Vitamin D and COVID-19: Update, November 25, 2020

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Disclosure

- I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR), a supplier of research-grade vitamin D at low cost.
- I also work closely with two vitamin D-advocacy organizations:
  - GrassrootsHealth.net
  - VitaminDWiki.com

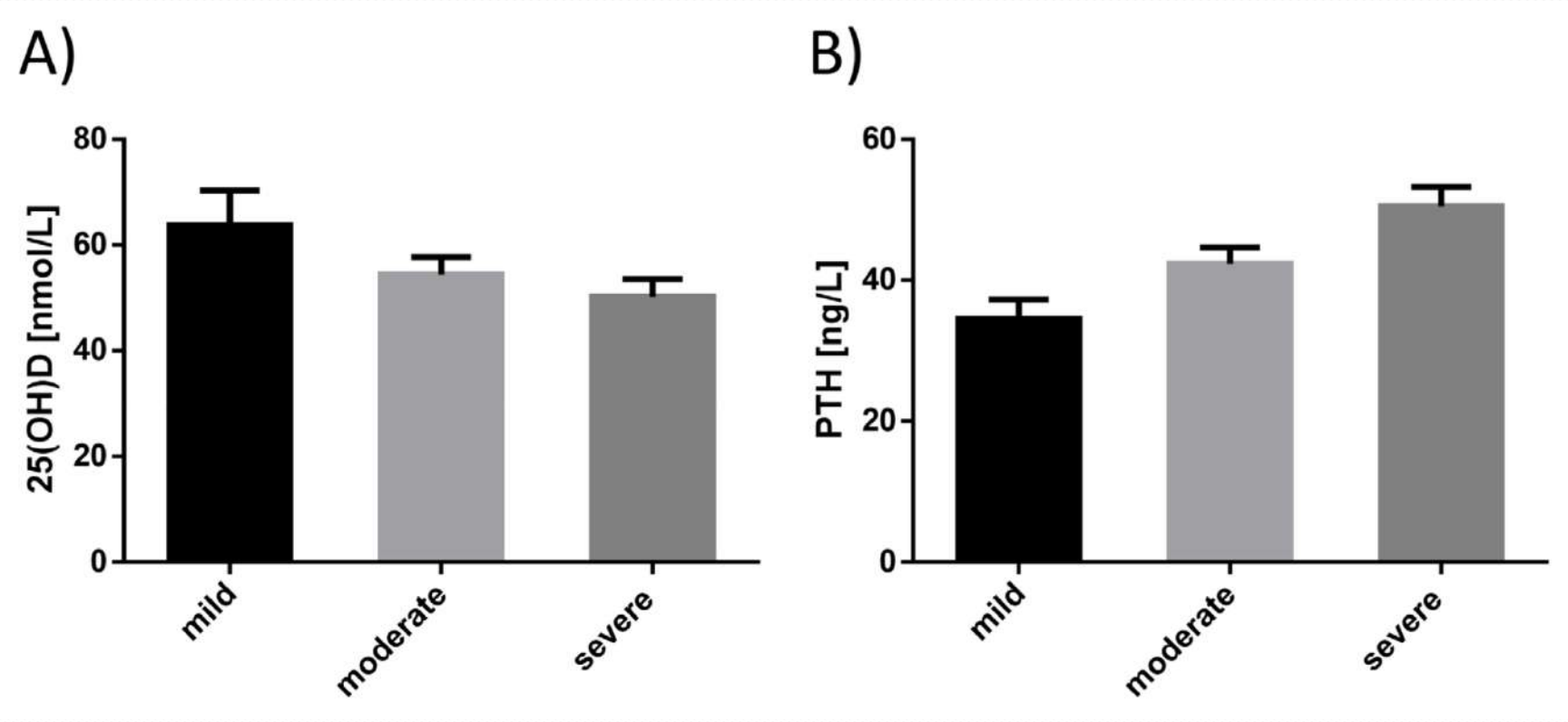
Outline

- Observational studies of COVID-19 and 25(OH)D
- 2 “Quasi-experimental” studies of vitamin D supplementation of COVID-19 patients
- 2 RCTs of vitamin D treatment of COVID-19
- Mechanisms of vitamin D in reducing COVID-19 risk
- SARS-CoV-2 seropositivity with respect to 25(OH)D
- Racial disparities of seropositivity related to 25(OH)D
- Age effects on COVID-19 deaths
- Seasonality of viral infections that peak in winter
- Recommendations for vitamin D re COVID-19
- For more information

Observational Studies of COVID-19 with Respect to serum 25(OH)D

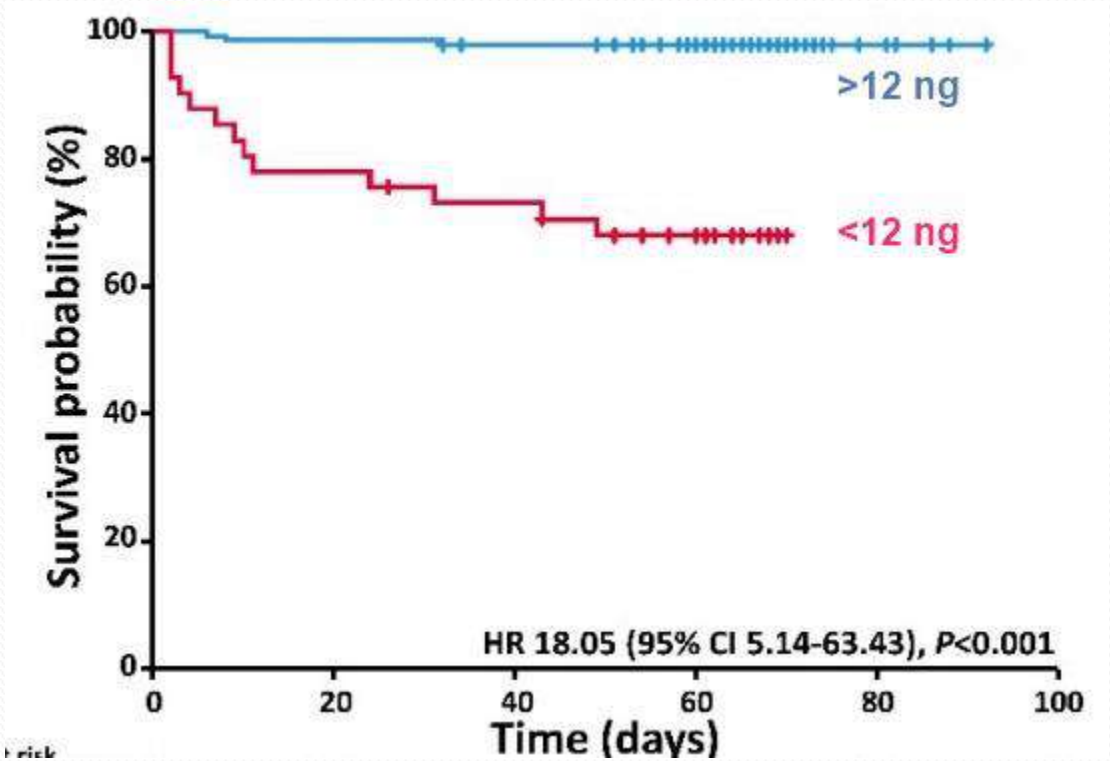
- To date there have been at least 15 reports of COVID-19 with respect to serum 25(OH)D concentration.
- Most have reported inverse correlations of COVID-19 risk, severity and/or death with respect to serum 25(OH)D concentration.
- In general:
  - Death: 25(OH)D <10 ng/mL (25 nmol/L)
  - Severe disease: 25(OH)D <20 ng/mL
  - Moderate disease: 20 ng/ml <25(OH)D <30 ng/mL
  - Mild disease: 25(OH)D >30 ng/mL

25(OH)D vs. Severity in Austria for 109 COVID-19 Patients aged 58 ± 14 years



Pizzini et al., *Nutrients* **2020**, *12*(9), 2775

Much More Likely to Die of COVID-19 if 25(OH)D <12 ng/ml (30 nmol/L)



Based on 185 Patients aged 50-70 years in Germany

HR 15 (95% CI 4–52, $p < 0.001$)

Nutrients 2020, 12(9), 2757; https://doi.org/10.3390/nu12092757

Quasi-Experimental Study

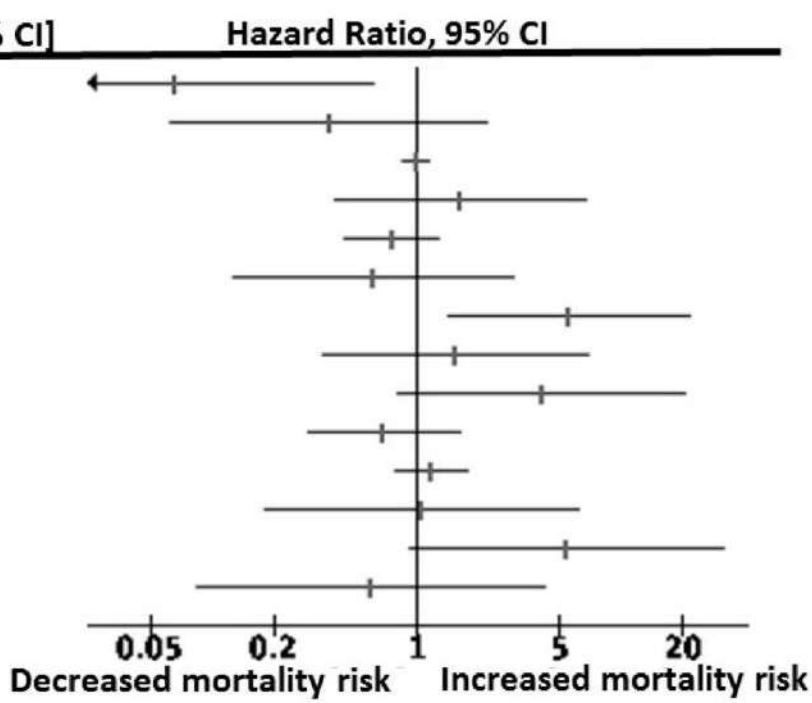
- Population: 66 residents of a nursing home in France with recently diagnosed COVID-19; mean age 88±9 yrs.
- Intervention: 57 had received 80,000 IU vitamin D the previous month or within one week after diagnosis of COVID-19.
- Outcome: During follow up of 36±17 days, 83% of supplemented residents survived; only 44% of comparator group (N = 9) survived; aHR = 0.11 (95% CI, 0.03 to 0.48, p=0.003).
- Annweiler et al. JSBMB
- https://doi.org/10.1016/j.jsbmb.2020.105771

Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study

- An observational study in France.
- 77 patients consecutively hospitalized for COVID-19 in a geriatric unit were included. Intervention groups were participants regularly supplemented with vitamin D over the preceding year [50,000 IU/month vitamin D3 or 80k-100k every 2-3 months (Group 1)], and those supplemented with 50,000 IU vitamin D_3 after COVID-19 diagnosis (Group 2). There was also a comparator group not supplemented with vitamin D.

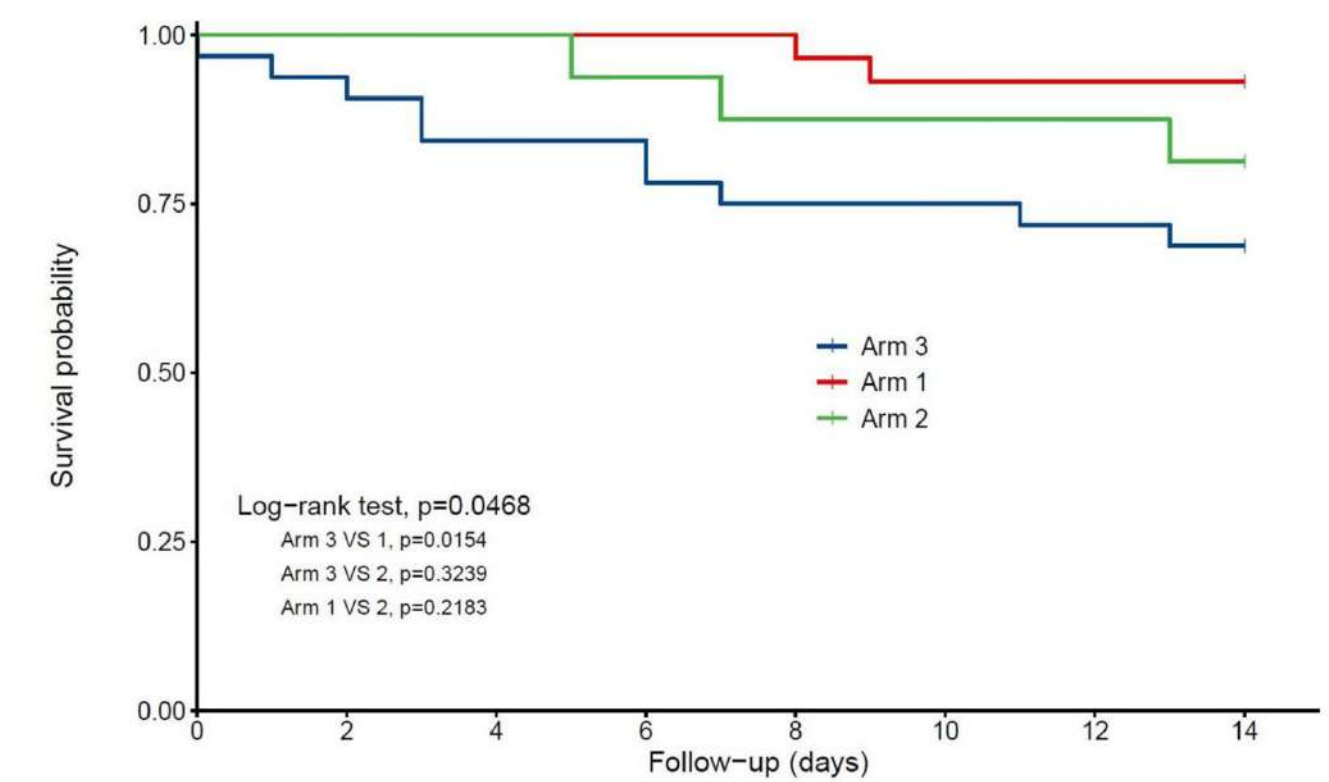
Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: 14-day outcomes

Characteristics	Hazard Ratio [95% CI]
Group 1: regular vitamin D supplementation*	0.07 [0.01;0.61]
Group 2: recent vitamin D supplementation*	0.37 [0.06;2.21]
Age	0.99 [0.85;1.15]
Female gender	1.63 [0.39;6.75]
GIR score	0.75 [0.44;1.27]
Severe undernutrition†	0.61 [0.13;2.93]
History of cancer	5.56 [1.42;21.90]
History of hypertension	1.54 [0.35;6.85]
History of cardiomyopathy	4.04 [0.81;20.30]
Glycated hemoglobin	0.69 [0.29;1.62]
Number of acute health issues	1.16 [0.77;1.75]
Use antibiotics‡	1.06 [0.18;6.26]
Use systemic corticosteroids	5.42 [0.92;31.74]
Use treatments of respiratory disorders‖	0.60 [0.09;4.18]



Compared to the non-supplemented group, adjusted for age, gender and GIR score (a measure of functional ability)

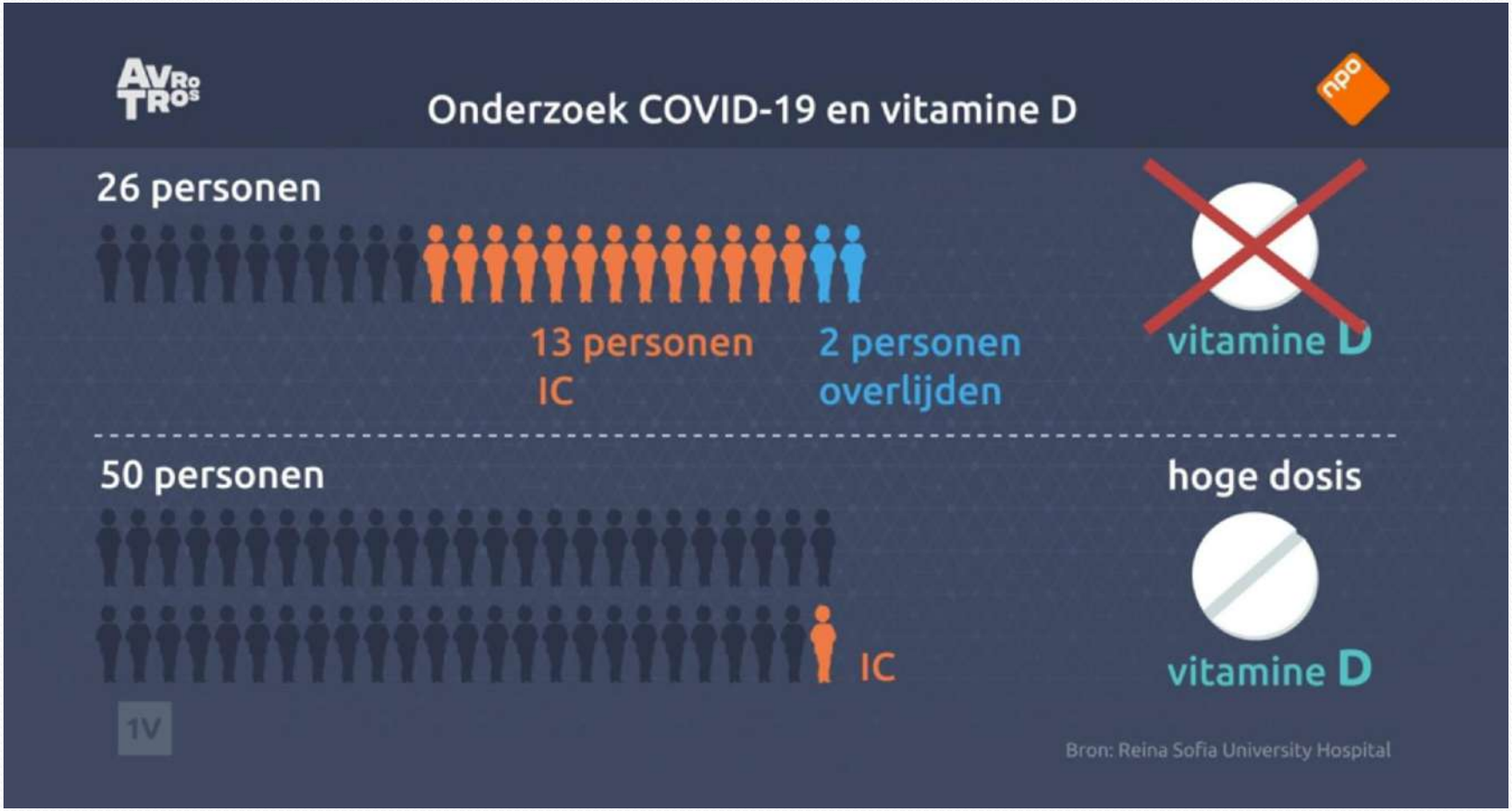
Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: Kaplan-Meier estimates



"Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on ICU Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study"

- All hospitalized patients (76) received as best available therapy the same standard care of a combination of hydroxychloroquine and azithromycin. Eligible patients (50) were allocated to take oral calcifediol (0.532 mg), or not. Patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission.
- (Calcifediol is 25(OH)D_2 and week one treatment: 130,000 IU vitamin D_2. Calcifediol acts faster that vitamin D by a day or two due to bypassing conversion in the liver.)
- Entrenas Castillo et al. J Steroid Biochem Mol Biol. 2020 Oct;203:105751 doi: 10.1016/j.jsbmb.2020.105751. Epub 2020 Aug 29.

Results of the Pilot Randomized Clinical study – Entrenas Castillo et al., 2020



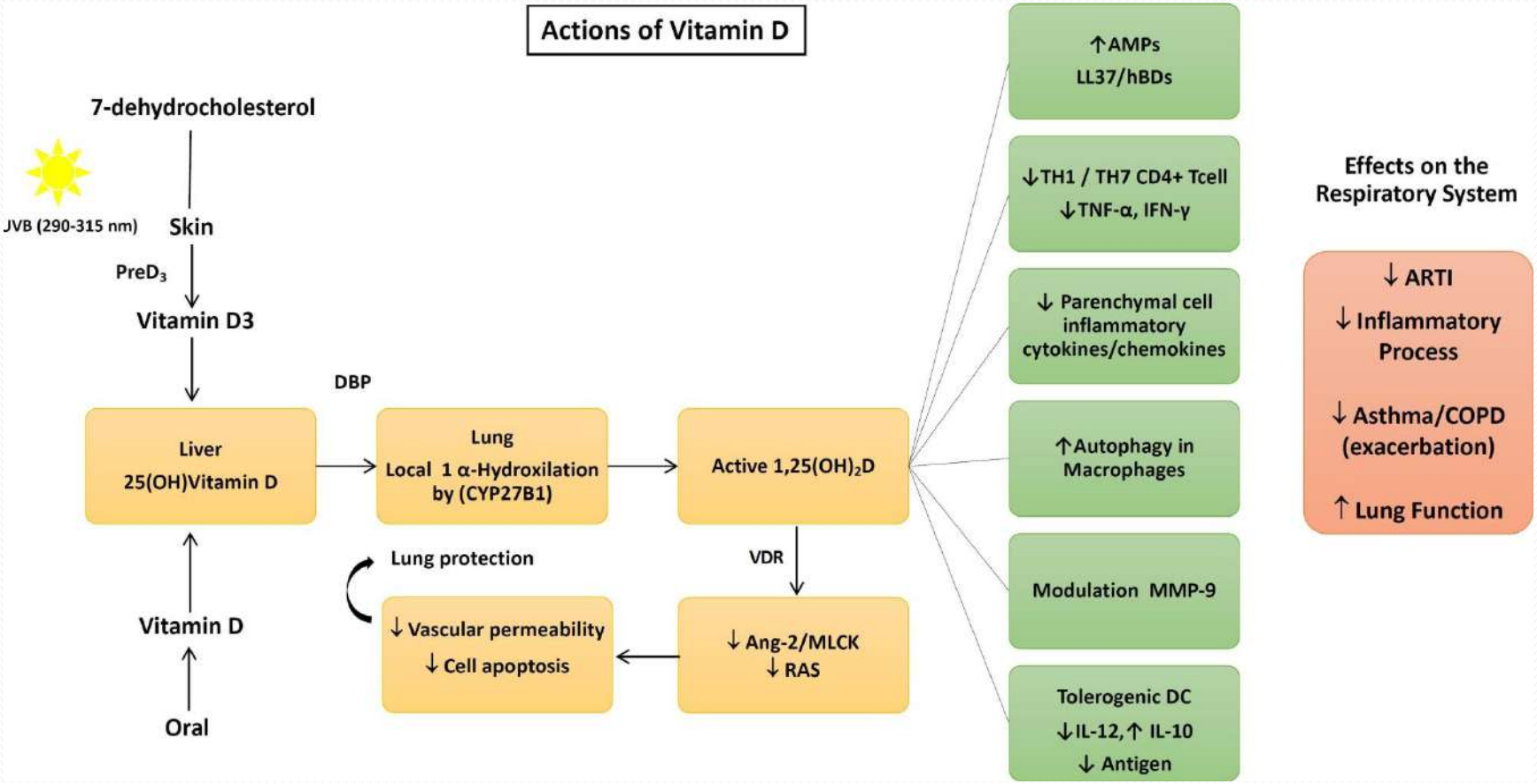
Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)

- An RCT conducted in India involving 40 asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH)D<20 ng/ml) individuals admitted to a tertiary hospital in north India without major comorbidities or requiring invasive ventilation or having 25(OH)D >20 ng/ml.
- 16 intervention participants, 6 males, age 50 (36-51) years, 25(OH)D = 9 (7 – 13) ng/ml
- 24 controls, 14 males, age 48 (39 – 49) years, 25(OH)D = 10 (8 – 13) ng/ml
- Rastogi A, et al, Malhotra P.Postgrad Med J. 2020 Nov 12:postgradmedj-2020-139065. doi: 10.1136/postgradmedj-2020-139065.

Short term, high-dose vitamin D supplementation for COVID-19 disease: Results

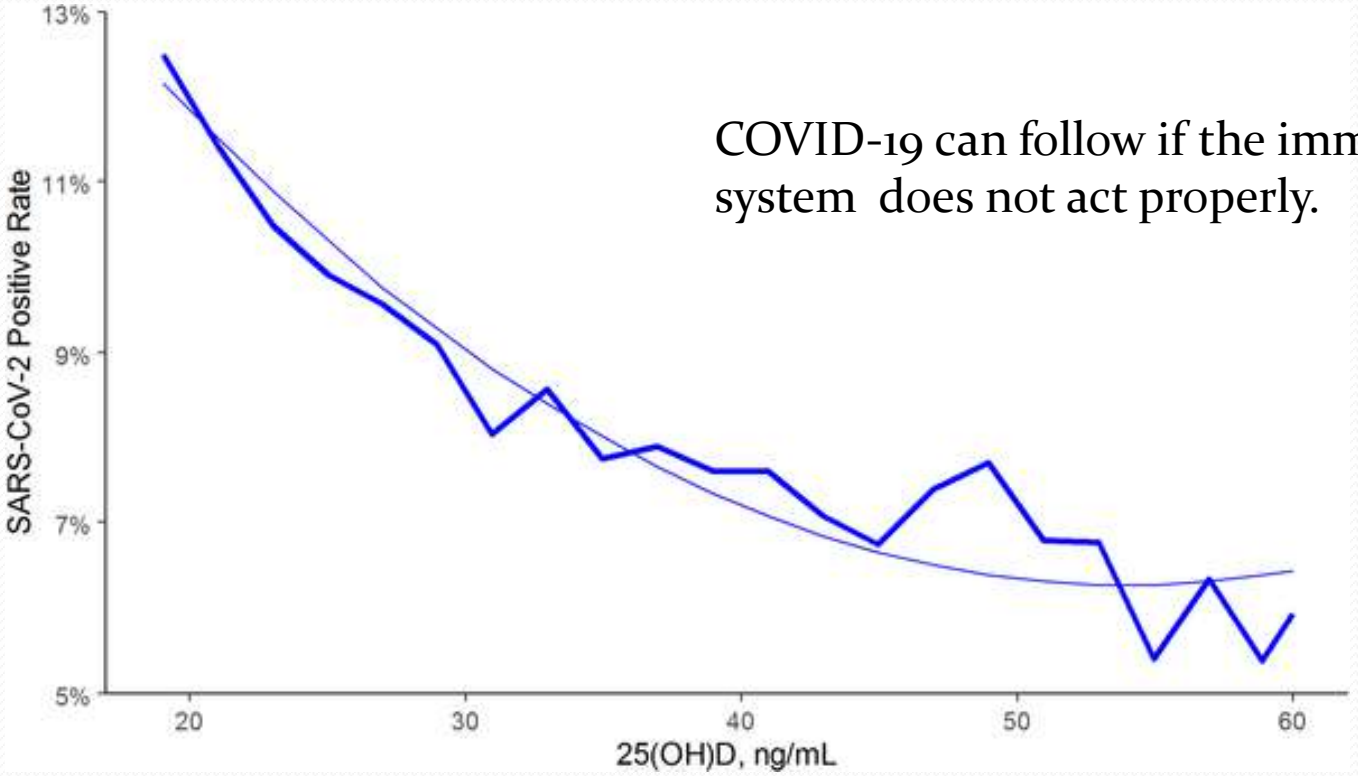
- 10 out of 16 patients achieved 25(OH)D>50 ng/ml by day-7 and another two by day-14 [day-14 25(OH)D levels 52 (49 to 60) ng/ml in intervention group and 15 (13 to 20) ng/ml ($p<0.001$) in the control group].
- 10 (63%) participants in the intervention group and 5 (21%) participants in the control arm ($p<0.02$) became SARS-CoV-2 RNA negative.
- Fibrinogen levels significantly decreased with vitamin D_3 supplementation (intergroup difference 0.70 ng/ml; $P=0.007$) unlike other inflammatory biomarkers.

Mechanisms



Dos Santos et al. Arch Endocrinol Metab. 2020;S2359-39972020005006214.

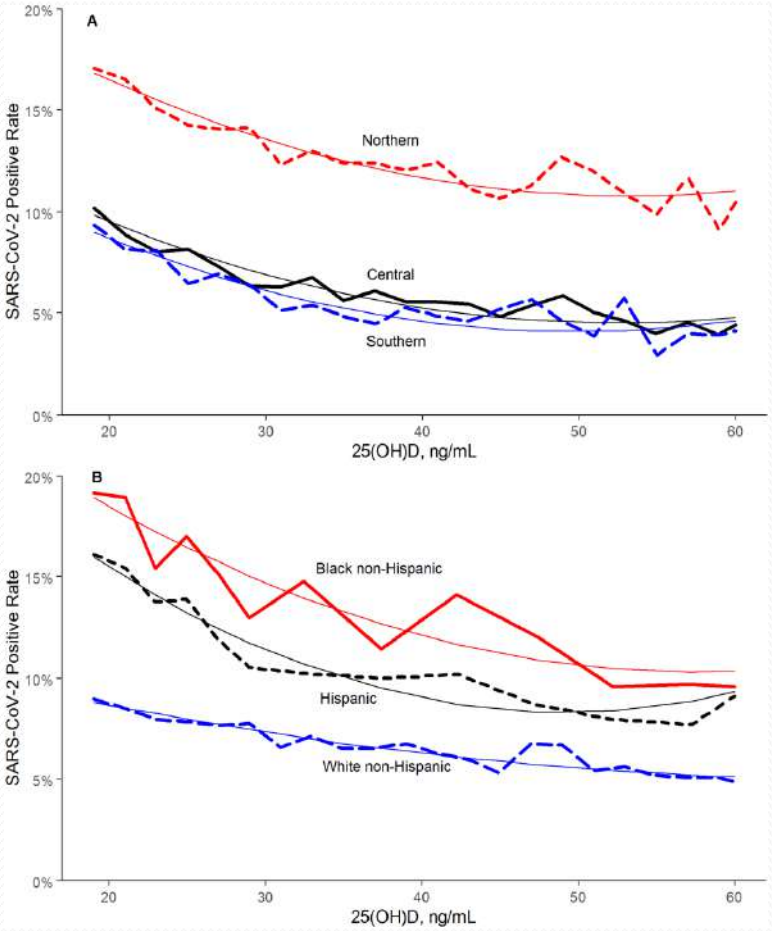
SARS-CoV-2 NAAT positivity rates and circulating 25(OH)D levels in the total population



COVID-19 can follow if the immune system does not act properly.

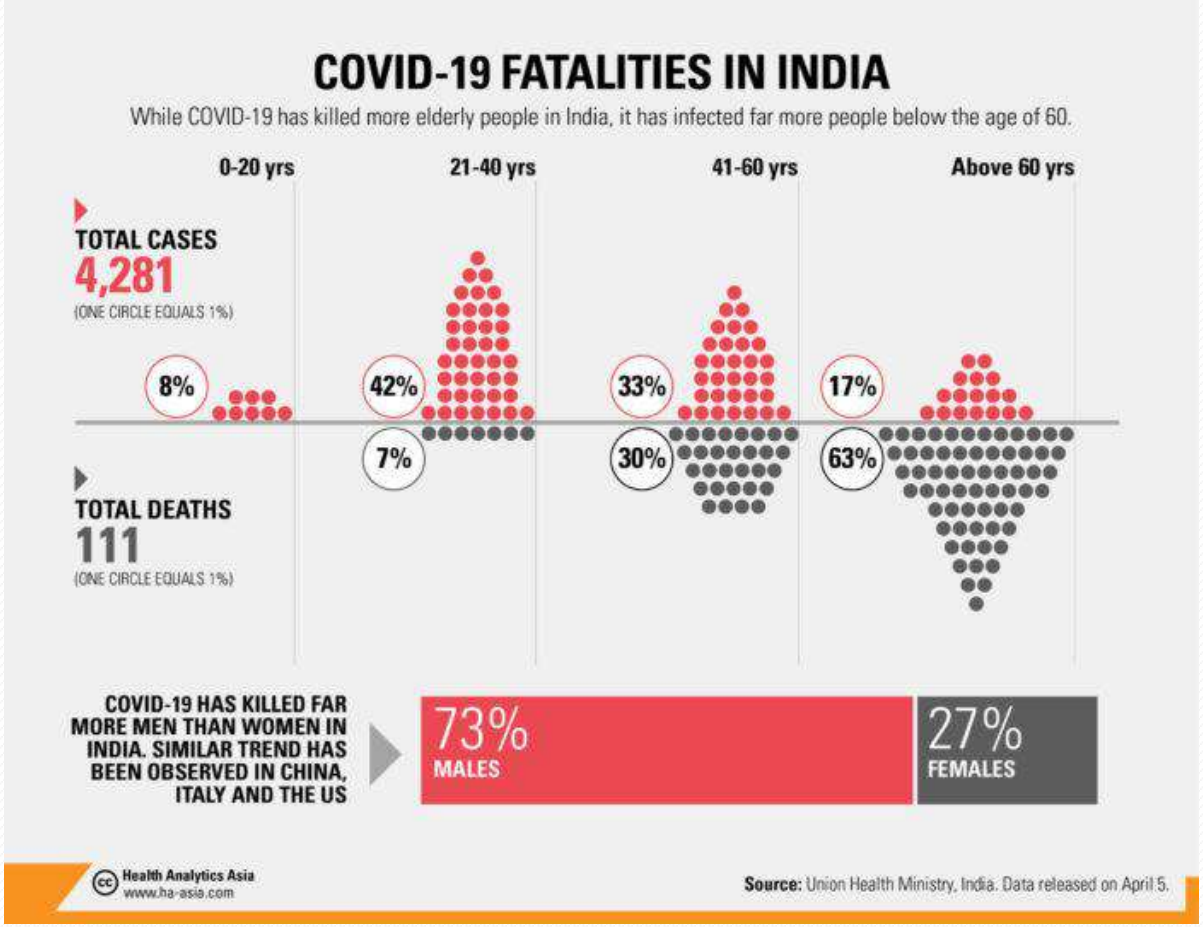
Kaufman,… Holick, PLoS One. 2020 Sep 17;15(9):e0239252.

Effects of Race and 25(OH)D on SARS-CoV-2 seropositivity

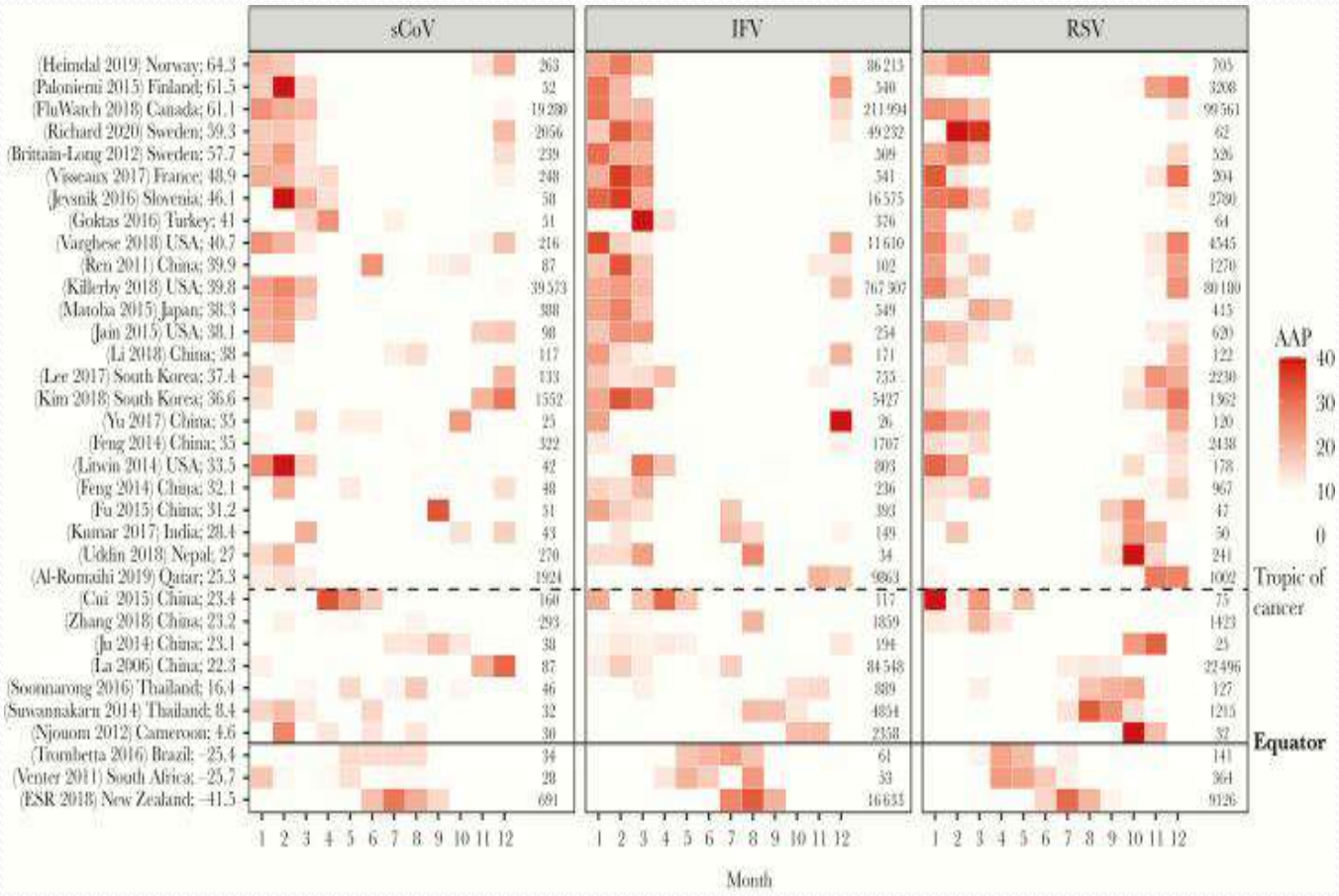


The findings regarding race/ethnicity and seropositivity indicate that blacks and Hispanics have higher rates than whites primarily due to non-vitamin D effects. However, if blacks and Hispanics were to increase 25(OH)D concentrations by vitamin D supplementation, they could reduce seropositivity by about 30%

Effect of Age on Incidence, Death

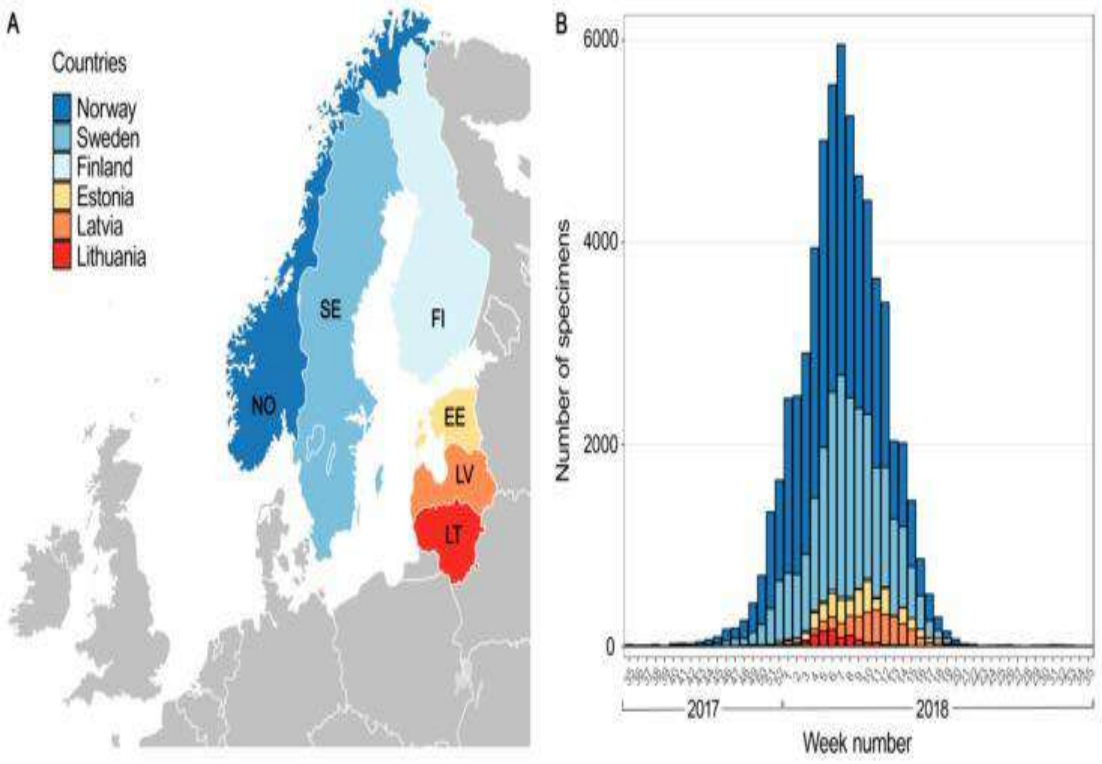


Seasonality of Viral Infections



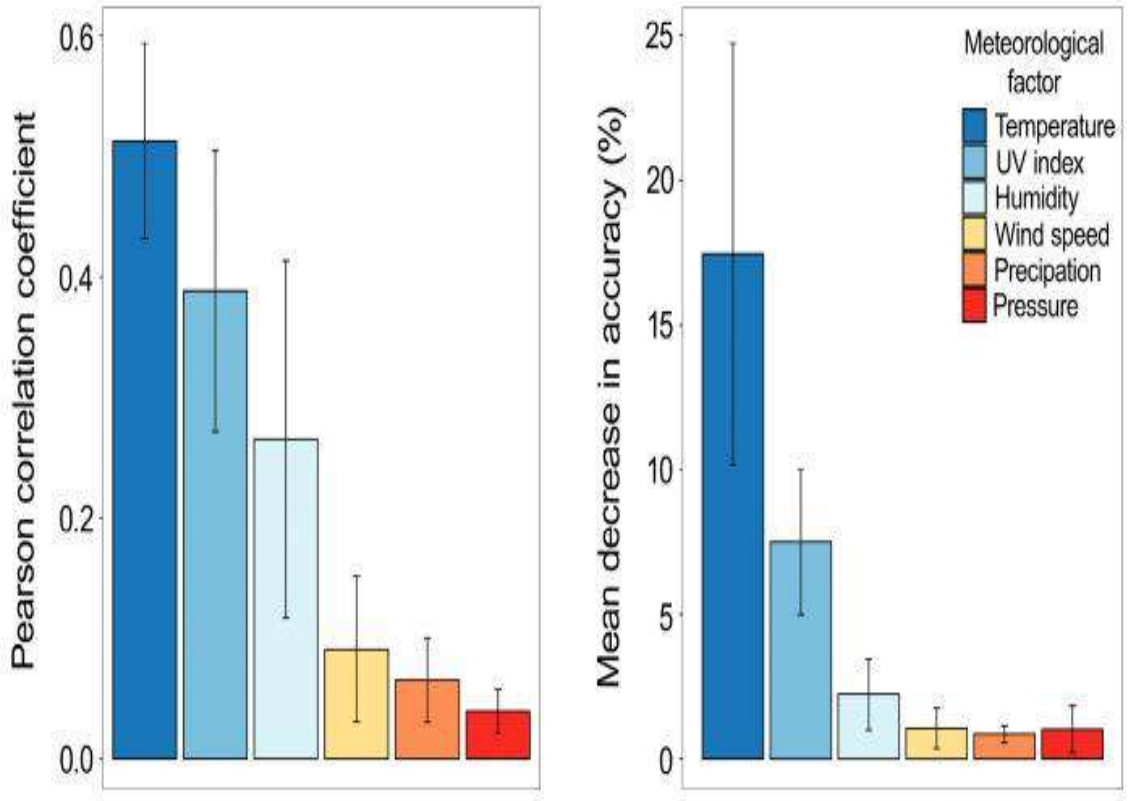
You Li et al. J Infect Dis. 2020 Sep 1;222(7):1090-1097. doi: 10.1093/infdis/jiaa436

Low Temperature and Low UV Indexes Correlated with Peaks of Influenza Virus Activity in Northern Europe during 2010–2018



Ianevski et al. Viruses. 2019 Mar 1;11(3):207. doi: 10.3390/v11030207.

Low Temperature and Low UV Indexes Correlated with Peaks of Influenza Virus Activity in Northern Europe during 2010–2018



Implications:
Influenza rates are reduced in winter at high latitudes due to lower temperature, UV dose, and humidity due to reduced viability of the virus outside the human body.

One-third of Mayo Clinic Staff are SARS-CoV-2 Seropositive, Nov. 17

- ROCHESTER, Minn. — Over 900 Mayo Clinic staff have contracted COVID-19 in the past two weeks, according to a Tuesday briefing by Dr. Amy Williams, dean of clinical practice.
- Williams said that 93 percent of staff who have contracted the virus did so in the community, and that the majority of those who contracted the virus at work did so while eating in a break room with a mask off.
- "It shows you how easy it is to get COVID-19 in the Midwest," said Williams, during an afternoon press call. "Our staff are being infected mostly due to community spread, and this impacts our ability to care for patients. We need everyone in the communities we serve to do their part to limit the spread of COVID-19."

Recommendations

- For health care workers dealing with COVID-19 patients;
- For those at greatest risk of COVID-19 (elderly, obese, chronic diseases, lung diseases, high social contact);
- For those with recently diagnosed COVID-19 or SARS-CoV-2 seropositivity:
- Consider taking 100,000-200,000 IU vitamin D_3 within a week to rapidly raise 25(OH)D concentration, followed by 4000 or 5000 IU/d or up to 50,000 IU/week.
- No adverse effects of high-dose vitamin D supplementation have been found for COVID-19 patients.

Details Regarding 14 Observational Studies, 3 Treatment Studies, and Mechanisms are Discussed in This Open Access Review

- Mercola J, Grant WB, Wagner CL.
- Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity.
- *Nutrients*. 2020 Oct 31;12(11):E3361.
- doi: 10.3390/nu12113361.

For Further Information

- Does Vitamin D Protect Us from COVID-19? What Is the Required Dosage? Can Too Much Vitamin D Harm Us?By Michael F. Holick, October 30, 2020, VuMedi.com
- Search for journal publications
  - https://pubmed.ncbi.nlm.nih.gov/
  - https://scholar.google.com/
- Vitamin D advocacy organization
  - Grassrootshealth.net
  - VitaminDWiki.com (has a large collection of vitamin D information)