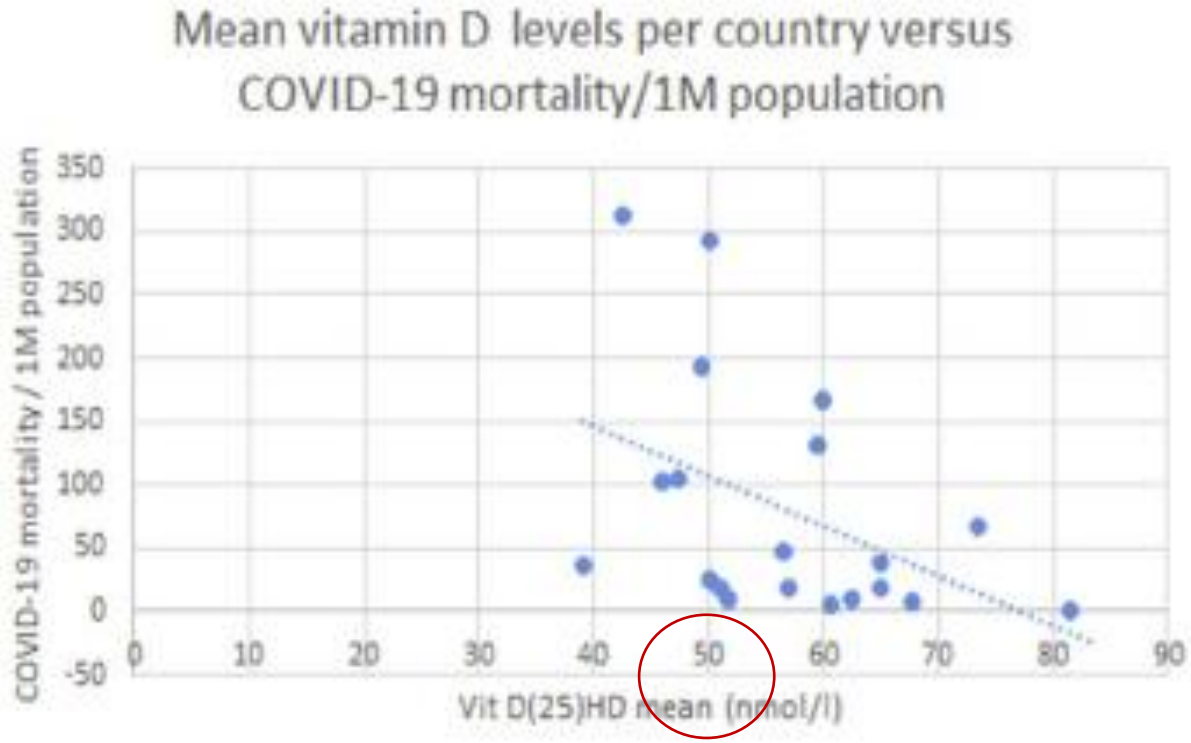
Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-020-01570-8

SHORT COMMUNICATION

The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality

Petre Cristian Ilie[1] · Simina Stefanescu[2] · Lee Smith[3]

Negative correlations between mean 25(OH)D in each of 20 European countries and number of COVID-19 cases/1 M (mean 295.9 and mortality/1M (mean 5.9) were observed.



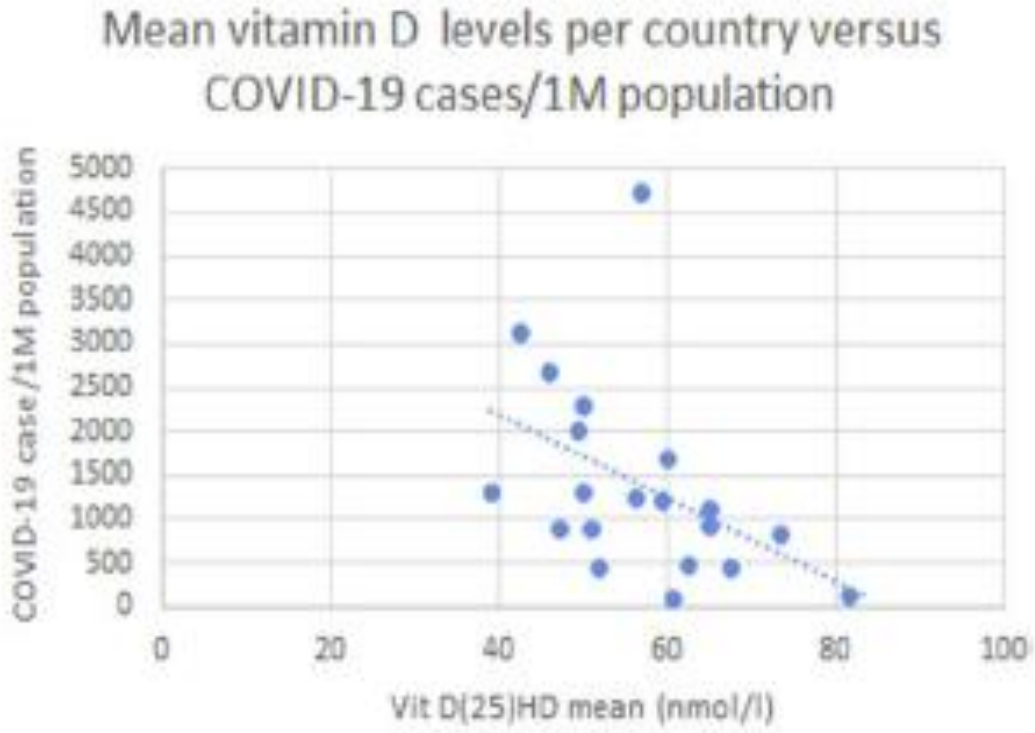


Fig. 1 Mean vitamin D levels per courtry versus COVID-19 cases and mortality/1M population

USA New Orleans

- Medical records of 20 COVID-19 patients between March 27, 2020 and April 21, 2020; New Orleans

	Overall (n=20)	ICU (n=13)	Floor (n=7)	p-value
Demographics				
Age (years)	65.2 ± 16.2	61.5 ± 15.7	72.0 ± 14.8	0.19
Male	9 (45.0%)	8 (61.5%)	1 (14.3%)	0.07
African American	15 (75.0%)	11 (84.6%)	4 (57.1%)	0.29
BMI	31.4 ± 9.3	35.2 ± 7.6	24.5 ± 8.3	0.02
Comorbidities				
Hypertension	15 (75.0%)	10 (76.9%)	5 (71.4%)	1.00
Diabetes	7 (35.0%)	6 (46.2%)	1 (14.3%)	0.33

VDI Metrics	Reference Range				
VDI		15 (75.0%)	11 (84.6%)	4 (57.1%)	0.29
Serum 25OHD (ng/mL)	30.0 - 100.0	22.9 ± 12.8	19.2 ± 10.8	29.8 ± 13.3	0.12
Lowest Platelet Count (10^3/uL)	130 - 400	191.7 ± 74.4	201.0 ± 79.8	174.3 ± 59.2	0.44
Absolute Lymphocyte Count (10^3/uL)	1.10 - 5.00	0.55 ± 0.51	0.42 ± 0.32	0.80 ± 0.69	0.16

- VitDInsuff (VDI) = serum 25OHD < 30 ng/mL {75nmol/L}

- **Patients were low in vitamin D**
- **Risk factors correlate, e.g. obese are low in D**
- **Coagulopathy: VDI induces a prothrombotic state**

Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, Cirillo JD, Greiffenstein P.Vitamin D insufficiency is prevalent in severe COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.04.24.20075838.

Brief Report

25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2

Nutrients **2020**, 12, 1359; doi:10.3390/nu12051359

Antonio D'Avolio [1,*], Valeria Avataneo [1], Alessandra Manca [1], Jessica Cusato [1], Amedeo De Nicolò [1], Renzo Lucchini [2], Franco Keller [2] and Marco Cantù [2]

25-hydroxyvitamin D (25(OH)D) concentrations in plasma obtained from a cohort of patients from Switzerland. In this cohort, significantly lower 25(OH)D levels ($p = 0.004$) were found in PCR-positive for SARS-CoV-2 (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL); this was also confirmed by stratifying patients according to age >70 years. On the basis of this

50 nmol/L

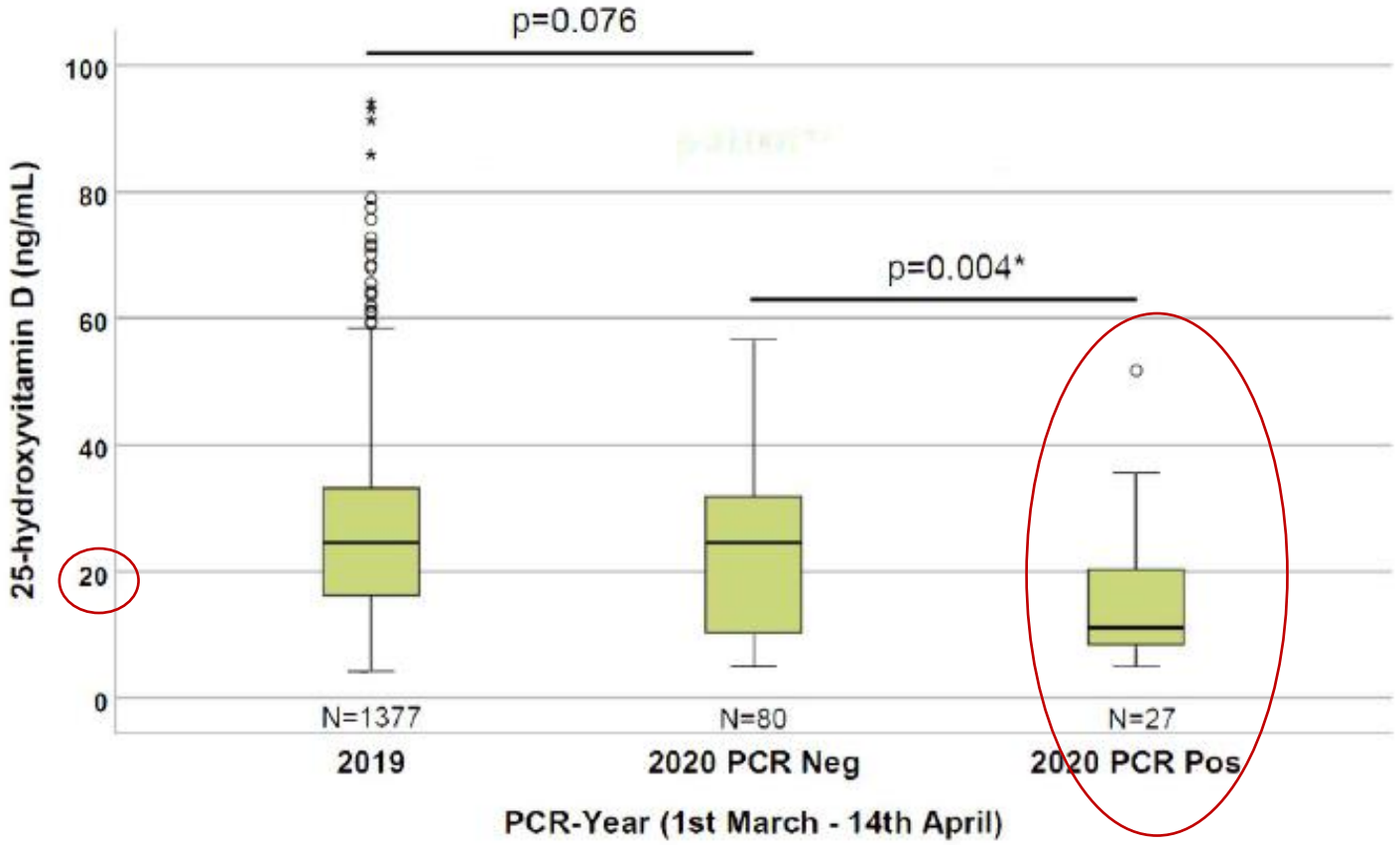


Figure 1. 25-hydroxyvitamin D concentrations in the three evaluated groups (patients from 1 March to 14 April of 2019 and 2020 with a negative PCR, and of 2020 with a positive PCR for SARS-CoV-2. *: significant results.

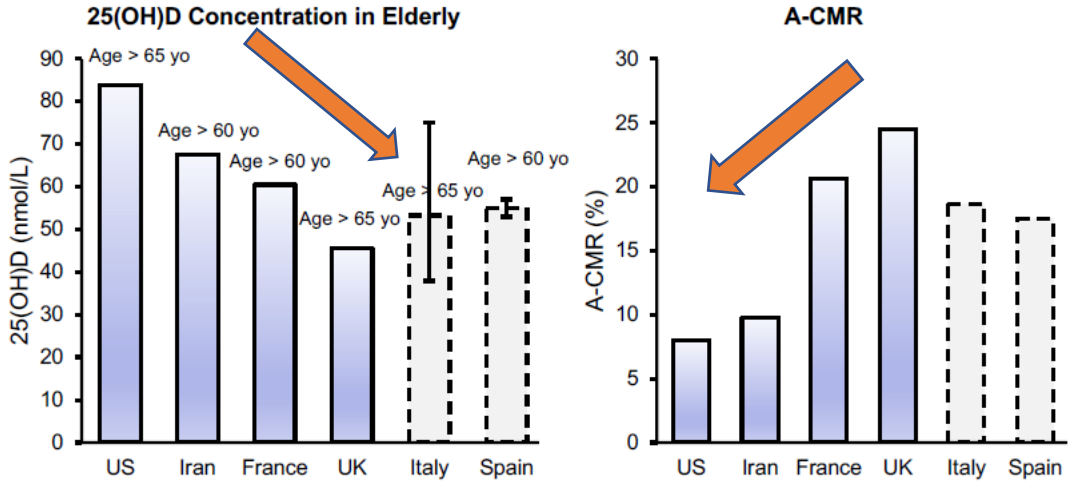
PCR Pos patients Median age 73y << 50 nmol/L

VITAMIN D & Cytokine Storm MORTALITY

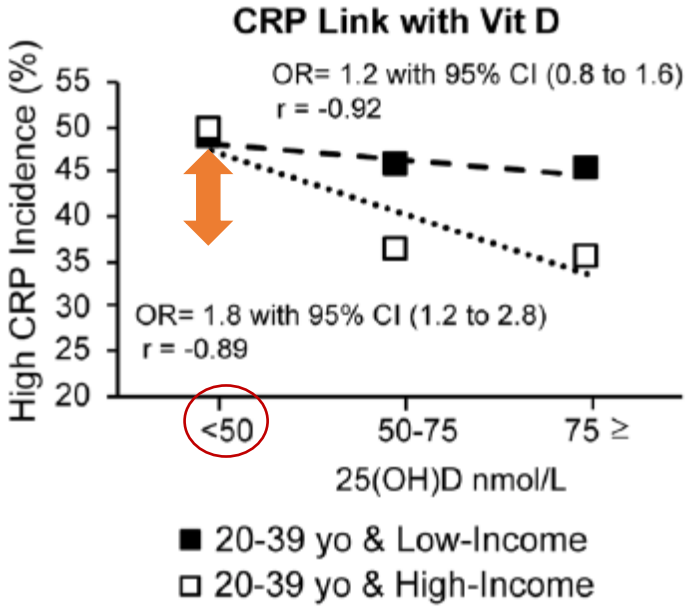
- The time-adjusted case mortality ratio (T-CMR) was estimated as the number of deceased patients on day N divided by # confirmed cases on day N-8.
- Mean 25(OH)D) in elderly in countries with similar screening strategies were compared to investigate the potential impact of Vit D on average T-CMR (**A-CMR**).
- Daily admission, recovery and deceased rate data for patients with COVID-19 were collected from Kaggle as of April 20, 2020. **Country data**
- The correlation between Vit D and CRP was calculated based on Subject-level data from NHANES, 2009-2010.

RESULTS

- A link between 25(OH)D and A-CMR in the US, France, Iran and the UK (similar screening) may exist.
- Inverse correlation (r: -0.84 to -1) between high CRP and 25(OH)D.



CRP Is a surrogate marker for cytokine storm



Daneshkhah A, V Agrawal, A Eshein, H Subramanian, HK Roy, V Backman. The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients. medRxiv PREPRINT

Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-2019)

Mark M. Alipio

Using the database of three hospitals in Southern Asian countries, a retrospective multicentre study of 212 cases with laboratory-confirmed infection of SARS-CoV-2 was conducted. Data pertaining to clinical features and serum 25(OH)D levels were extracted from the medical records. No other patient information was provided to ensure confidentiality.

Vitamin D status of the cases were also classified based on their serum 25(OH)D level: (1) normal - 25(OH)D of > 30 ng/ml, (2) insufficient - 25(OH)D of 21-29 ng/ml, and (3) deficient - 25(OH)D of < 20 ng/ml. A previous report guided this classification.[10] All data pertaining to the serum

Table 1. Descriptive statistics

Variables	Overall N (%)	Clinical Outcomes				
		Mild	Ordinary	Severe	Critical	p-value
Overall N (%)	212 (100.0)	49 (23.1)	59 (27.8)	56 (26.4)	48 (22.6)	
Serum 25(OH)D, ng/ml	23.8	31.2 ± 1.08	27.4 ± 2.14	21.2 ± 1.12	17.1 ± 2.39	<0.001
Vitamin D status						
Normal	55 (25.9)	47 (85.5)	4 (7.3)	2 (3.6)	2 (3.6)	<0.001
Insufficient	80 (37.7)	1 (1.3)	35 (43.8)	23 (28.8)	21 (26.3)	
Deficient	77 (36.3)	1 (1.4)	20 (26.0)	31 (40.3)	25 (32.5)	

Table 2. Multinomial logistic regression analysis

Predictor	Mild	OR	p-value
Serum 25(OH)D, ng/ml	Ordinary	0.614	0.007
	Severe	0.126	<0.001
	Critical	0.051	<0.001

212 cases in Asia:
Mild cases 25OHD > 75 nmol/L
Critical cases 25OHD < 50 nmol/L;
Significant odds ratio for prediction of severity

Established 1887

Issue: Ir Med J; Vol 113; No. 5; P84

Vitamin D Deficiency and ARDS after SARS-CoV-2 Infection

J.L. Faul[1], C.P. Kerley[1], B. Love[2], E. O'Neill[3], C. Cody[4], W. Tormey[5], K. Hutchinson[6], L.J. Cormican[1], C.M. Burke[1]

Following institutional review board approval and informed consent from participants, we analyzed serum 25OHD levels in 33 adult, male, Caucasian patients, over the age of 40 years, who were admitted to Connolly Hospital Blanchardstown for SARS-CoV-2 related pneumonia (four quadrant infiltrates on chest radiograph, with respiratory failure requiring FiO_2 greater than 0.4, with SARS-CoV-2 detectable by RT-PCR of nasopharyngeal swab) during March 2020. None had cancer, diabetes mellitus, cardiovascular disease, or had received chronic immunosuppressive therapy. Twelve progressed to ARDS and required intubation and mechanical ventilation. There were four deaths after mechanical ventilation (at days 3, 6, 7, and 15) in the ARDS group and none in the non-ARDS group. Overall, the twelve patients who progressed to ARDS (mean age 60 years, SD 15) had a lower serum 25OHD level on presentation to hospital (*mean* = 27, *SD* = 12 $nmol.l^{-1}$), compared to the twenty one patients hospitalized with less severe pneumonia who did not progress to ARDS (mean age 56 years, SD 14). Their 25OHD level was 41 $nmol.l^{-1}$ (*SD*

Treatment

- Paper relating to using vitamin D in ICU:
  - Amrein K, A Papinutti, E Mathew, G Vila and D Parekh.. Endocrine Connections (2018) 7, R304–R***Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa***315
- Some examine how an intervention can raise 25(OH)D levels from < 50 nmol/L to > 100 nmol/L

ICU Studies of Quickly Raising 25(OH)D

Author, Journal, Year	Design Population	No of patients	Intervention	Outcomes
Completed trials				
Amrein K, *Critical Care*, 2011 Graz, Austria (49)	RCT Medical ICU, 25OHD <20 ng/mL	25	1 × 540,000 IU D_3, enteral vs placebo	Normalization of vitamin D levels in most patients, no adverse events; no difference in 28-days mortality or length of stay
Amrein K, *JAMA*, 2014 Graz, Austria (50)	RCT Mixed ICU, 25OHD <20 ng/mL	475	1 × 540,000 IU D_3, enteral, then 5 × 90,000 IU D_3/month vs placebo	No difference in hospital length of stay, overall no significant mortality benefit, but large and significant mortality benefit in the predefined subgroup with severe vitamin D deficiency (25OHD) <12
Quraishi S, *Critical Care Medicine*, 2015 Boston, USA (51)	RCT ICU, sepsis	30	1 × 200,000 IU D_3, enteral or 1 × 400,000 IU D_3, enteral vs placebo	Rapid correction of vitamin D deficiency, increase in LL-37 compared to the placebo group
Han JE, *Journal of Clinical and Translational Endocrinology*, 2016, *Nutrition*, 2017 Atlanta, USA (52)	RCT ICU, mechanically ventilated	30	5 × 50,000 IU D_3, enteral or 5 × 100,000 IU D_3, enteral vs placebo	Shorter hospital stay, dose dependent increase of vitamin D levels and increased hCAP18 mRNA-expression compared to the placebo group
Alizadeh N, *International Journal of Clinical Practice*, 2016 Teheran, Iran (86)	RCT Surgical ICU, stress-induced hyperglycemia	50	600,000 IU D3, IM vs placebo	25OHD levels increased significantly in the vitamin D group at day 7, fasting plasma adiponectin levels increased significantly in the vitamin D group, but not the placebo group
Miroliaee AE, *Iranian Journal of Pharmaceutical Research*, 2017 Teheran, Iran (87)	RCT ICU, ventilator associated pneumonia 25OHD <30 ng/mL	46	300,000 IU D3, IM vs placebo	PCT levels significantly lower in the vitamin D group compared to placebo group, no significant difference in SOFA score between groups, mortality rate of patients in the vitamin D group was significantly lower than in the placebo group

Amrein K, A Papinutti, E Mathew, G Vila and D Parekh. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. Endocrine Connections (2018) 7, R304–R315

Recommendations for Adjuvant Use of Vitamin D

In summary, given the high prevalence of vitamin D deficiency and in order to rapidly, safely, and significantly raise serum concentrations, high-dose vitamin D intervention with potential benefit in decreasing risk of COVID-19 severity and mortality is suggested, which is a safe and noninvasive treatment. Patients would take large doses of vitamin D for a week, followed by several thousand IU/d vitamin D for a period of 2 weeks. This will provide a quick and sustainable restoration of serum vitamin D levels, thus, potentially triggering an improvement in clinical status and prognosis. However, prospective clinical studies are required to address this speculation and overcome the obstacles in our current understanding of vitamin D role as an adjuvant therapy in patients with COVID-19.

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PERSPECTIVE

Nutrition in acute and chronic diseases

Perspective: improving vitamin D status in the management of COVID-19

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Registered Trials on Vitamin D and Covid-19

- Clinicaltrials.gov search: 19 registered by May 27, 2020
  - Lau (New Orleans preprint) – coagulopathy related
- Many well known D researchers have expressed interested in starting trials:
  - Joanne Manson (Harvard PI of VITAL study) recommends 2000 IU/d [50 µg/d]
  - Michael Holick
  - Bruce Hollis

Conclusions

1. Overview of Vitamin D metabolism
   - Both **Endocrine** and **Paracrine/Autocrine** pathways
   - Population 25(OH)D should be **> 50 nmol/L** (20 ng/ml)
   - Vitamin D deficiency is common in Ethiopia
     - Most at risk are **women** and **persons in urban areas**
2. Functions of vitamin D in inflammation and immune response
   - Innate and Acquired immunity
   - Acute Lower respiratory infection prevention [meta-analysis]
   - Biologically plausible
3. How vitamin D status affects covid-19 outcomes
   - Prevention is population initiative; reduction in severity by aggressive treatment is patient-oriented
4. Discussion

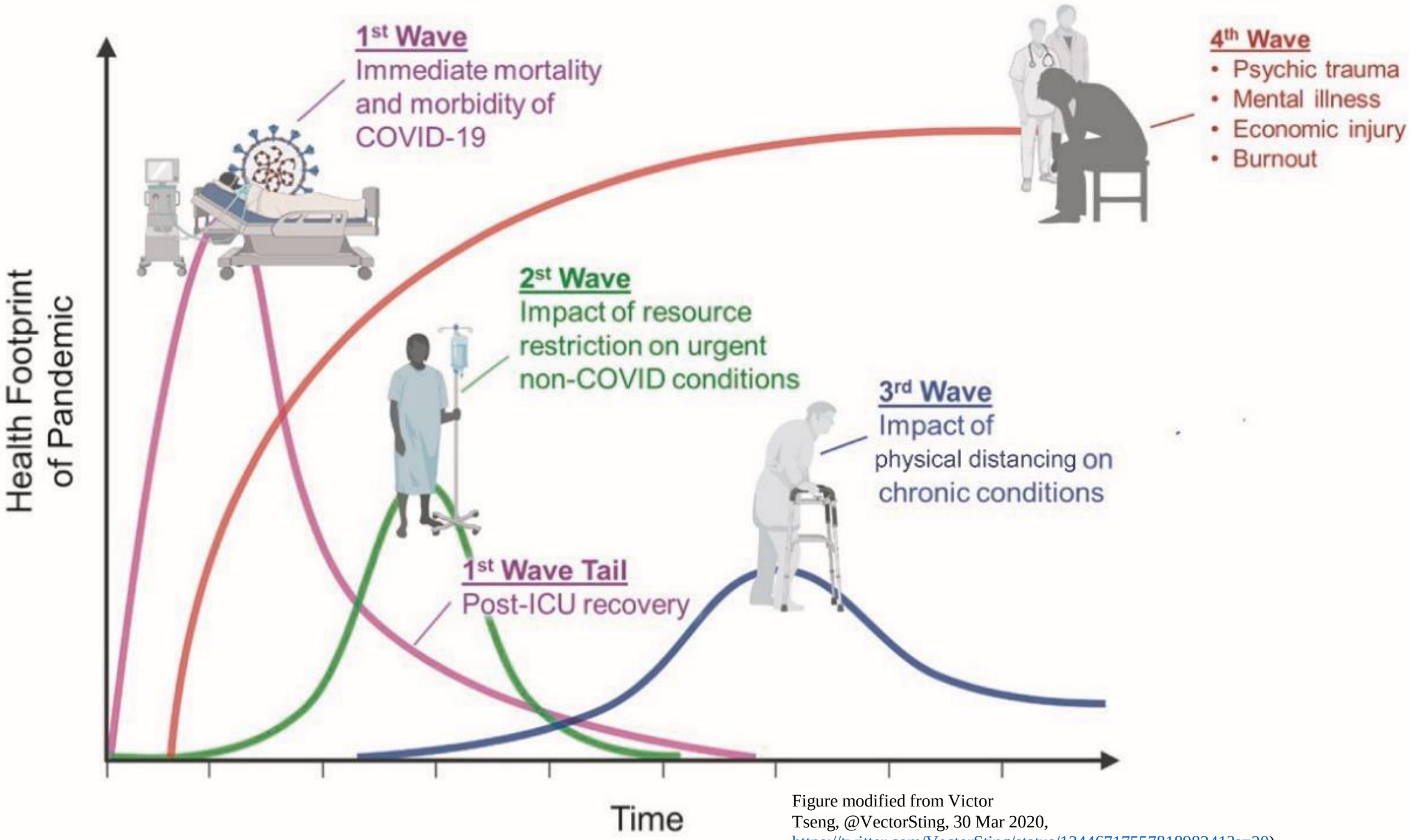


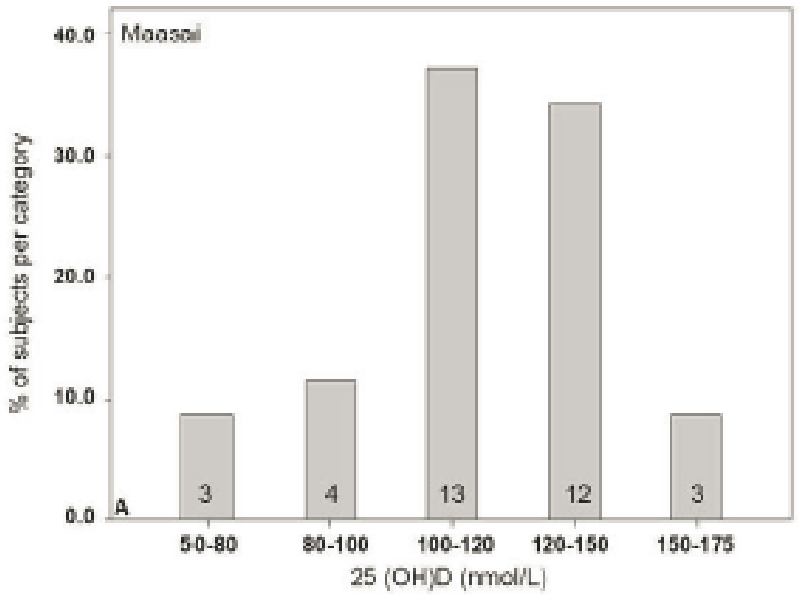
Figure modified from Victor Tseng, @VectorSting, 30 Mar 2020, https://twitter.com/VectorSting/status/1244671755781898241?s=20)

Getting all vitamin D from sun

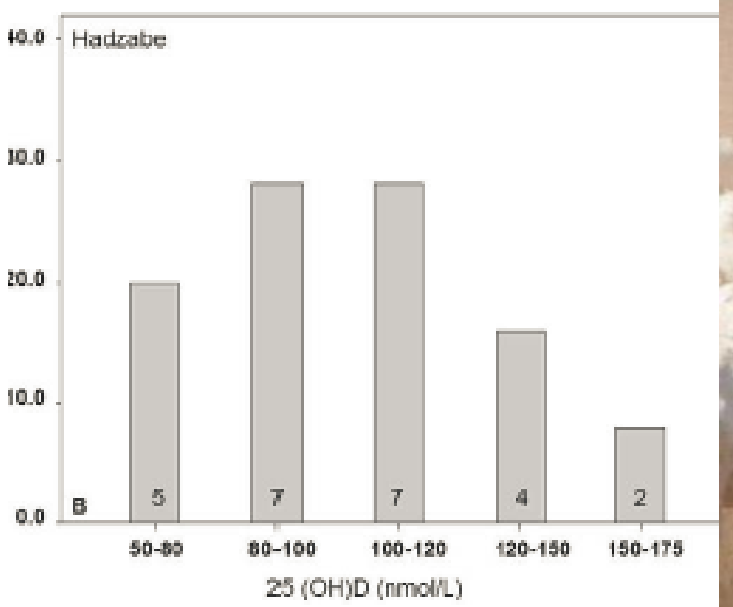
People living and working outside in Equatorial East Africa

no one < 50 nmol/L

Maasai (n = 35)



Hadzabe (n = 25)



Luxwolda et al. Br J Nutr 2012

Getting most vitamin D from diet

People living in Arctic areas eating a traditional diet

no one < 50 nmol/L

SEA MAMMALS	mcg (IU)
Hooded seal blubber (100 g)	16 (640)
Harp seal blubber (100 g)	2.9 (116)
FISH	
Halibut, Greenland, raw (100 g)	27.4 (1096)
Autumn mackerel (100 g)	12.5 (500)
Sockeye salmon (100 g)	16.7 (668)
Salmon, canned (85 g)	9.9 – 16.2 (396 – 649)