

Vitamin D

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of September 5, 2020

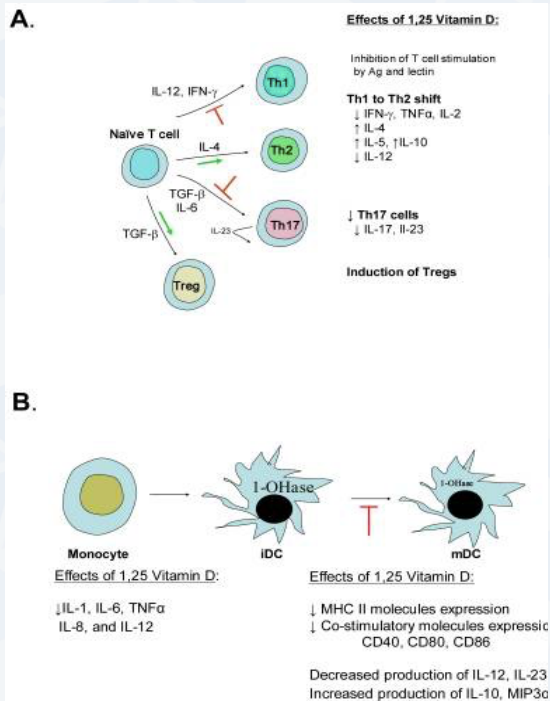
Mechanism of Action

• Vitamin D and Immunologic Function

- Inhibits B cell proliferation
- Blocks B cell differentiation and immunoglobulin secretion
- Suppresses T cell proliferation
 - \downarrow inflammatory cytokine production (e.g. Interleukin (IL) -17, IL-21)
 - \uparrow production of anti-inflammatory cytokines (e.g. IL-10)
- Inhibits monocyte production of inflammatory cytokines (e.g. IL-1, IL-6, IL-8, IL-12 and Tumor Necrosis Factor α (TNF) α)
- Inhibits dendritic cell (DC) differentiation and maturation
 - Preservation of an immature phenotype

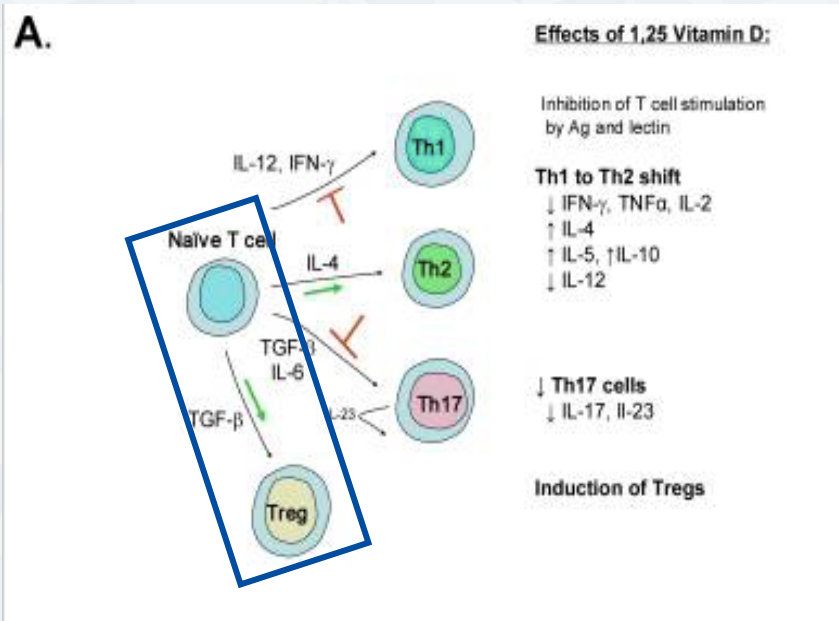


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Mechanism of Action

- **Vitamin D and proposed mechanism in COVID-19**
 - \downarrow inflammatory cytokines to \downarrow concern for possible cytokine storm
 - \uparrow T regulatory lymphocytes resulting in diminished severity and lower levels of respiratory viral disease
 - Protective effects involved in coagulation



Dosing

Recommended Daily Intake Levels

Age	Male	Female	Pregnancy	Lactation
0-12 months	400 IU (10 mcg)	400 IU (10 mcg)		
1-13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14-18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19-50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51-70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

Tolerable Upper Intake Levels

Age	Male	Female	Pregnancy	Lactation
0-6 months	1,000 IU (25 mcg)	1,000 IU (25 mcg)		
7-12 months	1,500 IU (38 mcg)	1,500 IU (38 mcg)		
1-3 years	2,500 IU (63 mcg)	2,500 IU (63 mcg)		
4-8 years	3,000 IU (75 mcg)	3,000 IU (75 mcg)		
9-18 years	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)
19+ years	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)



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IU: International Unit
Mcg: microgram

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7-12 months				
1-3 years				
4-8 years				
9-18 years				
19+ years	(100 mcg)	(100 mcg)	(100 mcg)	(100 mcg)

Toxic effects include:

- anorexia
- weight loss
- polyuria
- heart arrhythmias
- ↑ level leads to vascular and tissue calcification = subsequent damage to the heart, blood vessels, and kidneys



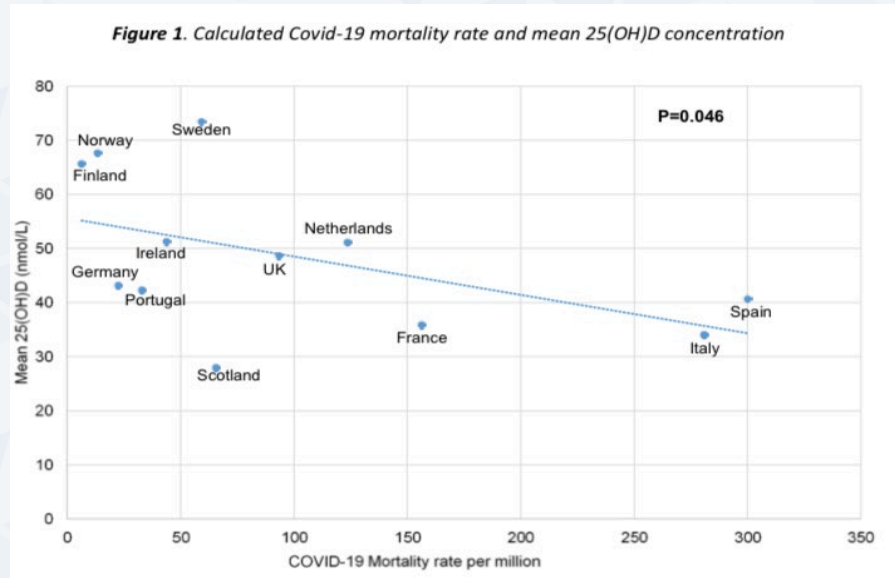
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Vitamin D

- Sources of vitamin D
 - Foods
 - salmon, tuna, and mackerel
 - beef liver, cheese, and egg yolks
 - fortified foods can include:
 - milk, breakfast cereals, orange juice, yogurt, and margarine products
 - Dietary supplements
 - Ultraviolet (UV) rays from sunlight

What effect does the sun have?



- mortality plotted against latitude = countries below 35° north latitude have relatively low mortality¹
 - Spain and Northern Italy have high rates of vitamin D deficiency and higher COVID-19 mortality rates
 - Exceptions of Norway, Sweden, and Finland have adequate food Vitamin D fortification and supplement use
 - **Author conclusion:** circumstantial and experimental evidence suggests vitamin D may play a supportive role for the immune system, particularly in regulating cytokine response
- More active sun exposure = anti-thrombotic events²

Research

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

BMJ 2017 ; 356 doi: <https://doi.org/10.1136/bmj.i6583> (Published 15 February 2017)

Author Conclusions:

“Vitamin D supplementation was **safe and it protected against** acute respiratory tract infection overall. Patients who were **very vitamin D deficient** and those **not receiving bolus** experienced the most benefit.”

Martineau, AR, et al. 2017 Feb 15;356:i6583. doi: [10.1136/bmj.i6583](https://doi.org/10.1136/bmj.i6583)



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Vitamin D supplementation for Acute Respiratory Infection (ARI)

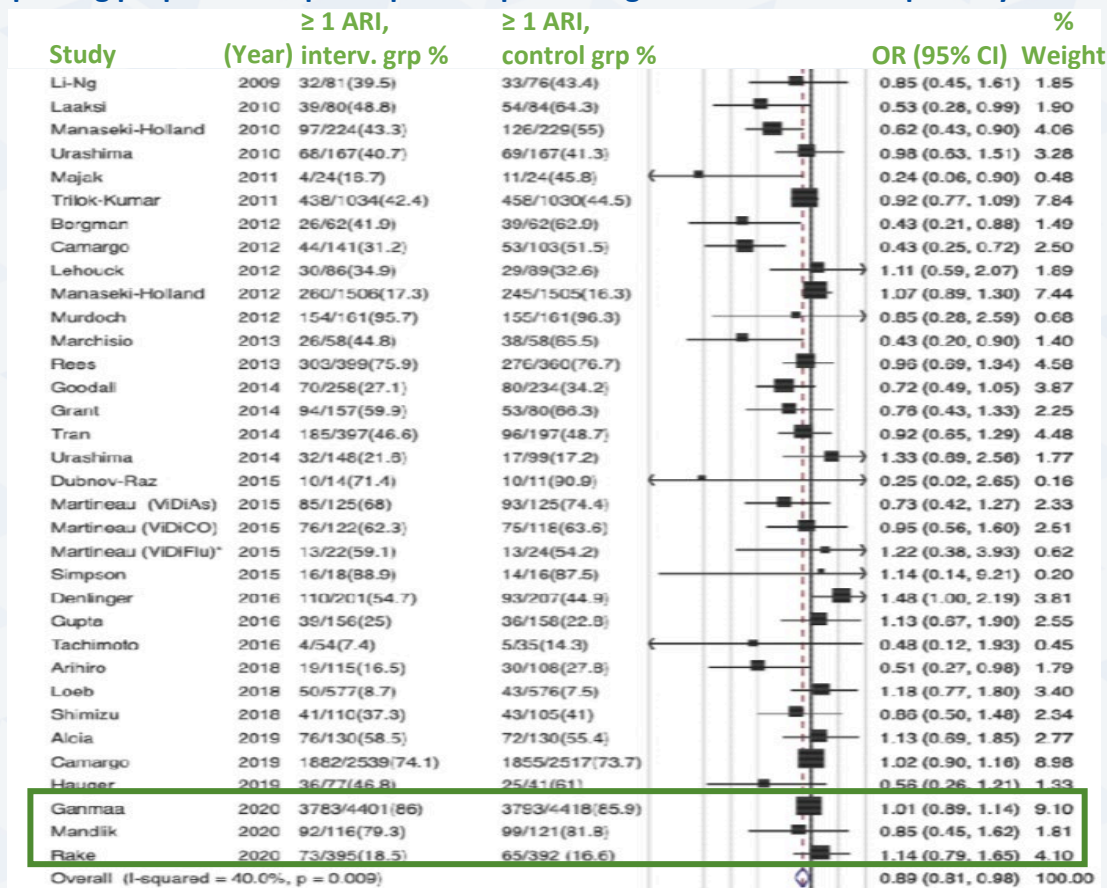


*relevance to
COVID-19?*

Note: Preprint, non peer-reviewed article



Figure. Forrest plot of placebo-controlled Randomized Controlled Trials (RCTs) reporting proportion of participants experiencing 1 or more acute respiratory infection.



Vitamin D Supplementation Trials:

Completed

NCT04407572

Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women

Role: Serum zinc, Vitamin D, Vitamin B12 levels of 45 patients will be measured and evaluated together with the information of the patients.

NCT04435119

Covid-19 and Vitamin D in Nursing-home

Role: Determine whether bolus Vitamin D3 supplementation taken during or in the month before COVID-19 was effective in improving survival among frail elderly nursing-home residents infected with COVID-19 compared to those having received supplementation longer ago.

NCT04485169

Therapeutic Plasma Exchange (TPE) for Covid-19 Cytokine Release Storm (CRS)

Role: NON TPE arm Only supportive treatment offered including Vit C, Zinc, Vit D, famotidine, enoxaparin and Methylprednisolone

NCT04491994

Clearing the Fog: Is Hydroxychloroquine Effective in Reducing COVID-19 Progression

Role: Patients selected in supportive arm will be given standard doses of oral Vit C, Vit D, Zinc and panadol

Only one of these four trials is directly assessing Vitamin D as related to COVID-19.

Note: 18 trials are currently recruiting with several more directly focused on Vitamin D and COVID-19.



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www.clinicaltrials.gov

Drug-Drug Interactions


- steroids
 - ↓ vitamin D metabolism
- orlistat
 - ↓ vitamin D absorption
- cholestyramine
 - ↓ vitamin D absorption
- phenobarbital
 - ↑ vitamin D metabolism to inactive compounds
- phenytoin
 - ↑ vitamin D metabolism to inactive compounds

Groups at Risk of Vitamin D Inadequacy

- Obesity
 - Body Mass Index (BMI) ≥ 30 is associated with lower serum 25(OH)D levels
- Dark Skin
 - Increased melanin reduces the skin's ability to produce vitamin D from sunlight
- Limited sun exposure (e.g. homebound, those that wear long robes and head coverings for religious reasons)
 - Unlikely to obtain adequate vitamin D from sunlight

Vitamin D Levels

**Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health*
[1]**



nmol/L**	ng/mL*	Health status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL).

** 1 nmol/L = 0.4 ng/mL

COVID-19 Guidelines

Guideline	Vitamin D Recommendation	Citation
IDSA (Infectious Diseases Society of America)	No mention	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
NIH (National Institutes of Health)	Insufficient data to recommend either for or against the use	https://covid19treatmentguidelines.nih.gov/introduction/
NICE (National Institute for Health and Care Excellence)	Not mentioned in specific guidelines, however, adherence to daily vitamin D levels is recommended	https://www.nice.org.uk/guidance/ng159 https://www.nice.org.uk/advice/es28/chapter/Advisory-statement-on-likely-place-in-therapy
SCCM (Society of Critical Care Medicine)	No mention	https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19
WHO (World Health Organization)	No mention	https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

Summary

- Data may support vitamin D supplementation for acute respiratory infections
- Data is lacking in regards to vitamin D supplementation for those with SARS-CoV-2
- 1 completed trial evaluated COVID-19 and vitamin D in nursing-home patients and results are not yet published
- 18 trials are currently recruiting
- No guideline provided recommendation for the use of supplemental vitamin D

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