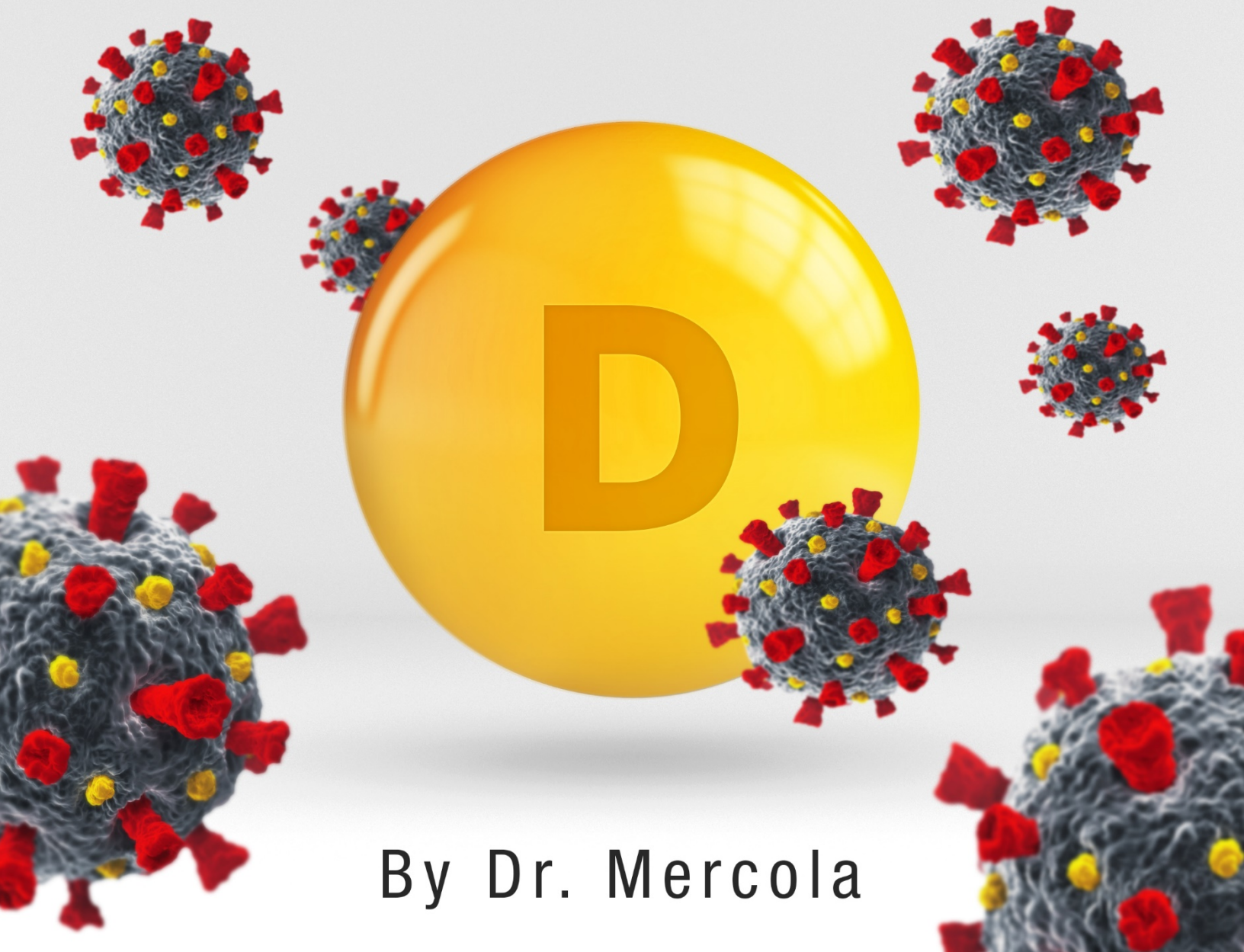
Vitamin D

in the Prevention of

COVID-19



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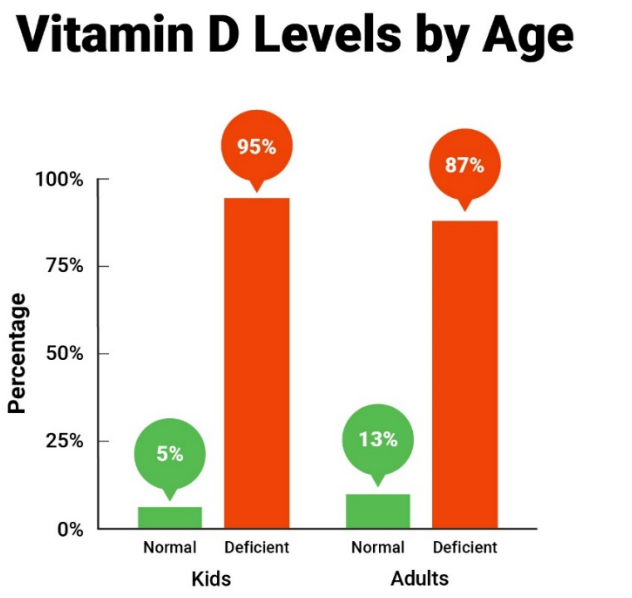
Vitamin D deficiency represents a global pandemic afflicting more than one billion individuals across all age groups worldwide[1, 2-4] The current pandemic of vitamin D deficiency has collided with the COVID-19 pandemic and likely radically increased the number of deaths because of vitamin D insufficiency.[5]

So just how many people are suffering from not having enough vitamin D?

A lot more than you probably thought or understood.

As you can see in Figure 1 below, 95% of children and 87% of adults have less than the ideal level of vitamin D in their blood, which is 40 ng/ml or 100 nmol/liter. Only 5% of children and 13% of adults have achieved ideal levels. But this is for all ethnicities. As you can see in Figure 20 at the end of the document, **less than 1% of Black children have achieved this healthy level.**

Note that we are using 40 ng/ml as the ideal vitamin D level which many vitamin D experts propose.[6] However, some believe that 30 ng/ml is sufficient.



SOURCE: Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2013-2014. https://wwwn.cdc.gov-/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2013

Figure 1

Although there are currently no prospective controlled studies demonstrating vitamin D's effectiveness in COVID-19, there are many such studies underway. One can visit the clinical trials registry to review the current state of these trials.[7, 8] As of early June 2020 there were over 20 studies in progress on the use of vitamin D in COVID-19.

The purpose of this report is to help you understand why it is so important to optimize your vitamin D level in order to have healthy immune functions, and then provide you with a detailed strategy for how to do that.

This report can be an invaluable tool to share with your family and community to help prepare for a second wave of the pandemic, which is expected in the fall.

The interest in the health-promoting effects of vitamin D has increased substantially during the 21st century. There were approximately 5,500 vitamin D-related articles indexed to the U.S. National Library of Medicine database in the past five years. The observational studies on vitamin D have received a considerable amount of attention due to a vast body of publications reporting inverse associations between vitamin D status and multiple diseases, including COVID-19.

Even a former director of the Centers for Disease Control and Prevention, Dr. Tom Frieden, proposed using vitamin D to combat the COVID-19 pandemic on March 23, 2020.[9] There have been many recent calls for widespread high-dose vitamin D supplementation in the prevention and mitigation of COVID-19.[10-13]

A recent June 2020 article caused the editors at the BMJ Nutrition Prevention and Health to write the following supportive statement about vitamin D and COVID-19:

> *"Categorical general statements about the lack of benefit from vitamin D are not supported by any evidence at this time, not least because a growing number of observations and study results that point to an important role (of vitamin D)."*[14]

Vitamin D_3 is an ancient molecule that is produced from the direct cholesterol precursor (7-dehydrocholesterol) which is normally present in your skin using energy provided by the UV-B component of sunlight in a reaction that does not require any enzyme assistance.[15] In its classical pathway, vitamin D_3 is converted to its single hydroxy form (25-hydroxyvitamin D) in your liver and then to its double hydroxy form (1,25-dihydroxyvitamin D) in your kidneys and even in your immune cells that fight infection.[1-3, 16]

Vitamin D differs from most vitamins, in that your body can produce it on its own with exposure to sunlight, and that its primary active metabolite is a steroid hormone. Unlike most vitamins, which act as antioxidants or enzyme co-factors, the $1,25(OH)_2D$ form of vitamin D works by binding to

the vitamin D receptor that is present in the cell membrane, or the nucleus. Once vitamin D activates the receptor it becomes a master regulator of cell function (Fig. 2).

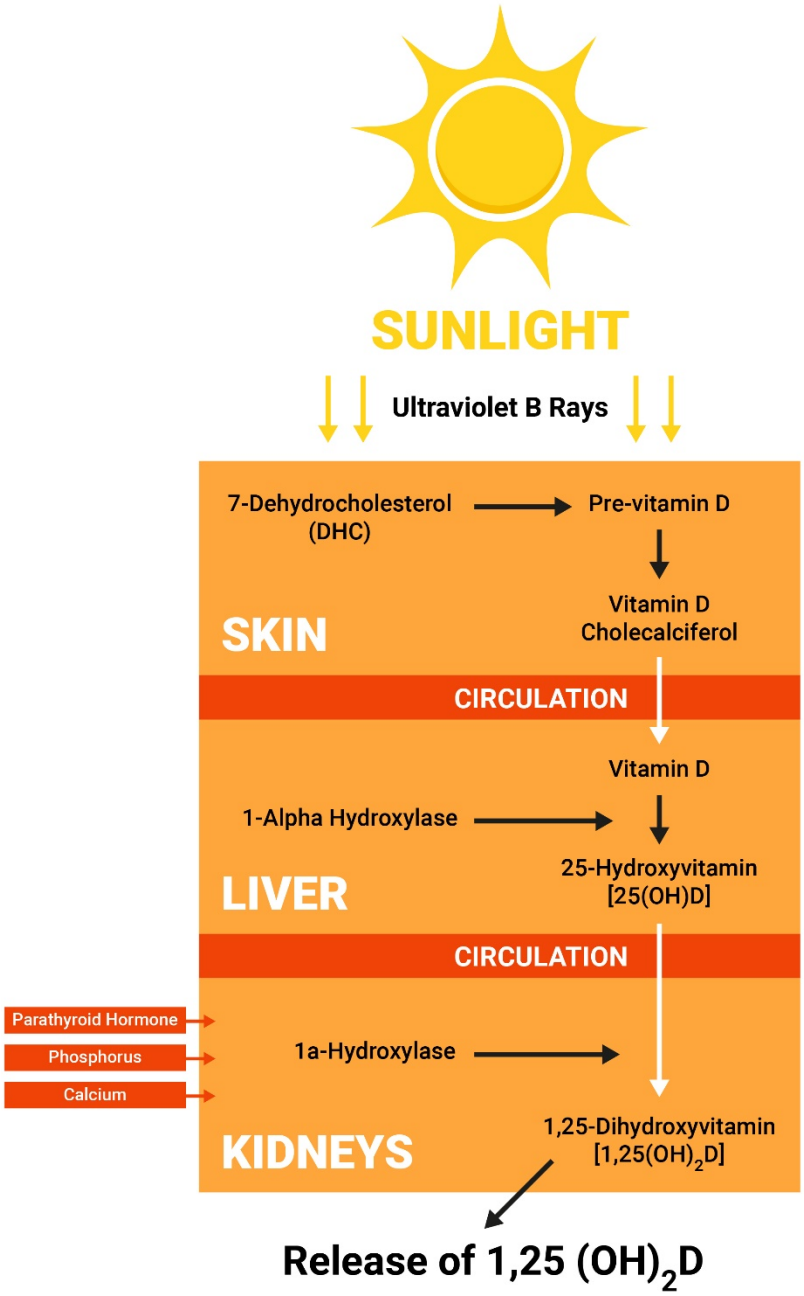


Figure 2

Until the 21st century, vitamin D was primarily recognized for its role in the regulation of calcium and bone health and the prevention of rickets.[17] In the last 20 years, however, research has shown that vitamin D also has profound influences on immune cells and causes a general

lowering of inflammation.[18, 19] It is a powerful epigenetic regulator influencing over 2,500 genes[20] and impacting dozens of our most serious health challenges, like heart disease and cancer, autoimmune diseases like MS,[21] and others listed in Figure 3 below.

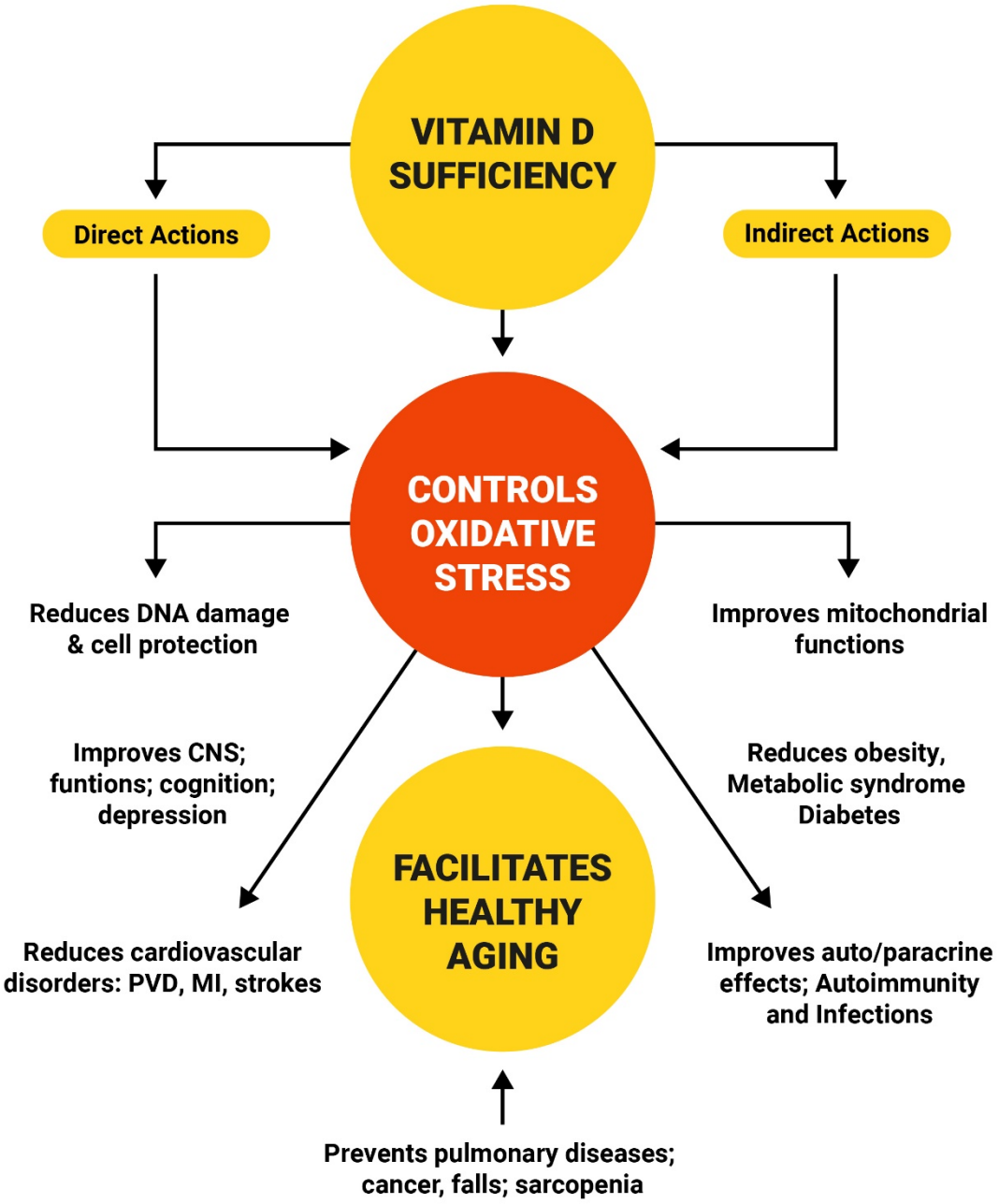


Figure 3

Your Innate and Adaptive Immune System

In the frame of infectious diseases, the purpose of your immune system is to recognize invading pathogens, prevent their spread, and eliminate them from your body. This extraordinarily complex system relies on billions of cells patrolling your body and a dynamic complex network.[22]

To help you understand how vitamin D impacts your immune system, it is first important to appreciate some fundamental elements of your innate and adaptive immune system. Your immune system comprises two distinct but interacting types of immunity: innate and adaptive.

Your innate immunity kicks in hours following a foreign pathogen, while your adaptive immunity takes days to react but provides long-term, typically lifelong immunity, to an infection, as illustrated in Figure 4 below.

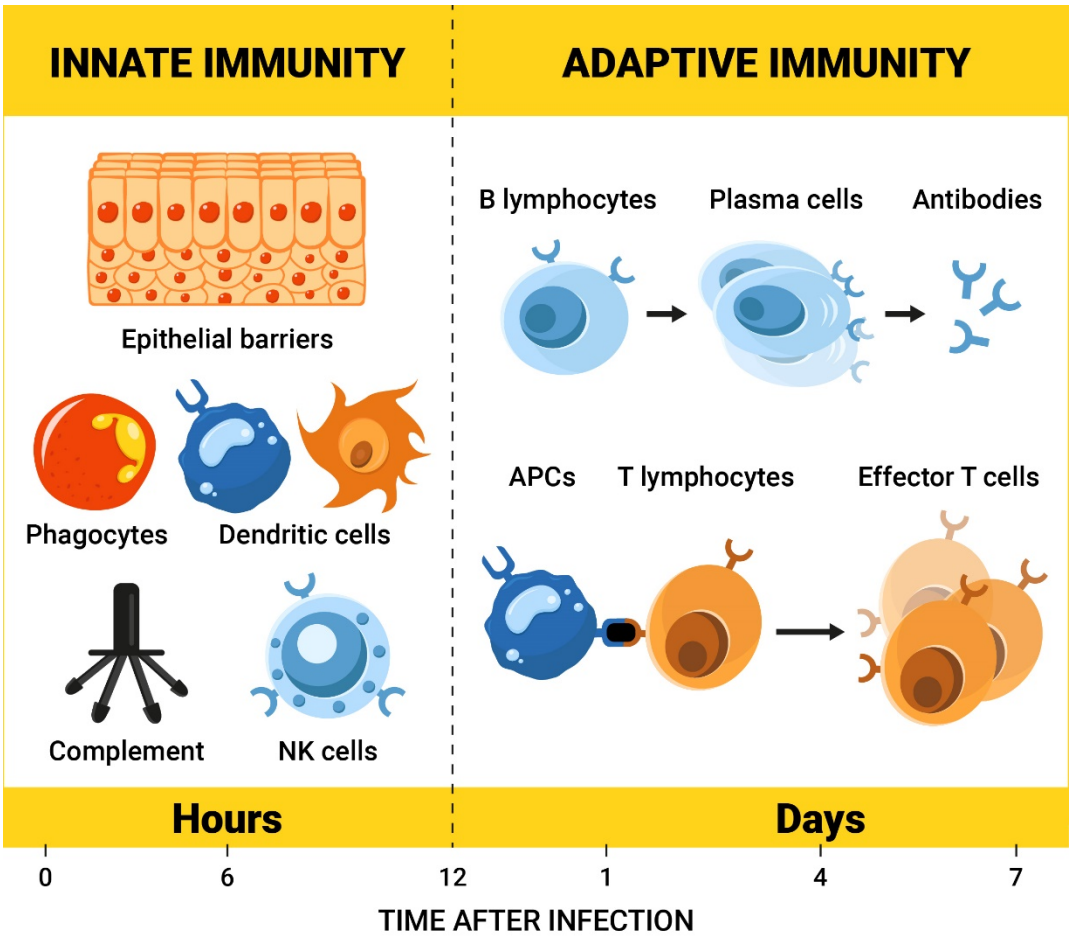


Figure 4

Innate Immune System

Your innate immune system is your first line of defense against infections, and rapidly fights against invading pathogens. It responds in a generic way without conferring long-lasting and specific immunity.

Unlike your adaptive immune responses, innate immune responses are always general, or not specific to a particular pathogen, and depend upon a group of cells and proteins that recognize conserved features of microbes that quickly promote clearance of infectious agents.

Your innate immune system includes physical barriers, such as your skin and the cells lining your gut and blood vessels, and chemical barriers such as your saliva and stomach acid. These barriers help to block the entry of disease-causing organisms into your body.[23]

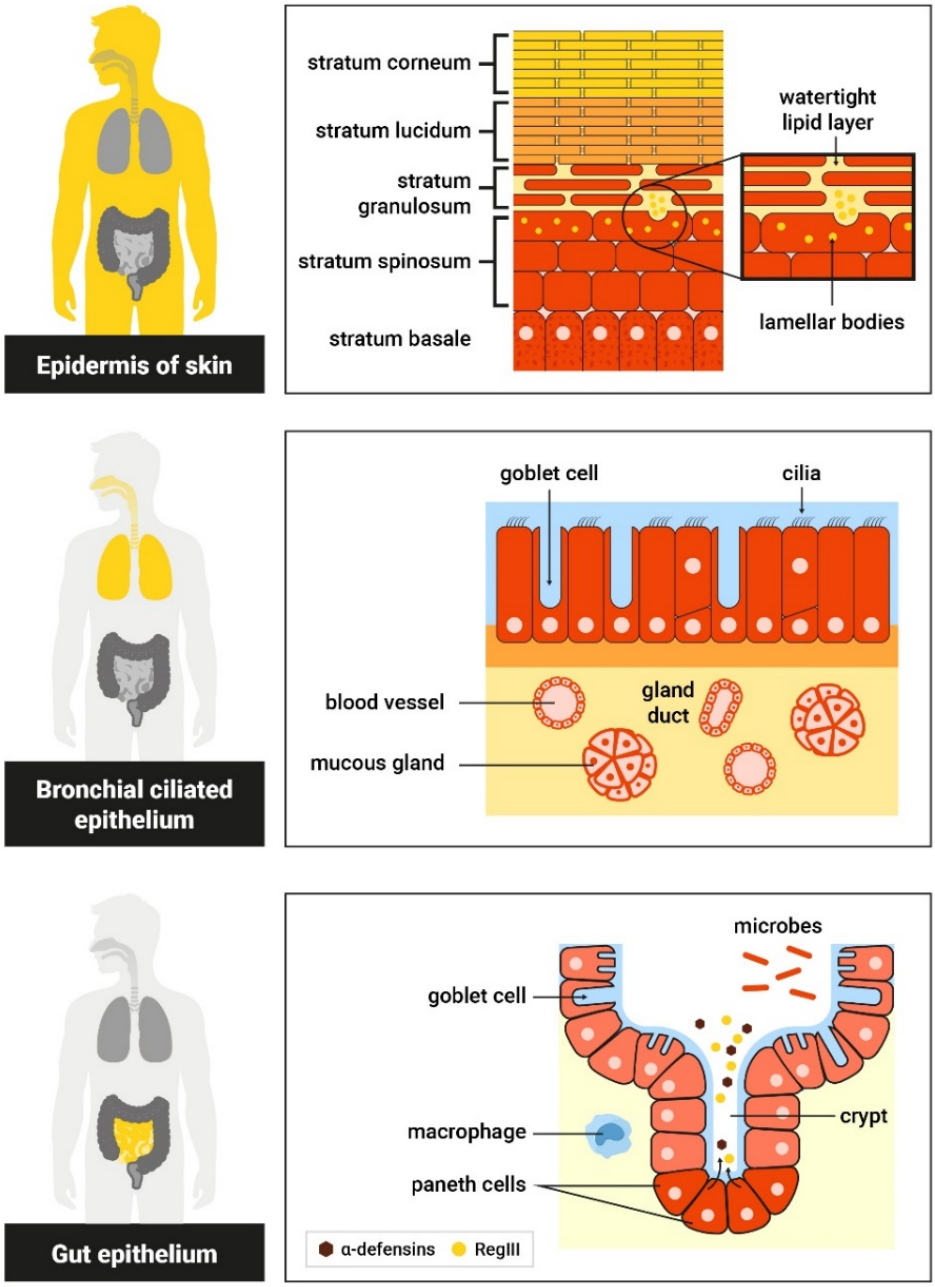


Figure 5

Vitamin D is a well-known regulator of the physical barrier portion of your innate immune system and is responsible for improving the epithelial cells that line your intestines. It also modulates your bowel's immune system. Low levels of vitamin D will increase your gut permeability and allow pathogens to sneak into your blood stream causing low-grade inflammation.

White blood cells are also part of your innate immune system, and they serve as the primary initial defenders against pathogens in your body.[24] Neutrophils are your most abundant white blood cell and contribute to your first line of defense against microbial pathogens.

Neutrophils can clear microbes through a process called phagocytosis, or simply digesting them inside your white blood cells, where they are exposed to reactive oxygen species, which are generated in response to the pathogens, which further leads to the production of biologically active antimicrobial molecules.[25]

Dendritic cells play a key role in innate immune and adaptive immune responses. As the strongest antigen-presenting cells, they effectively stimulate the activation of T-lymphocytes and B-lymphocytes, thus combining innate and adaptive immunity.

Dendritic cells permanently survey your body and are specialized in absorbing antigens from pathogens. Upon exposure to inflammatory signals, they mature and migrate to your lymph nodes, and present their captured antigens to the T cells, thereby priming an antigen-specific adaptive immune response.

Macrophages are another type of white blood cell that add to the first line of your innate defense against pathogens. They are important in engulfing bacteria, as white blood cells do, but also in making and secreting a whole host of inflammatory and anti-inflammatory signaling proteins.

For a more complete picture of the cells involved in your innate and active immunity you can view Figure 6 below.

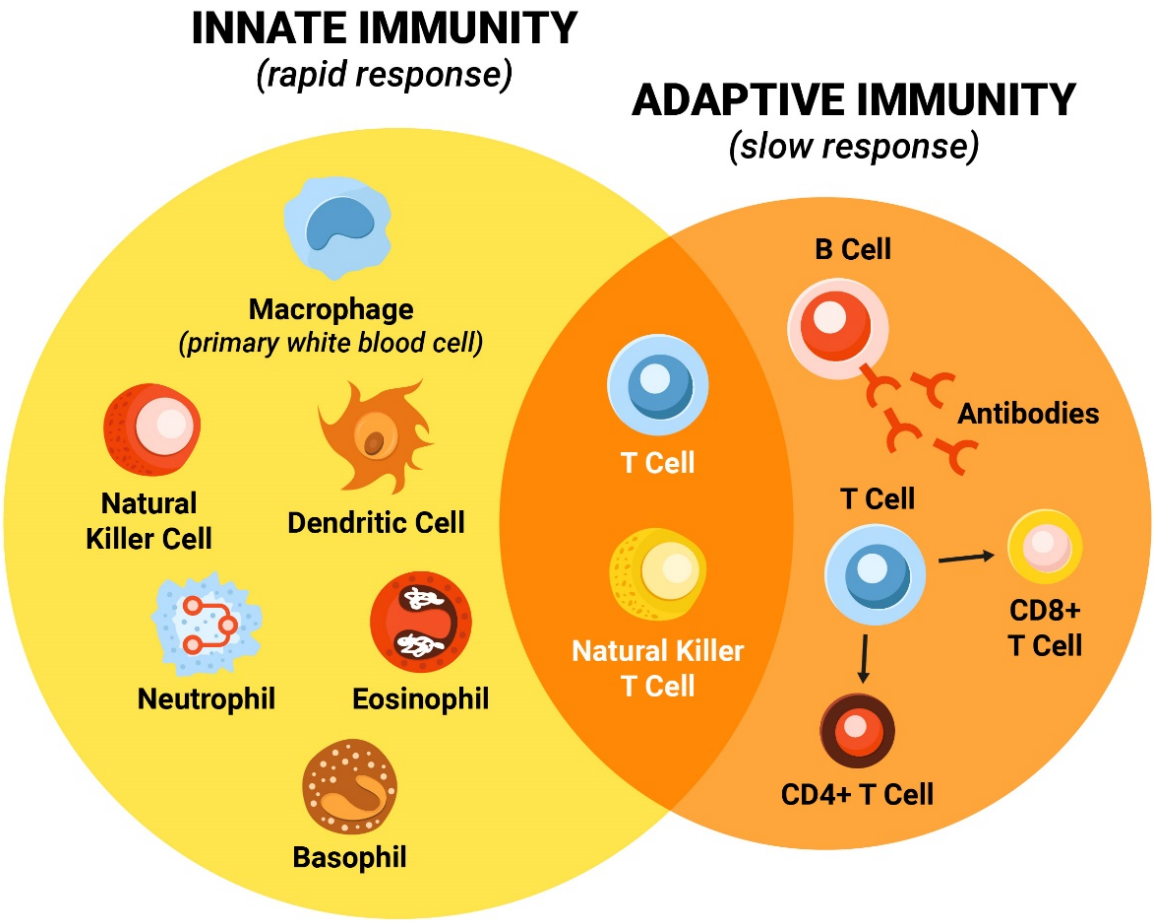


Figure 6

Adaptive Immune System

Your adaptive immune system is primarily composed of your T and B lymphocytes, as represented in Figure 6 above. Compared with your innate immunity, your adaptive immunity is slower to start but typically strong enough to finalize the clearance of infections that elude your innate immunity. Adaptive immunity is best characterized by its specificity to foreign antigens and its ability to generate long-lasting immune memory.

The activation of your adaptive immune system often starts with the antigen presentation by innate cells to T helper cells, which leads to their interaction with native B cells. This then assists in activating and differentiating them into memory and antibody-secreting B cells that produce

the antibodies to protect you from future infections, and which are measured to demonstrate protective immunity.

T cells, CD4+ T cells, and CD8+ T cells, particularly, play a significant antiviral role by balancing the combat against pathogens and the risk of developing autoimmunity or overwhelming inflammation.[26]

CD4+ T cells promote the production of virus-specific antibodies by activating T-dependent B cells. However, CD8+ T cells are toxic to pathogens and can kill viral infected cells. CD8+ T cells account for about 80% of total inflammatory cells in the lungs of coronavirus-infected patients and play a vital role in clearing the virus in infected cells and inducing immune injury.[27]

The activation of naive CD4+ T cells generates different helper T-cell classes, which differ according to the type of immune response they produce. Thus, the type 1 response T helper cells support cell-mediated immunity, whereas type 2 helper T-cell response mediates the humoral response.[28]

This entire process is summarized in Figure 7 below.

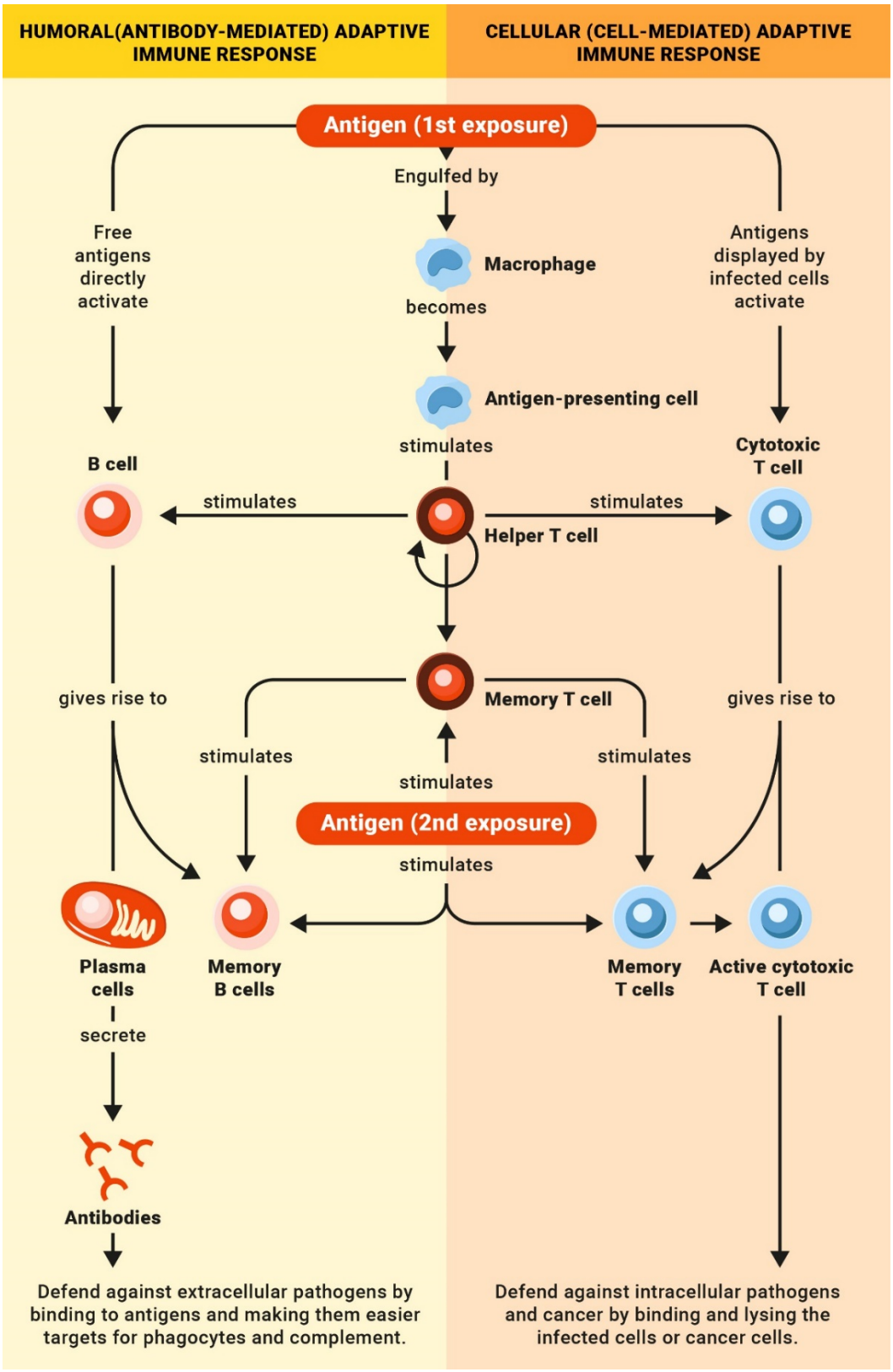


Figure 7

Vitamin D, Cytokine Storms and COVID-19

Cytokines are small proteins secreted by cells in your innate and adaptive immune systems. They serve to regulate diverse functions in your immune response. Cytokines are released by cells into your circulation or directly into your tissues. The cytokines locate target immune cells and interact with receptors on the target immune cells by binding to them. The interaction triggers or stimulates specific responses by the target cells.

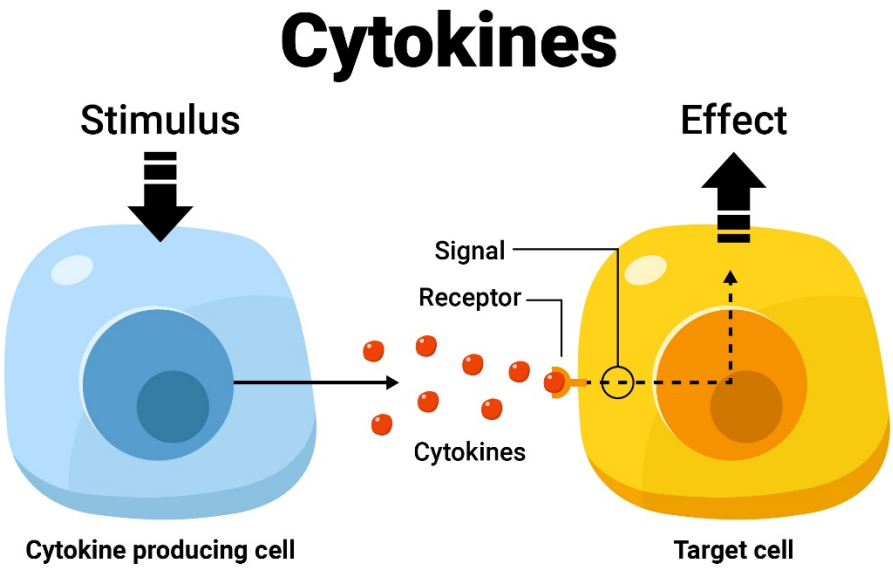


Figure 8

In response to bacterial and viral infections such as COVID-19, your innate immune system generates both pro-inflammatory and anti-inflammatory cytokines.[29] The inflammatory response plays a crucial role in the clinical manifestations of COVID-19. SARS-CoV-2 triggers an immune response against the virus, which, if uncontrolled, may result in lung damage, functional impairment, and reduced lung capacity.[30-33]

The SARS-CoV-2 viral infection-related inflammation and the subsequent cytokine storm in severe cases plays a crucial role in patient survival.[34] The extensive and uncontrolled release of proinflammatory cytokines is termed the cytokine storm. Clinically, the cytokine storm commonly presents as systemic inflammation and multiple organ failure. [35]

The inflammatory cytokines that mediate this response are TNFα, and interleukins are produced at an early stage of your innate immune response to the virus. These cytokines, among others, contribute to the recruitment and activation of cells of your adaptive immune response.[36, 37]

Two recent reviews carefully cover the physiology of how vitamin D specifically lowers the risk of cytokine storms,[38, 39] but the process is summarized below.

There is compelling research demonstrating that vitamin D can improve endothelial stability even in cytokine storms.[40] This may be due to vitamin D's role in modulating your T helper cell and cytokine production, but also through promoting T regulatory cells, which are responsible for anti-infectious action, for suppressing immune responses, and for limiting inflammatory processes[41] for which vitamin D may play an important role.[42]

Vitamin D helps to down-regulate the immune responses mediated by your T helper cells, thus inhibiting the production of pro-inflammatory cytokines, such as type 1 interferon gamma, and interleukins like IL-6, IL-2, along with tumor necrosis factor alpha (TNF-α)[43, 44] as indicated in Figure 9 below.

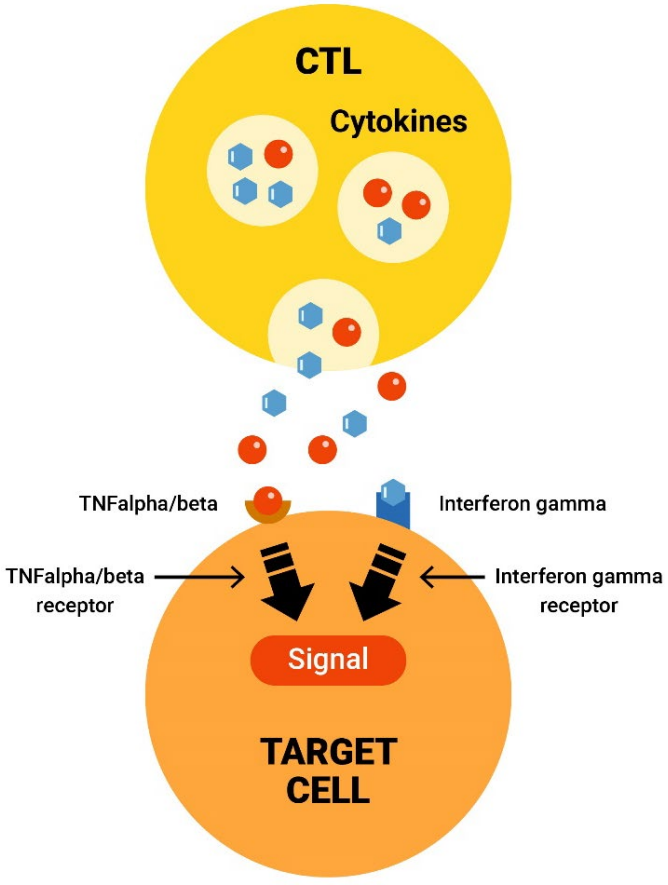


Figure 9

It has been well established that vitamin D deficiency enhances the cytokine storm.[45-47] This is because vitamin D modulates your adaptive immunity and suppresses responses mediated by your T helper cells by repressing production of inflammatory cytokines like TNFα and interleukins like IL-2 and interferon gamma.[48, 49] Furthermore, vitamin D promotes and stimulates the production of your T regulatory cells that inhibit inflammatory processes.[50]

There appears to be enormous value of vitamin D in COVID-19 infections, as administering it reduces the expression of these pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages.[51, 52] It has been shown that vitamin D regulates the inflammatory response, altering the pro-inflammatory/anti-inflammatory balance toward an anti-inflammatory state that controls the inflammatory burst once it is triggered.[53]

Cell culture studies have shown that vitamin D decreases the expression of pro-inflammatory cytokines, increases the production of antiviral proteins, and also has antiviral efficacy, especially facing enveloped viruses; therefore, it would likely be effective against the enveloped SARS-CoV-2 causing COVID-19.[54, 55]

As further support of the likelihood that vitamin D reduces inflammation is a recent study showing a strong correlation with vitamin D levels and C-reactive protein (CRP). Given that CRP is a surrogate marker for the cytokine storm, this supports a role for vitamin D in reducing complications attributed to unregulated inflammation due to the COVID-19 cytokine storm.[56]

Vitamin D Helps Your Immune Cells Create Antimicrobial Peptides

Vitamin D receptors have been identified in nearly all of your immune cells, including monocytes, B and T lymphocytes, white blood cells, macrophages and dendritic cells, as well as the epithelial cells in your lungs.[57] This is important because if you have sufficient vitamin D in your blood it can activate these cells to create what researchers call antimicrobial peptides (AMPs).[58]

Many studies have shown that vitamin D activates your immune cells to produce AMPs which include molecules known as cathelicidins and defensins.[59-62] AMPs have a broad spectrum of activity, not only microbial but also antiviral, and have been shown to inactivate the influenza virus.[63] The antiviral effects of AMPs are the result of, among other effects, the destruction of envelope proteins done by cathelicidin.[64]

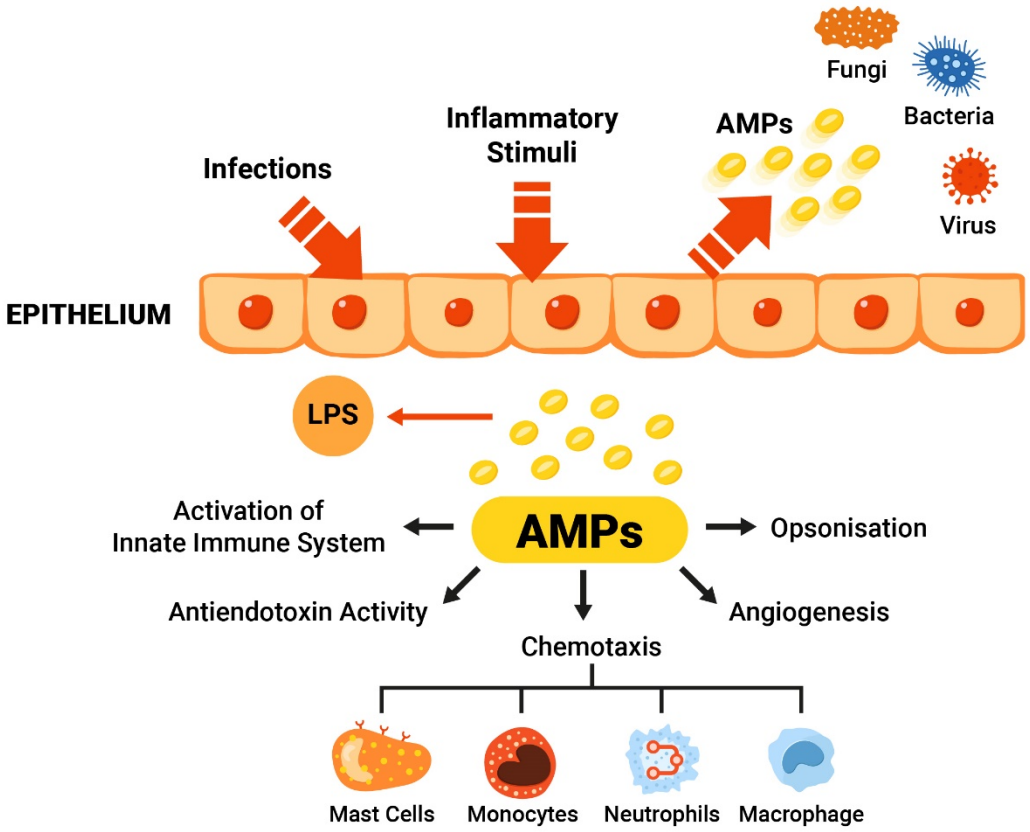


Figure 10

Cathelicidins are a distinct class of proteins present in the innate immunity of mammals. In humans the primary form of cathelicidin is known as LL-37.[65] LL-37 also blocks viral entry into the cell in a similar manner to what is seen with other antimicrobial peptides.[66]

Epidemiologic evidence describes a positive vitamin D-related immune effect that includes many studies which feature enveloped viruses like SARS-CoV-2. This supports the notion that LL-37's anti-viral effects may be partially mediated by envelope disruption,[67] as LL-37's anti-microbial effect is linked to its ability to disrupt the lipid envelopes of viruses through electrostatic interactions.[68]

Vitamin D also regulates another type of AMP called beta defensin 2. Its antiviral effects result from its impact on your white blood cells, such as neutrophils and monocytes.[69]

Vitamin D Deficiency Increases Your Risk for COVID-19

A recent retrospective analysis at the University of Chicago of over 4,000 patients[70] was designed to examine whether vitamin D deficiency and treatment are associated with testing positive for COVID-19. They found that vitamin D deficiency that was not sufficiently treated was associated with an increased risk for COVID-19 infection.

Another observational study involving 212 patients in Southeast Asia did multinomial logistic regression to predict clinical outcomes of patients infected with COVID-19 based on their vitamin D levels.[71] The results are summarized in the graph below, which shows that of those with a COVID-19 case that was critical or severe, only 4% had normal levels, while 96% with mild COVID-19 had normal vitamin D levels.

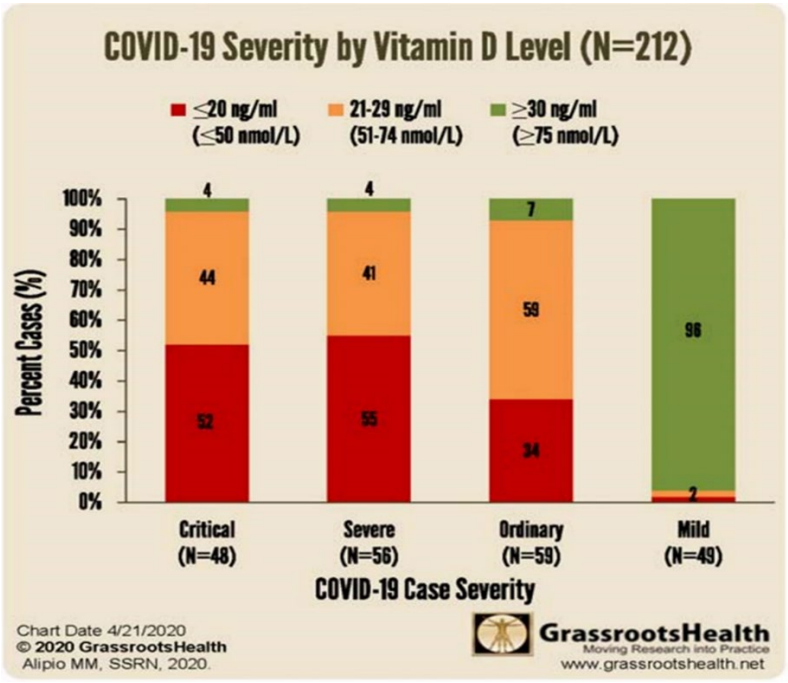
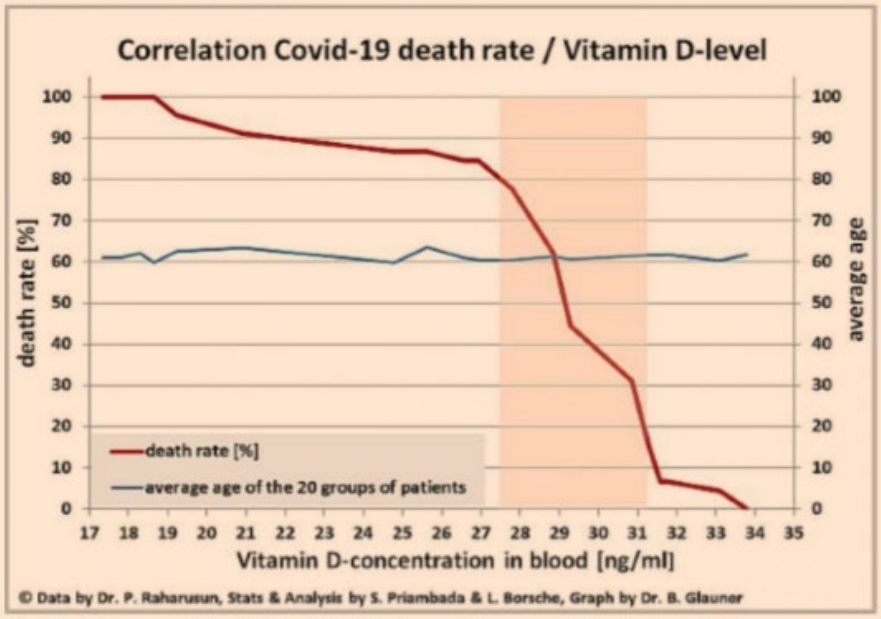


Figure 11

Another retrospective study involved 780 cases with laboratory-confirmed infection of SARS-CoV-2 in Indonesia. When controlling for age, sex, and comorbidity, they found that vitamin D status was strongly associated with COVID-19 mortality outcome of cases.[72] A summary of these findings are in the impressive graph below that demonstrates a radical reduction in the death rate from COVID-19 as the vitamin D level increases to over 30 ng/ml.

A picture is worth a thousand words:



Results of the age-adjusted clinical study by the working group of Dr. Prabowo Raharusun.

Figure 12

Similarly, a recent retrospective analysis from Sweden of 107 patients[73] found that vitamin D concentrations were significantly lower in patients with positive PCR (polymerase chain reaction) tests for SARS-CoV-2. The researchers concluded that vitamin D3 supplementation would be useful in the treatment of COVID-19 infection, in preventing a more severe disease and/or in reducing the presence of the virus in the upper respiratory tract and making the patients less infectious.

Evidence was recently outlined to show that vitamin D deficiency could explain much of the reason for higher case and mortality rates for Black, Asian, and Minority Ethnic (BAME) residents in England.[74]

There is also a preprint publication demonstrating a connection between vitamin D insufficiency and COVID-19. Louisiana State University Health Sciences Center studied 20 ICU COVID-19 patients and nearly 85%, vs. 57% in-floor patients were vitamin D insufficient.[75]

Israeli investigators tested 14,000 for COVID-19 from February 1 to April 30, 2020 and found if patient's vitamin D levels were greater than 30 ng of vitamin D, they were seven times less likely to have COVID-19.[76] Additionally, there have been strong retrospective correlations between vitamin D and COVID-19 mortality in Europe.[77-79]

How Vitamin D Reduces the Risk of Viral Infections

There are many reviews that consider the ways in which vitamin D reduces the risk of viral infections.[80-92]

Vitamin D likely reduces the risk of viral respiratory infections because it influences several of your immune pathways, with the net effect of boosting your mucosal barrier defenses while simultaneously dampening excessive inflammation.[93] Vitamin D appears to decrease the risk of respiratory tract infections by three main mechanisms:[94]

- It helps maintain tight junctions in the epithelial cells of the lungs and gut to prevent the infiltration of immune cells in lungs and other respiratory tissues,
- It inactivates some viruses through the stimulation of antiviral mechanisms such as antimicrobial peptides, as discussed in the section above.
- It reduces pro-inflammatory cytokines through the modulation of the immune system as discussed in the section above.

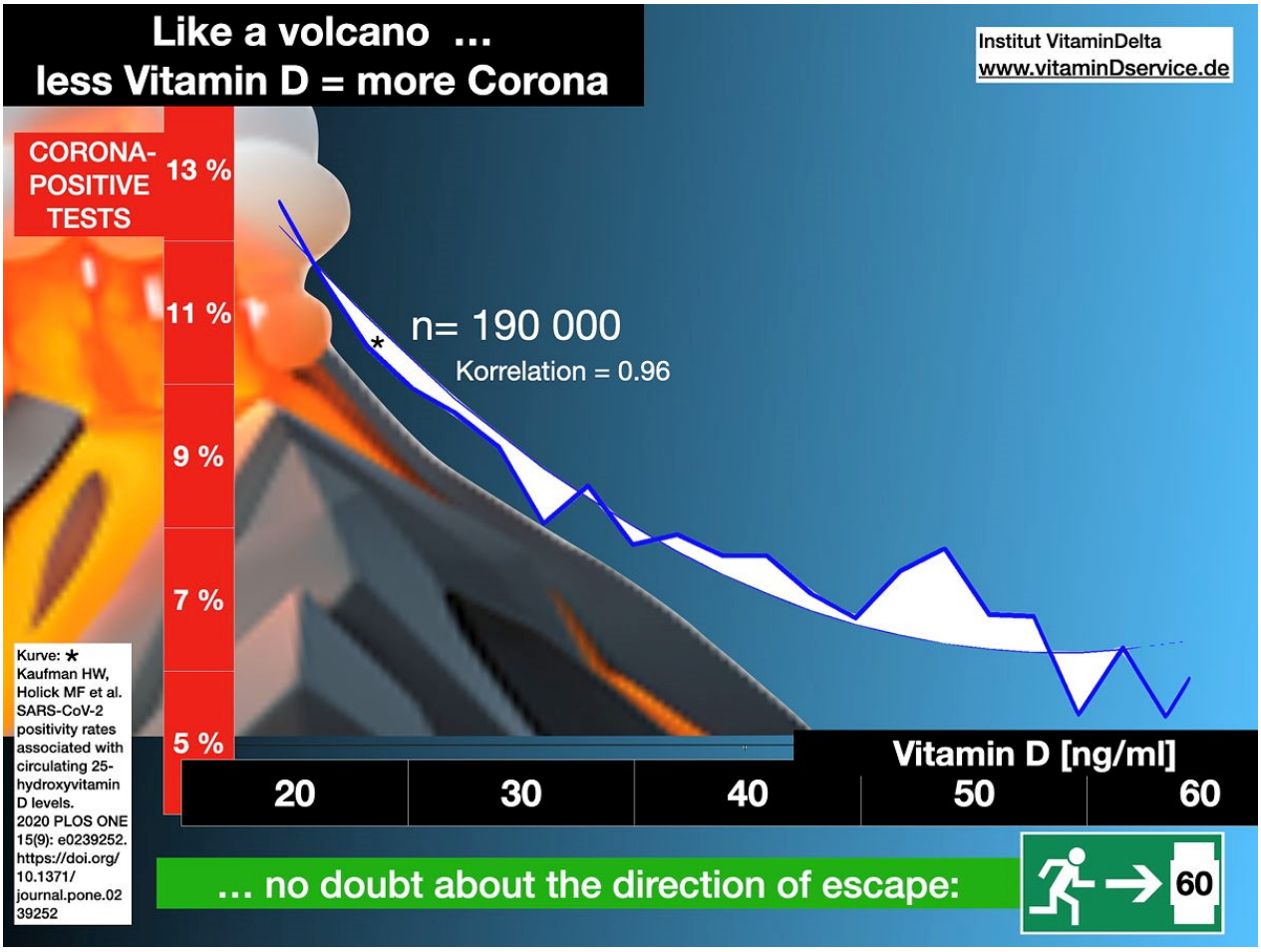


Figure 13

How Vitamin D Specifically Reduces the Risk of COVID-19

The type-II pneumocytes in your lungs are the primary target for coronaviruses because the ACE2 receptors to which the virus binds are highly expressed on these cells. One of the problems with COVID-19 infections is that it impairs the function of your type-II pneumocytes, which then decreases the surfactant level in your lungs.[95]

This is important because surfactant prevents the collapse of the alveoli in your lungs. Surfactant allows your alveoli to stay open and compliant during both inspiration and expiration. During inspiration, your alveoli may collapse if they do not contain surfactant. If they collapse, then gas exchange across the alveoli wall cannot occur.

Without surfactant, each breath taken is like blowing up a collapsed balloon and then letting the air out of that balloon (your lungs), and doing it all over again with the next breath cycle. Simply put sufficient surfactant is necessary for your alveoli to stay open and gas exchange to occur as shown in the Figure 14 below.

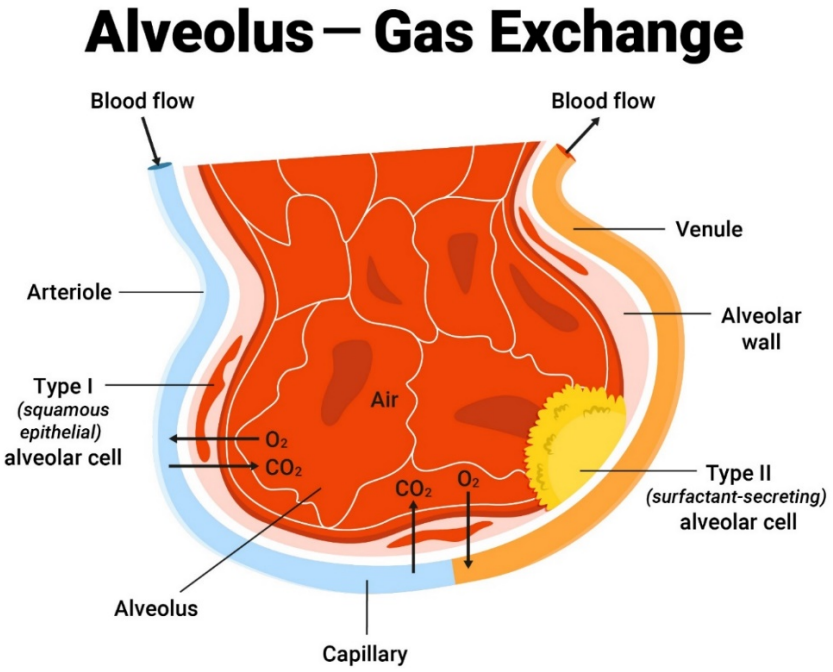


Figure 14

Fortunately, vitamin D comes to the rescue for this problem produced by COVID-19, as it is able to stimulate the production of surfactant in alveolar type-II cells.[96]

Vitamin D, Angiotensin II and ACE2 Receptors

Angiotensin-converting enzyme (ACE) is part of the renin-angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in your body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II.

Angiotensin II is a natural peptide hormone is best known for increasing blood pressure through stimulating aldosterone.[97] ACE2 normally consumes Angiotensin II, thereby lowering its levels. However, COVID-19 infection downregulates ACE2, which in turn leads to excessive accumulation of Angiotensin II.

Cell cultures of human alveolar type-II cells with vitamin D have shown that the SARS-CoV-2 virus interacts with the angiotensin-converting enzyme (ACE) 2 receptor expressed on the surface of your lung epithelial cells. Once the virus binds to the ACE2 receptor, it reduces its activity and, in turn, promotes ACE1 activity forming more angiotensin II, which increases the severity of COVID-19.[98, 99] This may also be related to the vitamin D-binding protein.[100]

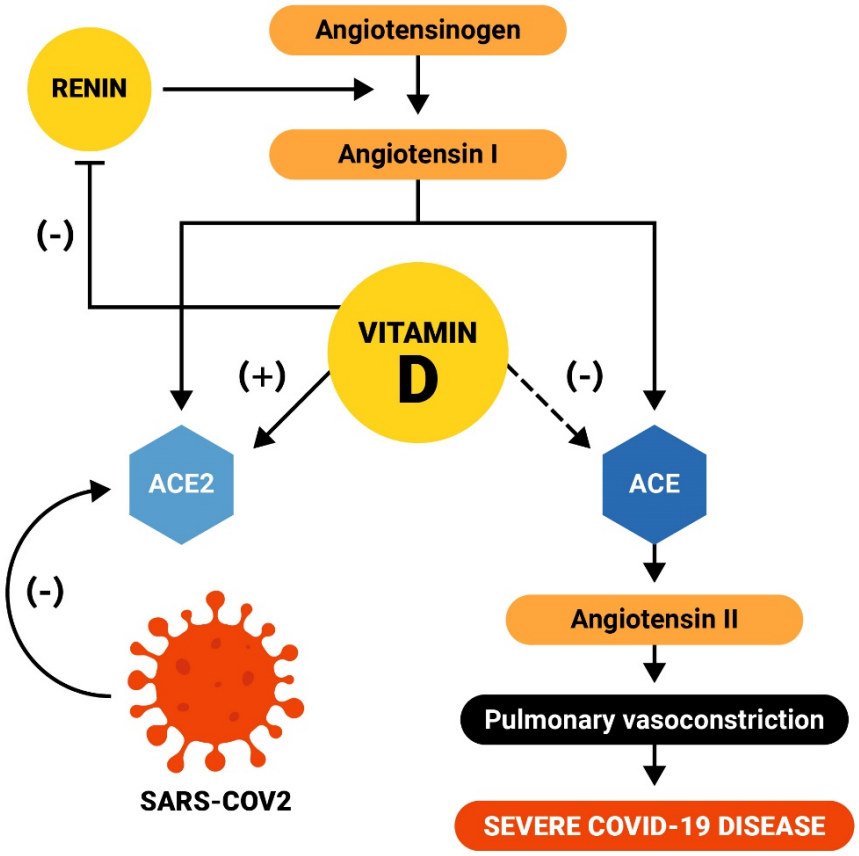
There is a paradoxical effect of vitamin D in limiting the severity of COVID-19. SARS-CoV-2 attaches to the ACE2 receptor expressed on the surface of alveolar epithelial cells. Once the virus binds to ACE2, it reduces its activity and, in turn, promotes ACE activity forming more angiotensin II, which then causes heightened pulmonary vasoconstriction and severity of COVID-19.

The vitamin D analogue calcitriol has been shown to increase the expression of ACE2 in the lungs in experimental animals.[101] The additional ACE2 expressed as a consequence of vitamin D supplementation might reduce lung injury[102] as it can promote binding of the virus to the pulmonary epithelium.

High levels of Angiotensin II may cause acute respiratory distress syndrome (ARDS) or heart injury. Renin, on the other hand, is a proteolytic enzyme and a positive regulator of Angiotensin II. Vitamin D is a potent inhibitor of renin.

Vitamin D supplementation has been shown to prevent Angiotensin II accumulation and to decrease proinflammatory activity of Angiotensin II by suppressing the release of renin in patients infected with COVID, thus reducing the risk of ARDS, myocarditis, or cardiac injury.[103]

The vitamin D renin suppression in turn may generate less angiotensin II resulting in less lung blood vessel constriction. Although vitamin D causes the expression of ACE2, which indeed promotes the binding of the virus, it prevents the lung blood vessel constriction response in COVID-19 as illustrated in Figure 15 below.



The role of vitamin D in COVID-19. SARS-CoV2 binds to the ACE2 of alveolar cells and disturbs the ratio of ACE2/ACE activity. It increases ACE activity and, in turn, results in more angiotensin II formation causing pulmonary vasoconstriction to precipitate severe COVID-19. Vitamin D induces ACE2 expression, which limits the formation of angiotensin II via ACE and reduces lung injury. Besides, vitamin D supplementation may have a protective role against COVID-19. *(Dashed line indicates indirect effect)*

Figure 15

Vitamin D Seasonality and COVID-19

"“Whoever wishes to investigate medicine properly should proceed thus: in the first place to consider the seasons of the year…” (Hippocrates, ca. 400 BC).”[104]

It is interesting to note that there is a strong inverse correlation between sunlight exposure and the case fatality during the 1918-1919 influenza pandemic.[105] This strongly suggests that there is

a relationship between sunlight exposure and the risk for developing severe viral infections and secondary bacterial pneumonias.

Over 50 years ago, R. Edgar Hope-Simpson, a British practitioner and self-educated epidemiologist, documented that influenza A epidemics in temperate latitudes are most intense in the months following the winter solstice.

He hypothesized that solar radiation produces a "seasonal stimulus" that affects the risk of influenza A. He theorized that there is a seasonal steroid hormone system with an impact on the human immune system whose substrate levels are low during the influenza season, but peak when influenza is rare.[106]

The winter incidence of influenza closely correlates with seasonal serum vitamin D levels.[107] A British study also revealed that the prevalence of respiratory infections displayed a strong seasonal pattern in the opposite direction to the pattern for vitamin D concentrations.[108] Seasonal variation in the blood levels of vitamin D, which contributes to immune function, is believed to be the underlying source of the observed influenza seasonality in temperate regions.[109]

More recently, vitamin D deficiency was shown to be a risk factor for and/or a driver of the exaggerated and persistent inflammation that is a hallmark of ARDS.[110, 111] This is further evidenced with COVID-19, where the mortality from the disease has been relatively low for countries below 35 degrees N latitude.[112]

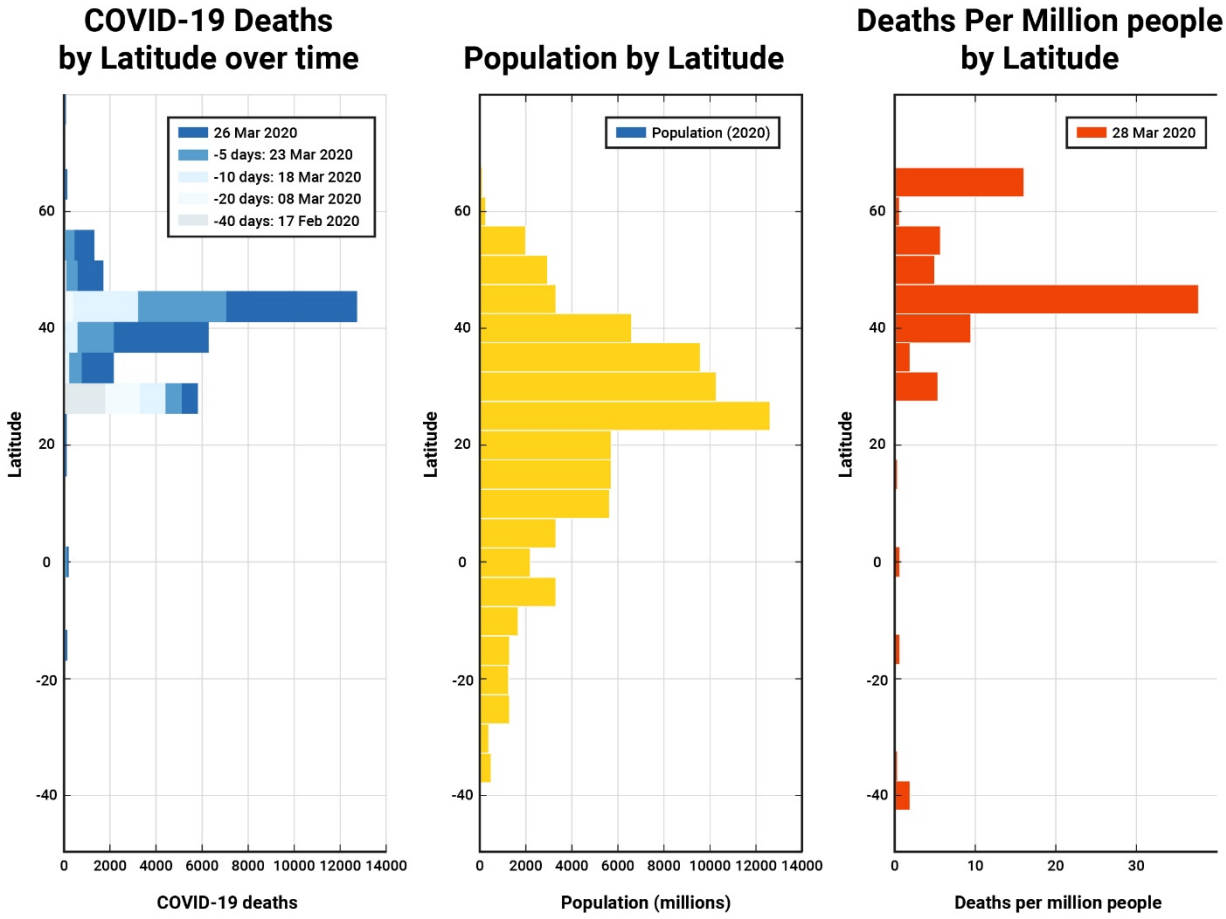
Similarly, researchers demonstrated that the age-specific case fatality rate of COVID-19 was highest in Italy, Spain, and France — the European countries with the highest incidence of severe vitamin D deficiency.[113]

Although some have found that the rates of the cumulative COVID-19 deaths were decreased in countries with more sunshine,[114] Grant's analysis finds that life expectancy is the most important risk factor for those in Europe contracting COVID-19.[115] A recent comprehensive review suggests this is likely due to the immune-senescence that occurs during aging, which contributes to increased levels of inflammation and an increase in cytokine storm risk.[116]

A recent preprint analyzed the impact of strict lockdown orders, clearly demonstrating how staying indoors reduced ultraviolet B exposure by 95% and its protective role in reducing COVID-19 deaths.[117]

Severe COVID-19 outbreaks do indeed show a striking latitude relationship with severe outbreaks occurring exclusively in locations above the 30 degrees N latitude line. Global reports of deaths and recoveries reveal that transmission rates and fatality rates from January to March 28, 2020, were significantly determined by latitude. Researchers aggregated world population

latitude data into corresponding bins and calculated deaths per million as a function of latitude to come up with some powerful observations in Figure 16 shown below.[118]



(Left) COVID-19 fatalities by latitude and over time; (middle) 2020 population by latitude; (right) COVID-19 fatalities per million people by latitude. Note: The Deaths per Million figure at -40°S is a statistical artifact due to dividing two small numbers and may be ignored.

Figure 16

It is important to note that vitamin D obtained through sensible sun exposure is likely superior to oral supplementation. This may be related to other red and near-infrared light frequencies that could provide a therapeutic effect through photobiomodulation mechanisms that could elicit beneficial physiological effects such as increases in nitric oxide.[119]

Safety and Efficacy of Vitamin D Supplementation

The conventional media widely dismisses nutritional supplementation and vitamin D specifically. CNN has recently claimed vitamin D supplementation can actually "hurt you"[120] and compared it to hydroxychloroquine whose "landmark" study the WHO used to justify stopping clinical trials — the same study that was later retracted by The Lancet for fraudulent data use.[121]

A recent June 2020 review from the National Institute for Health and Care Excellence (NICE) which focused on seven studies (despite many hundreds more that were readily available,) found that that there was no evidence for using vitamin D in the treatment of COVID-19.[122] This is consistent with the pharmacological perspective which seeks to limit any threat to a drug therapy for COVID-19.

The New York Times has also recently warned readers to exercise caution in using vitamin D for COVID-19.[123] ABC News cautions people that studies have yet to prove that taking a supplement will help, and actively discourages vitamin D use.[124]

This differs considerably from the stance that the U.K. has taken.[125] In April 2020, Public Health England issued its advice on vitamin D, recommending that those on coronavirus lockdown (including children, pregnant and breastfeeding women and older people) should consider taking a daily supplement of vitamin D, even during the summer months, if they are not going outdoors often.[126]

Public health officials in the United Kingdom have launched an urgent review into the potential role of vitamin D in protecting people against the coronavirus.[127] The British media's Daily Mail suggested that vitamin D may be a cheap and safe way to treat the pandemic, as mounting evidence supports this.[128] The Sun ran a story documenting how those with low vitamin D levels almost certainly die if they are hospitalized.[129]

The Guardian also chimed in affirmatively[130] and reporting that public health officials are urgently reviewing the potential ability of vitamin D to reduce the risk of coronavirus.[131] Scotland also seems to be enthusiastic about adopting vitamin D strategies for COVID prevention.[132]

There are two primary concerns many experts have with using vitamin D as a supplement for helping improve immune functions so your body can do its job to help mitigate the severity of infections like COVID-19. Those questions are: is it safe and does it work?

First, let's address the safety of vitamin D at the serum levels that are needed to achieve therapeutically meaningful blood levels, and what it takes to get there. To evaluate this, you need to understand what the existing conventional medical guidelines are for vitamin D supplementation.

The U.S. Institute of Medicine issued vitamin D and calcium guidelines nearly ten years ago.[133] Their guidelines are seriously dated and have not kept up with the current science, as their recommendation was based solely on the effects of vitamin D for bone health and not for any of the metabolic benefits reviewed in this paper.

The institute recommended vitamin D supplementation of 600 IU/d for people younger than 70 years, 800 IU/d for those older than 70 years, and a serum 25(OH)D concentration of at least 20 ng/mL (50 nmol/L). While these doses will likely lower the risk of rickets, it will not be sufficient to decrease the risk of viral infections in those who are vitamin D deficient.

The institute did admit that no studies had reported adverse effects of supplementation with less than 10,000 IU/day of vitamin D, but still set their upper intake recommendation at 4,000 IU/day, partly out of concerns stemming from observational studies that found U-shaped 25(OH)D concentration-health outcome relationships.

However, later investigation determined that their recommendation was flawed, as most reports of J- or U-shaped relationships were from observational studies that did not measure serum vitamin D blood levels, and that the likely reason for those relationships was a result of enrolling some participants who had started taking vitamin D supplements shortly before enrolling.[134]

It is useful to understand that significant levels of vitamin D can be produced from sun exposure during non-winter months. Approximately 10,000 to 25,000 IUs of vitamin D3 can be produced in a short time in the sun with full-body exposure, so it is obvious that your body can handle that amount easily.[135]

So, let's look at some of the recent studies that support a higher dose of vitamin D. One was done in a psychiatric hospital in Cincinnati, Ohio. The age range was from 18 to 90 years. Half the patients were black, and nearly half were white.

All patients entering since 2011 were offered supplementation of 5,000 or 10,000 IU/day of vitamin D3. For 36 patients who received 5,000 IU/day for 12 months or longer, vitamin D levels rose from 24 to 68 ng/mL, whereas for the 78 patients who received 10,000 IU/day, mean concentrations increased from 25 to 96 ng/mL. No cases of vitamin D-induced hypercalcemia were reported.[136]

Another recent study used 10,000 IU/day of vitamin D for 8 to 12 weeks, and 93% of the subjects had vitamin D blood levels at or greater than 30 ng/mL after the first month; in two months the percentage increased to 100%. They also had no cases of hypercalcemia occur.[137]

Although doses of 15,000 IU/day are rarely needed or recommended, they were found to be safe.[138] Data were collected for 3,882 participants in a community program. Blood vitamin D

levels were measured at program entry and at follow-up within 6 to 18 months between 2013 and 2015.

Participants supplemented with a wide range of vitamin D doses (1,000 to 15,000 IU/day). To achieve vitamin D levels above 40 ng/mL, on average they needed vitamin D intakes of 6,000 IU/day for normal Body Mass Index (BMI); 7,000 IU/day for overweight; and 8,000 IU/day for obese. They found no evidence of elevated calcium levels in the blood or urine at any vitamin D dose.

It has been suggested that the tolerable limit could be increased to 10,000 IU/day, as hypercalcemia is rarely encountered at lower doses, and most reports of other symptoms of vitamin D toxicity such as severe fatigue, confusion, vomiting, arrhythmia, and calcium kidney stones only occurred at doses exceeding 40,000 IU/day.[139] In confirmation of this, a 2020 Canadian trial found the safety profile of vitamin D supplementation was similar for doses of 400, 4,000 and 10,000 IU/day in nearly 400 elderly patients.[140]

A recent trial on a high-dose vitamin D supplementation in New Zealand involving 5,110 participants reported that, over a median of 3.3 years, monthly supplementation with 100,000 IU of vitamin D3 did not affect the incidence rate of kidney stone events or hypercalcemia.[141] However, it should be noted that doses less than once a week are not recommended as they are not as effective.

A large meta-analysis of 25 randomized controlled trials of nearly 11,000 individual patients concluded that vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. However, it also showed that the benefit from vitamin D was stronger for those who received daily doses of vitamin D, but not in those who received large infrequent doses more than every two weeks.[142, 143]

The second important question, does vitamin D supplementation work? This becomes somewhat confusing because there are many vitamin D trials showing that it is ineffective with no clinical benefit.[144]

In nearly every case this is due to a common methodological flaw in the study. Typically, all of these studies that fail to show a benefit of vitamin D used a specific dose of vitamin D rather than adjusting the dose to achieve an optimal vitamin D blood level. Further, they have failed to measure major co-factors such as nutrient intake such as magnesium, calcium and vitamins K2 and C.

They also are designed similar to pharmaceutical trials where a study participant is randomized to a drug or placebo, where all participants start with a baseline concentration of zero. With vitamin D studies, individuals start with varying 25-hydroxyvitamin D levels in their blood so the

dose response will vary according to the blood level. In addition, the blood level does not mean that is what is the level is within the cells or at the cellular level.

Randomized controlled trials evaluating the impact of vitamin D supplementation on clinical outcomes simply need to use a study a design based on serum levels of 25-hydroxyvitamin D concentrations rather than administered vitamin D doses.[145, 146] Once you understand this and you carefully review the methods section of the study, you will find that nearly every negative vitamin D study failed to individualize dosing based on blood levels. Further, one of the biggest omissions was any defined co-factors.[147]

Vitamin D Levels

Researchers have shown that levels of at least 30 ng/mL are necessary for the optimal induction of the antimicrobial peptide LL-37 (cathelicidin)[148] (as discussed in an earlier section here), while vitamin D levels of approximately at or greater than 40 ng/mL seem to provide protection against acute viral respiratory infections.[149, 150]

A meta-analysis of 25 trials, of over 11,000 participants, showed vitamin D supplementation to reduce the risk of acute respiratory infections, including viral, by 12% in all participants. This was most pronounced in patients with serum vitamin D levels below 20 ng/mL.[151]

Maintenance of circulating 25-hydroxyvitamin D levels of 40 to 60 ng/mL would be optimal, since concentrations of 40 ng/mL represent the beginning point of the plateau where the synthesis of the active form of vitamin D becomes consistent.[152, 153]

The upper limit of 60 ng/ml is based on a recent prospective study that reviewed over 15,000 people over an 8 year period and found that vitamin D was non-linearly associated with lower risk of all-cause, CVD, and cancer mortality that leveled off at 60 ng/ml.[154]

Since vitamin D can be made in your skin, the term “vitamin” seems inappropriate. However, compared to the past, most of us spend far more time indoors, largely cover our skin with clothing when outdoors, and often live at latitudes where, during winter, UV-B radiation is inadequate for many months. Therefore, most are unable to generate healthy levels of vitamin D, which is why most people benefit from vitamin D supplementation.

It is important to understand that blood levels targeted to a specific dose of vitamin D will be highly variable between individuals due to several demographic and biological factors:

- Baseline vitamin D status
- Status of co-factors such as magnesium, calcium, vitamin K2, vitamin C, and omega 3s
- Lower levels of 7-dehydrocholesterol in the skin[155]
- Ethnicity and skin color
- Body fat percentage
- Genetics
- Seasonal variations and time of sun exposure[156]
- Type and timing of vitamin D supplements[157]
- Malabsorption of fats from the GI tract, such as with cystic fibrosis or inflammatory bowel disease

Increased skin pigmentation reduces the efficacy of UVB because melanin functions as a natural sunblock. In addition, aging decreases the ability of the skin to produce vitamin D3.[158] During the winter months at latitudes of greater than 28˚N,[159] little or no UVB radiation reaches the surface of the earth.

However, residence at low latitude does not guarantee adequate vitamin D levels. Social and cultural norms may limit sun exposure,[160] particularly as we age, leading to a tendency of serum vitamin D levels to decrease with age[161] — which is important for COVID-19 because case-fatality rates (CFRs) increase with age.[162]

Finally, pharmaceutical drug use typically increases with age, and drugs such as antiepileptics, antineoplastics, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine drugs, and some herbal medicines can decrease vitamin D levels by activating the pregnane-X receptor.[163]

Vitamin D Dosing

Ideally, one should test his/her vitamin D blood level as this will help to identify the ideal starting dose. GrassrootsHealth has analyzed data from over 15,000 people taking vitamin D and put together a calculator.

All you need to do is input your weight, vitamin D level and desired level and it will suggest a dose for you. It can be found at https://www.grassrootshealth.net/project/dcalculator/.

Please understand though, that this is just an estimate and it would be ideal to retest in about three to six months since vitamin D levels rise slowly. But as mentioned above, since there is

virtually no risk of taking a dose of 8,000 units per day, this seems to be a safe strategy. However, if you are normal body weight or underweight you can reduce this amount by 1,000-2,000 units per day as less vitamin D is needed.

Other Nutrients that May Augment the Effectiveness of Vitamin D Supplementation

Magnesium supplementation is recommended when taking vitamin D supplements. Magnesium helps activate vitamin D. All the enzymes that metabolize vitamin D seem to require magnesium, which acts as a co-factor in the enzymatic reactions in the liver and kidneys.[164] The dose of magnesium should be in the range of 250 to 500 mg/day, along with twice that dose of calcium.

Magnesium activates more than 600 enzymes and influences extracellular calcium levels.[165] It is essential for the stability of cell function, RNA and DNA synthesis, and cell repair, as well as maintaining the antioxidant status of the cell. It is an important co-factor for the activation of a wide range of transporters and enzymes.[166, 167]

A recent review found that as many as 50% of Americans taking vitamin D supplements may not receive significant benefits. This happens when the vitamin D they take gets stored in its inactive form because they have insufficient magnesium levels. Magnesium supplementation has been shown to markedly reduce the resistance to vitamin D treatment.[168-170]

In a preliminary analysis, GrassrootsHealth found[171] that individuals who do not take supplemental magnesium need, on average, 146% more vitamin D to achieve a blood level of 40 ng/ml (100 nmol/L), compared to those who take at least 400 mg of magnesium per day.

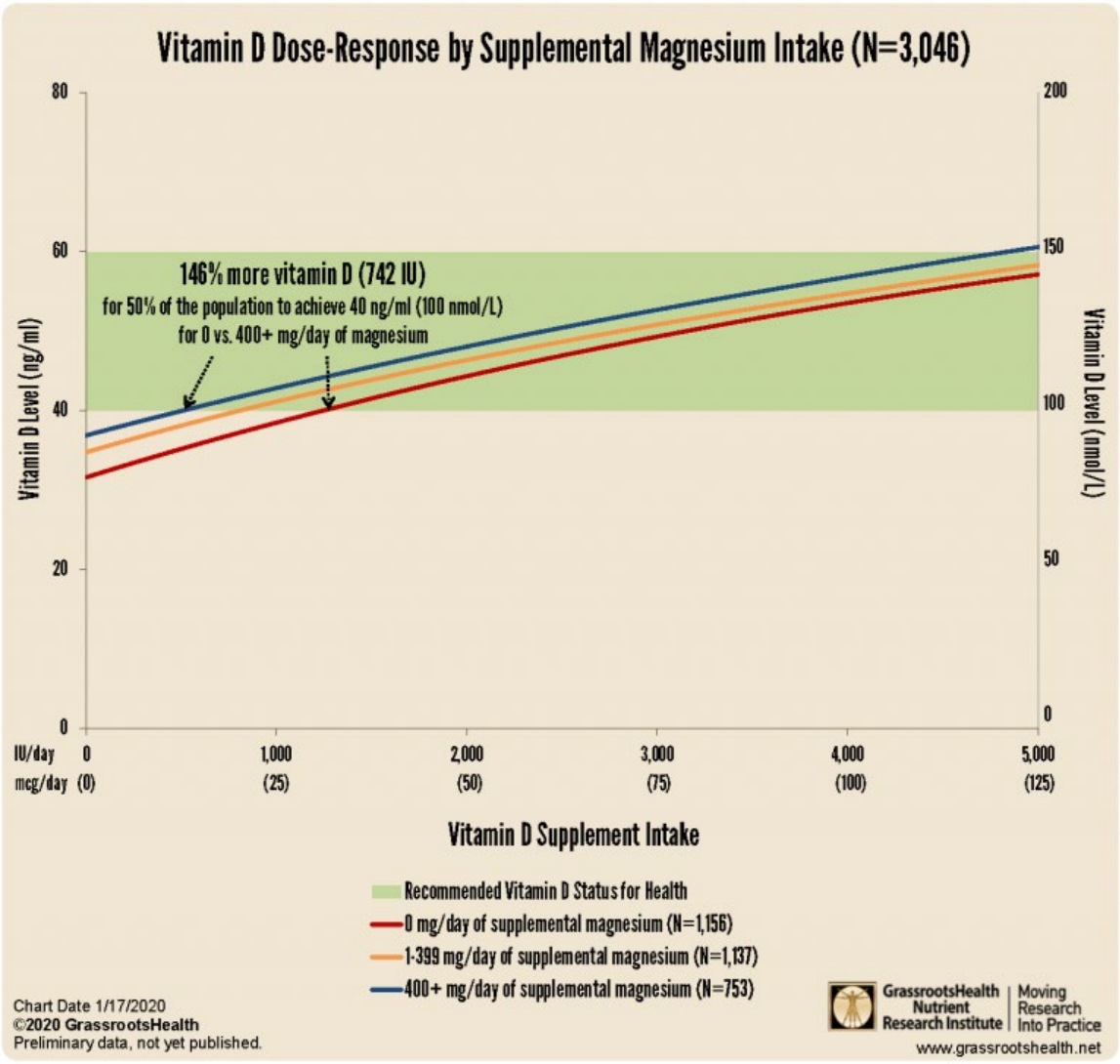


Figure 17

The interplay between magnesium and vitamin D isn't a one-way street, though. It goes both ways. Interestingly, while vitamin D improves magnesium absorption,[172] taking large doses of vitamin D can also deplete magnesium.[173] Again, the reason for that is because magnesium is required in the conversion of vitamin D into its various forms. If the level is about 20 ng/mL, it takes about 35 days to reach 60 ng/mL with a daily dose of 10,000 IU of vitamin D, and 85 days with 4,000 IU/day.[174]

If one is challenged with an acute scenario, it may even be wise to use a very large initial dose. A randomized controlled trial (RCT) published in 2015 showed that after a single dose of 250,000 IUs of vitamin D3 given to healthy volunteers between the ages of 18 and 65 years with

baseline serum levels under 17 ng/ml, serum 25(OH)D concentrations at five days increased to an average of 41 ng/ml with no adverse effects.[175]

After five days it would be reasonable to start a dose of 5,000 units a day, as after 90 days, vitamin D levels will drop back to near baseline values.[176]

While vitamin D supplementation could stop COVID-19 from developing at the beginning of symptoms, it probably would not be very useful after lung and organ damage occurs in the acute stage.[177]

While vitamin D is likely the most important nutrient to optimize for COVID-19 prevention, other nutrients, micronutrients, and phytonutrients are also known to impact your immune system and infection risk.[178, 179]

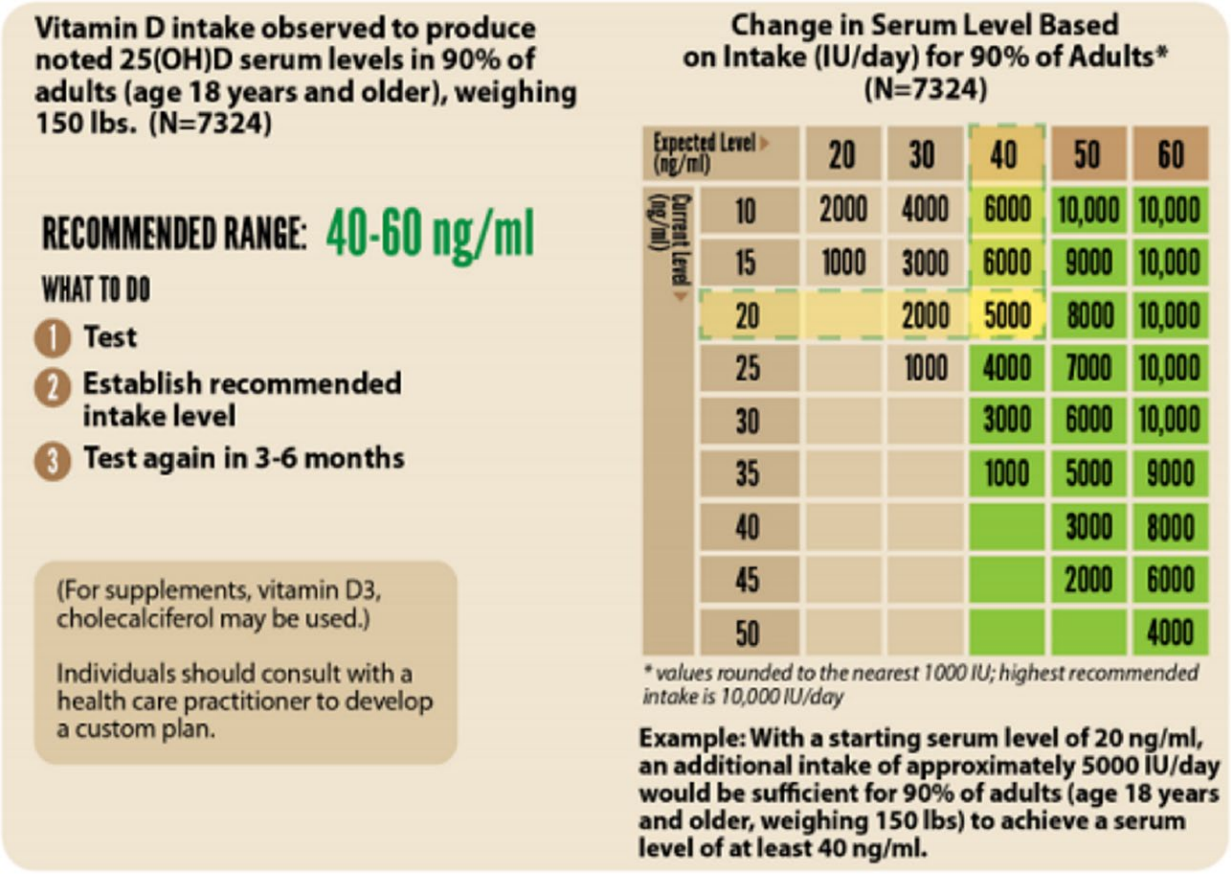


Figure 18

Target of Vitamin D Campaign

If you have ever flown you will likely recall the flight attendant's take-off briefing, which tells you that, in the event of an emergency, an oxygen mask will automatically appear in front of you. But they also tell you that if you are traveling with a child or someone who requires assistance, to secure your own mask first, and then assist the other person.

The lesson here is that it will be important to adopt the vitamin D recommendations and its co-factors in this paper for yourself and family first. But it is the intention of this document to create and empower an army to target the populations that are most at risk for the next wave of COVID-19 or any other respiratory infection that comes our way. The target populations are the elderly and people of color (and those with chronic diseases, and pregnant and nursing mothers).[180]

It is important to know that YOU can make a difference by taking this information and sharing it with others, especially those that have influence to spread this message to these at-risk populations.

By a little investment of time you can save many lives at virtually no cost. Remember: if it is the late spring, summer or early fall, you likely can get enough vitamin D for free by merely going outside around solar noon, just being careful to never get burned.

If you live below 27 degrees N latitude you can get vitamin D most of the year from the sun. But, if you don't live that far south or it is in winter, vitamin D supplements are some of the least expensive supplements you can purchase. All you need to do is follow the dosage recommendations above.

Black Americans and People of Color

Collectively, Black Americans represent one-eighth of the population in the U.S., but they have suffered one-fourth of known COVID-19 deaths. They are dying at twice their population share.[181] So what could explain this dramatic difference in death rates between white and Black Americans?

In the graph below that is compiled from approximately 15,000 tests done at GrassrootsHealth over the last 13 years, you will notice from the levels of vitamin D based on race in the U.S. that

only 16% of Black adults have adequate vitamin D levels, while over three times that number, or nearly 50%, of white adults have vitamin D levels over 30 ng/ml.

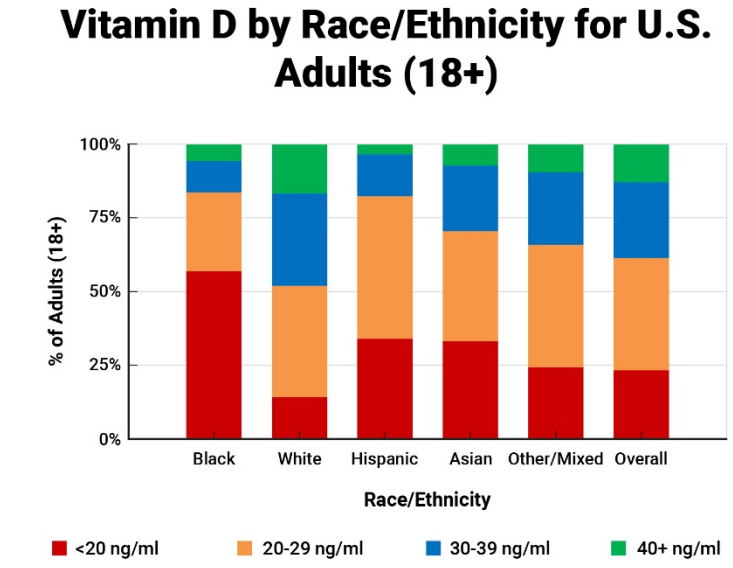


Figure 19

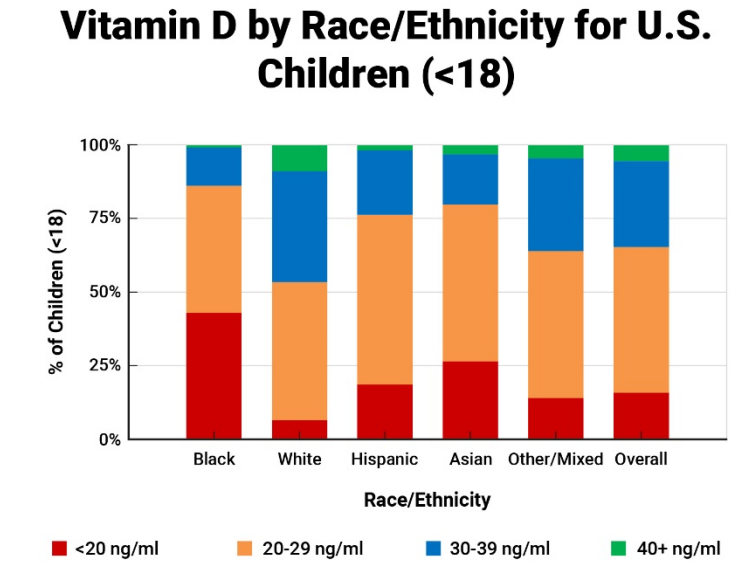


Figure 20

Elderly Focus

There are a number of very good reasons why one would expect the elderly to have an increased risk of developing COVID-19. During aging, there is a gradual decline in immune function called immunosenescence, which hampers pathogen recognition, alert signaling and clearance.[182] Other hallmarks of aging include known destructive processes to the immune system such as inflammation and inflammasomes, genomic instability, mitochondrial dysfunction, epigenetic alterations, telomere attrition, and impaired autophagy that result in variability in reserve and adaptation immune capacity.[183]

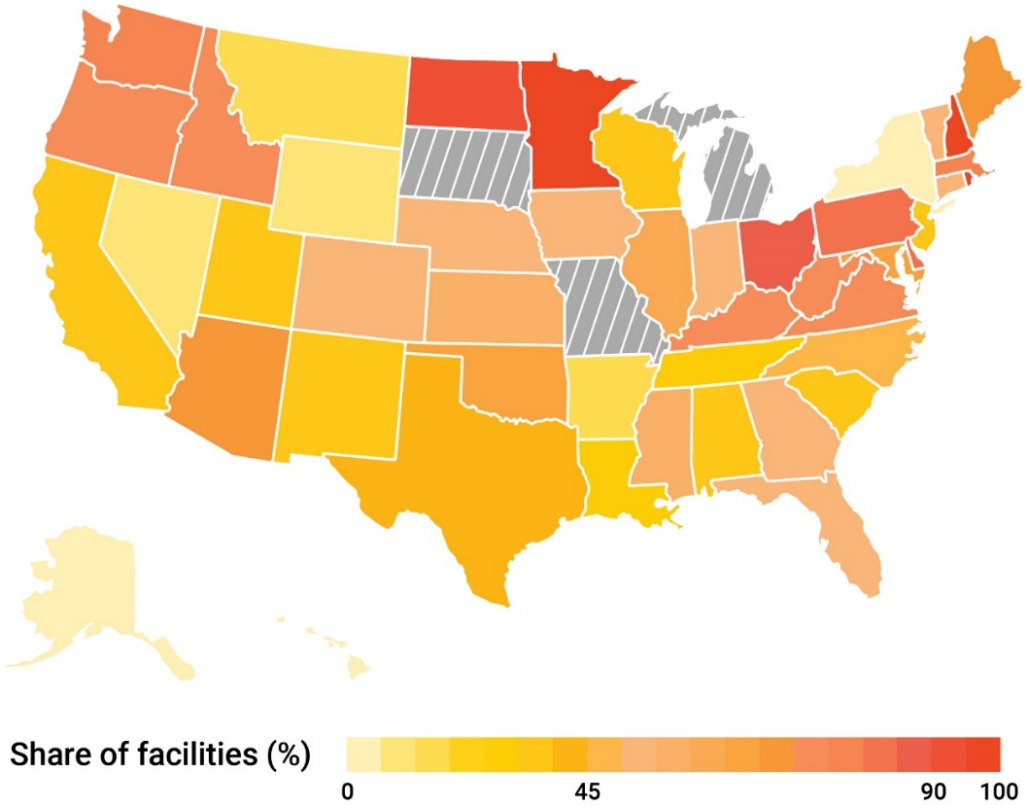
Based on a recent analysis of state-by-state COVID-19 fatality reports, it is clear that one of the most underappreciated aspect of COVID-19 is its effect on those living in nursing homes and assisted living facilities. This population is particularly at risk of vitamin D deficiency as they aren't able to go outside as much and even if they were able to have sun exposure, they have a diminished ability to convert that to vitamin D.[184]

A landmark study[185] by Gregg Girvan and Avik Roy of the Foundation for Research of Equal Opportunity was done on long-term medical care providers to the aged and medically infirm which consist of:

- Nursing homes and skilled nursing facilities;
- Assisted living facilities, i.e., residential care communities or personal care homes;
- Adult day service centers;
- Home health Agencies; and
- Hospices

The disease caused by SARS-CoV-2 affects the elderly far more severely, on average, than younger individuals. Those living in nursing homes and assisted living facilities seem to be at an extraordinarily increased risk of dying from COVID-19. As you can see in the graphic below from June 2020, 42% of deaths occurred in nursing homes and assisted living facilities.

42% of U.S. COVID-19 Deaths Occur in Nursing Homes & Assisted Living Facilities



42 percent of U.S. COVID-19 deaths have occured in nursing homes and assisted living facilities. Nursing homes are residential facilities for those needing 24/7 on-site medical supervision; assisted living facilities are for those not needing 24/7 medical supervision. The share of deaths occuring in nursing homes and assisted living facilities is highest in New Hampshire, Rhode Island, and Minnesota, using the latest data as of June 1, 2020.

SOURCE: The Foundation for Research on Equal Opportunity. G. Girvan & A. Roy / FREOPP

Figure 21

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