Office of the Prime Minister's Chief Science Advisor
Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia

Vitamin D status and COVID-19

Prepared under urgency – 2 June 2020

Summary

The human body mostly sources vitamin D through a reaction that requires UVB-light (sunshine). It can also be obtained from certain foods and oral supplements. Scientists have long studied the role of vitamin D in the body, and the implications of vitamin D deficiency.

Deficiency correlates with a wide range of diseases – including an increased prevalence and severity of viral respiratory infections.[1–10] Further, there is an observed overlap between several groups at-risk for severe COVID-19 disease and groups at-risk of vitamin D deficiency (although children are a prominent exception). There are also reports of correlation between disease seasonality, sun exposure and case mortality of COVID-19.

These observations perhaps justify further study on the use of vitamin D as a treatment option or preventative measure for COVID-19. They also lend support to recommendations for supplementation in at-risk populations.[11–15]

Reports specifically examining correlation between COVID-19 disease severity and vitamin D status are all observational studies. These show that there is possibly a correlation between vitamin D deficiency and disease severity/case fatality.[11,16–23]

Treatment

There is no evidence (yet) that vitamin D is an effective measure to reduce severity of COVID-19 once a patient is infected. All preprint papers (not yet peer-reviewed) recommend further study. To date, there are no clinical trials that determine the ability of vitamin D to suppress SARS-CoV-2 infection.

Prevention

Preliminary evidence suggests recommendations for at-risk groups to supplement may be beneficial – especially in regions where sunlight exposure is low or vitamin D deficiency is common. However, there are no clinical trials published that evaluate vitamin D supplementation as a prevention method for COVID-19.

Aotearoa New Zealand context

The latest data on vitamin D deficiency in Aotearoa New Zealand comes from two sources: a survey of GP perceptions in 2013[24] and an adult nutritional survey in 2008–9 that reported 5% deficiency and 27% insufficiency in the NZ population.[25] The findings of a survey that is over a decade old are not likely to be representative of today's population, however the groups identified as at-risk of deficiency are still considered at-risk:

- People with naturally dark skin
- People whose skin is not regularly exposed to sunlight, by:
    - regularly covering a lot of your skin (e.g. use of sunscreen or use of concealing clothing, such as a burka), or
    - not going outside.
- People who live in the South Island (especially south of Nelson-Marlborough) and get little time outdoors in the middle of the day between May and August, resulting in a risk of vitamin D deficiency in spring.
- People with liver or kidney disease, or who are on certain medications that affect vitamin D levels.

Testing for vitamin D status is more expensive than supplementing in NZ, so current policy is to supplement individuals at-risk of vitamin D deficiency at the discretion of GPs. This policy is probably also appropriate for managing individuals at-risk of severe COVID-19 disease in NZ until more information is gathered from clinical trials

Aotearoa New Zealand should consider re-evaluating the population in a nutritional survey to get a more accurate picture of health factors that are influenced by nutrition, including vitamin D deficiency.

Background

Sources of vitamin D and vitamin D metabolism

There are five forms of vitamin D. The two main forms are D2 (synthesised in plants) and D3 (synthesised in animals), collectively known as calciferol.

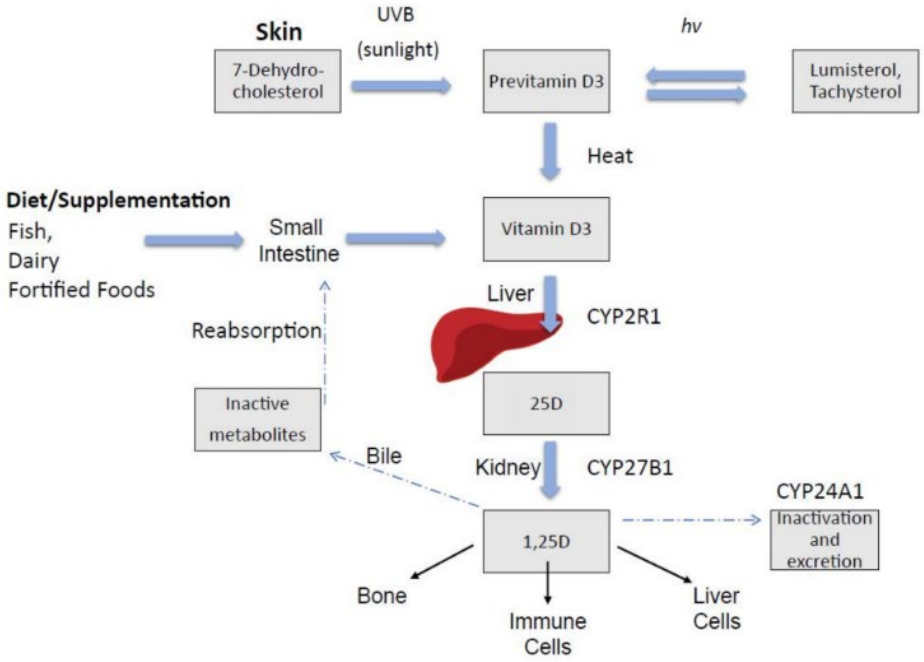

Figure 1: sourced from Keane et al. (2018).[2]

- Vitamin D can be absorbed from foods such as mushrooms, fish, eggs and liver. Additionally, we fortify some foods with vitamin D, such as milk and cereals, to prevent rickets.
- Vitamin D3 synthesis in humans occurs in the skin when exposed to sunlight. A pre-vitamin, 7-DHC undergoes UVB radiation-induced changes to form Vitamin D3. This route accounts for the majority of bioavailable D3 in the body (at least 80%).
- Vitamin D3 is metabolized by liver enzymes to 25D, also referred to as 25(OH)D. 25D is further metabolized by kidney enzymes to the physiologically active metabolite, 1,25D.[26]

Roles of vitamin D in the body

There are receptors for 1,25D expressed in virtually every tissue in the body, but at different levels in different cells types. The 1,25D receptor acts by regulating the expression of genes:

1. 1,25D is transported around the body by the circulatory system.
2. 1,25D can enter cells and then move to the nucleus where it binds to its receptor. This binding event initiates a cascade of biochemical interaction with other proteins in the cell to enable gene transcription machinery to work.
3. The transcribed genes exit the nucleus in the form of messenger RNA (mRNA) and are translated into proteins.

1,25D has also been shown to act on certain cells in a way that does not involve gene regulation but this mechanism of action is disputed and not well understood.[26]

The main role of 1,25D is to regulate the concentration of calcium and phosphorous in the blood by regulating the expression of enzymes involved with calcium or phosphate transport in the intestines, liver and kidneys. This regulation influences many of the body's processes:

- **Maintenance of normal bone mineralisation** – calcium and phosphorus regulation is needed for bone growth and remodeling by osteoclasts and osteoblasts. Vitamin D also regulates calcification of bones.[3]
- **Glucose homeostasis** – calcium is necessary for insulin secretion and the insulin-producing β-cells express vitamin D receptors. This indirectly suggests that vitamin D may contribute to maintaining glucose homeostasis.[3]
- **Modulation of cell growth** – many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are partially modulated by vitamin D. 1,25D exhibits anti-proliferative, pro-differentiating, anti-inflammatory and pro-apoptotic functions in a tissue- and cell-specific manner.
- **Regulation of blood pressure –** there is an inverse correlation between vitamin D and renin levels. Absence of vitamin D signaling causes an increase in renin gene expression and plasma angiotensin II that leads to an increase in blood pressure. This suppressive action of vitamin D on renin is independent of blood calcium or phosphorus levels.[27] The mechanism of blood pressure regulation is thought to occur by modulation of neuromuscular function in smooth muscle of the circulatory system (veins, arteries and capillaries).[28]
- **Neuromuscular function** – calcium ions are a critical component to the functioning of skeletal muscle. The concentration of calcium ions at the junction between muscle cells and nerve cells that communicate the need for muscle contraction is important for muscle function. This calcium ion concentration is modulated by the circulatory system and therefore by vitamin D.[28] 1,25D has also been shown to enhance intracellular calcium ion mobilization in vascular smooth muscle.
- **Modulation of inflammation** – vitamin D has been found to increase the production of anti-inflammatory cytokines while decreasing the expression of proinflammatory cytokines.[29–33]
- **Immune function** – several clinical studies have confirmed that vitamin D plays a crucial role in modulating innate immune responses towards various pathogens.[4,9,34,35]
    - Vitamin D is a component of the macrophage/monocyte response to infection.[1,4]
    - Adequate vitamin D levels have been associated with reduced incidence and severity of enveloped viruses such as herpes zoster, Epstein Barr, hepatitis, Ebola, HIV, dengue, measles and mumps.[15]
    - A number of studies have shown 1,25D inhibits differentiation, maturation and the immunostimulatory capacity of human dendritic cells.[29]
    - Vitamin D metabolites have also been reported to induce other innate antimicrobial effector mechanisms, including induction of antimicrobial peptides, induction of autophagy and synthesis of reactive nitrogen/reactive oxygen intermediates.[1,6]
    - More recent clinical studies indicate that vitamin D can regulate adaptive immune response in various inflammatory and autoimmune diseases. The regulation of adaptive immune response is not well understood.[36]

Vitamin D deficiency

A vitamin D deficiency can occur when:

- usual intake is lower than recommended levels over time,
- exposure to sunlight is limited,
- the kidneys cannot convert 25D to its active form, or
- absorption of vitamin D from the digestive tract is inadequate.

Testing for vitamin D status

What is measured: 25D and 1,25D are transported in the blood mostly by binding to proteins although small amounts are free in the circulation.[26] Serum 25D concentration is measured to determine vitamin D status because it reflects both sources of vitamin D and has a fairly long circulating half-life.[5] 1,25D is generally not a good indicator of vitamin D status because it has a short half-life and the serum concentrations don't typically decrease unless there is severe vitamin D deficiency.[5]

Testing methods: There is a lack of standardisation in testing methods for measuring serum 25D concentration with different tests providing different results. Most test methods require expensive equipment and experienced personnel (e.g. HPLC, LC/MS techniques).

Cost: Vitamin D testing is more expensive than vitamin D supplementation. This means that the general recommendation is to supplement for those who are at risk of deficiency without testing.

How is vitamin D deficiency defined?

There is no universally agreed definition of vitamin D deficiency, and no consensus on what a normal range for serum 25D should be. Different sources typically use their own definitions (Table 1). Typical units are ng/mL and nmol/L (conversion factor 2.5 for 25D).[5]

There is also some evidence of individual genetic variation in vitamin D levels. Using thresholds thus creates arbitrary levels. Clinical treatment should be guided but not dictated by these thresholds: other risk factors need consideration.

Table 1: definitions of vitamin D levels.

Classification	Expert consensus definition[5]	NZ definition*
normal	Serum 25D ≥ 30 ng/mL	Serum 25D ≥ 25 ng/mL
insufficient	Serum 25D of 21-29 ng/mL	Serum 25D of 11-25 ng/mL
deficient	Serum 25D ≤ 20 ng/mL	Serum 25D ≤ 10 ng/mL**

*2008/09 NZ adult nutritional survey.[25] **In the UK Serum 25D ≤ 10ng/mL is used as the indicator for deficiency, in agreement with NZ.

Populations with deficiency

Lack of vitamin D in the diet or poor absorption from the intestines can impact a person's vitamin D status. However, dermal synthesis is the major source of D3 so exposure to sunlight affects vitamin D status to a greater extent. Additionally, because D3 is inactive and requires enzymatic conversion in the liver and kidney to form the active form (1,25D) the functioning of this metabolic pathway affects vitamin D status (i.e. people with liver/kidney disease may have lower vitamin D levels).

Elderly people

- Ageing decreases the ability of the skin to produce D3.[37]
- More likely to be already immune suppressed.
- Rest home environment – most time spent indoors.

People with low levels of sun exposure

- High latitude.
- Winter months.
- Increased skin pigmentation.
- Social/cultural norms that involve skin coverage for example, Muslim women or sunblock use in NZ.
- People who are confined indoors.

Vitamin D deficient diets

- Milk allergy or lactose intolerance.
- Ovo-vegetarianism.
- Veganism.
- Poor absorption from the intestines (e.g. Chron's disease).
- Obesity is a causal factor in vitamin D deficiency.

Pregnant women, children under four years old and teenagers

- These groups have a higher vitamin D demand and so are considered higher risk of deficiency.

People with darker skin

- Higher pigment concentration in skin. Pigment reduces the absorption of UV light leading to decreased D3 synthesis.
- Māori and Pacific, Indian, African and Middle Eastern ethnicities have higher risk of deficiency and require longer periods of sunlight exposure to generate sufficient D3.

Adverse effects of deficiency

The adverse effects of vitamin D deficiency are correlated to its roles in the body. The mechanisms by which deficiency leads to adverse effects are often linked to several physiological processes.

- **Maintenance of normal bone mineralisation – weak bones**
  In the early 1920s it was recognised that the deficiency leads to rickets (weak bones). Recently, genetic variations in the vitamin D receptor have been linked to the development of osteoporosis.[2]
- **Glucose homeostasis – diabetes**
  Type 1 and type 2 diabetes mellitus and some metabolic syndromes have been linked to vitamin D deficiency.[3]
- **Modulation of cell growth – cancer**
  There is a relationship between deficiency and higher incidence of and/or increased risk for many types of cancer. Vitamin D has a growth inhibitory effect on prostate, colon, breast, lung, liver and pancreatic cancer cells which express vitamin D receptors.[3]
- **Regulation of blood pressure – cardiovascular diseases**
  Many observational studies confirmed the association of low vitamin D status with a higher incidence of cardiovascular events and mortality.[38,39] Further, vitamin D deficiency has been reported as an independent risk factor for cardiovascular events, in particular for sudden cardiac deaths. Available evidence on the effects of vitamin D on cardiovascular disease mechanisms has been inconclusive, but it is perhaps related to the regulation of blood pressure and the regulation of inflammation.

- **Neuromuscular function – muscle weakness**
  Genetic variation in the vitamin D receptor and vitamin D deficiency have been linked to impaired muscle function (osteomalacic myopathy).[40]
- **Modulation of inflammation – inflammatory diseases**
  Some studies have found that most asthmatic children are vitamin D deficient. Deficiency has been found to increase the risk of severe asthma exacerbation, defined as the need for emergency room evaluation or hospitalisation.[29] Vitamin D deficiency is also common in patients with inflammatory bowel diseases, including ulcerative colitis and Crohn's disease.[31] Experimental studies have demonstrated that vitamin D can control inflammation and oxidative stress that prevent multiple chronic inflammatory diseases including cardiovascular diseases, chronic kidney disease, liver inflammatory disease and multiple sclerosis.
- **Immune function – respiratory diseases**
  Observational studies report consistent independent associations between low serum concentrations of 25D and susceptibility to acute respiratory tract infections by viruses (e.g. respiratory syncytial virus, tuberculosis and influenza).[6] Vitamin D deficiency is also associated with adverse outcomes from respiratory diseases, likely linked to the role of modulating inflammation. It is also linked to an increased risk/incidence of exaggerated and persistent inflammation that is a hallmark of acute respiratory distress syndrome.[33] Additionally, there are laboratory studies showing that respiratory epithelial cells can convert vitamin D25 to its active form, these vitamin D metabolites do not prevent viral replication *in vitro* but the do increase production of inflammatory cytokines involved in immunity in response to respiratory viruses.

Vitamin D as a treatment

Vitamin D has not been shown to be effective in treatment of deficiency-related diseases. For example, the National Heart, Lung and Blood Institute published a study in 2019 that found that early administration of high-dose enteral vitamin D3 did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D–deficient patients.[41]

In a New Zealand randomized controlled trial, monthly high-dose vitamin D supplementation did not prevent acute respiratory infections in older adults with a low prevalence of vitamin D deficiency.[42]

Nonetheless, there are hundreds of clinical studies on the supplementation of vitamin D in deficient populations and the positive effects this has on both disease risk and decreasing severity of adverse effects.

Given the correlations between deficiency and a multitude of health issues, vitamin D supplementation is recommended as prophylactic measure for people at-risk of deficiency and deficiency-related disorders.

Vitamin D toxicity

Vitamin D toxicity can be caused by excessive oral intake through supplementation, but not by prolonged exposure of the skin to UV light. The clinical definition for vitamin D intoxication varies but it appears that it does not occur until blood levels are ≥150–200 ng/mL.[5] Blood calcium may reach levels that can cause unpleasant and potentially dangerous symptoms. Symptoms of vitamin D toxicity (hypervitaminosis D) include dehydration, vomiting, decreased appetite, irritability, constipation, fatigue and muscle weakness.[24]

Vitamin D deficiency in Aotearoa New Zealand

NZ vitamin D status definitions

- Deficient: serum 25D ≤ 25 nmol/L
- Insufficient: serum 25D between 25–50 nmol/L
- Normal: serum 25D 51–125 nmol/L

Publications

2008/09 New Zealand Adult Nutritional Survey (ANS)

The most recent data on vitamin D levels in NZ comes from the 2008/09 New Zealand Adult Nutritional Survey (ANS) in which participants (over 15 years old) filled out a survey and provided a blood sample every month.[25] The ANS found that:

- 5% of people were deficient and 27% of people were insufficient in vitamin D levels.
- The prevalence of vitamin D deficiency did not vary significantly by age or gender.
- Vitamin D deficiency was more prevalent in August, September and November.
- Latitude correlated with vitamin D deficiency.

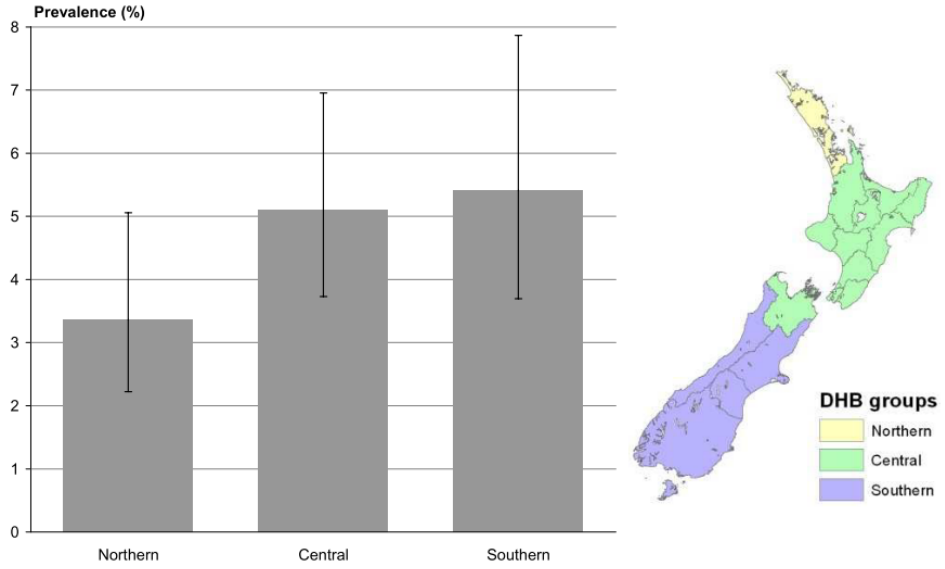

Figure 2: prevalence of vitamin D deficiency by region (unadjusted prevalence).

Ethnicity

- About 10% of Pacific people had vitamin D deficiency, tending to have lower levels of vitamin D than non-Pacific peoples.
- 6.7% of Māori women showed deficiency and Māori women were more likely to be below the recommended level of vitamin D than non-Māori women
- 5.2% of Māori men were deficient and there were no significant differences between Māori and non-Māori men.
- There were not enough Asian participants to draw clear conclusions on this cohort.

Socioeconomic status

The ANS found that prevalence of vitamin D deficiency tended to be higher in neighbourhoods with greater socioeconomic deprivation, as measured by NZDep2006 quintiles.

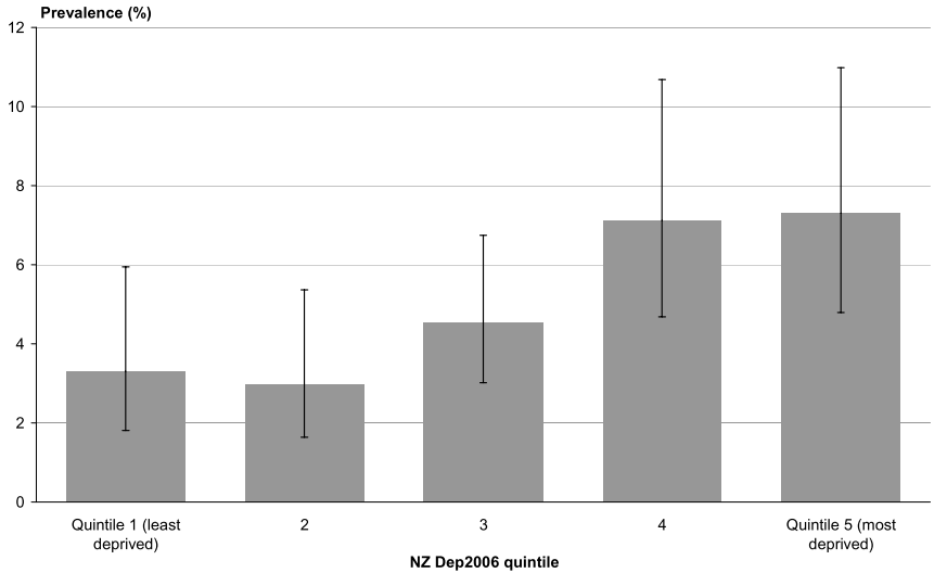

Figure 3: Prevalence of vitamin D deficiency by NZDep2006 quintiles among adults (unadjusted prevalence), 2008–9.

Obesity

The ANS used BMI as a measure of obesity and did not find significant differences in prevalence of deficiency by body size. The survey did find that:

- 4.2% of people who were at normal weight/underweight were vitamin D deficient, and
- 5.4% of obese people were deficient.

An updated survey is needed

The ANS is now more than a decade old, and a large body of international research on vitamin D and health has since been published. New evidence may necessitate a review and update of vitamin D advice.

For example, in a news article in 2019, Professor Jim Mann (University of Otago) and Honorary Associate Professor Winsome Parnell (former director of the ANS) said that "serious thought needs to go into planning for an updated national nutritional survey, with the last adult survey carried out a decade ago, and a children's survey in 2002."[43]

General practitioner survey

A 2013 publication by published Reeder *et al.* reports New Zealand general practitioner (GP) perceptions of:

- vitamin D sources;
- risk factors, prevention and management of vitamin D deficiency and insufficiency;
- supplement prescribing practices; and
- patients' enquiries.[24]

Sun exposure was considered the main vitamin D source in summer, but in winter supplements and food sources were more commonly mentioned.

GPs reported managing insufficiency and deficiency primarily through high-dose supplementation and advice to receive more sunlight.

Almost half of the GPs had received patient requests for vitamin D testing and 40% reported requests for prescribed vitamin D.

Policy

In Aotearoa New Zealand, the current recommendation is that it is not cost-effective to undertake widespread blood testing. This is because the cost of testing is far greater than the cost of treatment. There are some specific cases where vitamin D testing may be considered appropriate, but it is more important to identify those at most risk of deficiency by risk factor profile.

Risk factors in New Zealand include:

- Having naturally very dark skin. This includes people from Africa, the Indian subcontinent and Middle East.
- People whose skin is not regularly exposed to sunlight, e.g.
    - those avoiding the sun due to high risk of skin cancer or photosensitising medications
    - those regularly wearing clothing that covers a lot of skin, or
    - those not going outside.
- People who live in the South Island (especially south of Nelson-Marlborough) and get little time outdoors in the middle of the day between May and August.
- Liver or kidney disease.

COVID-19 context

Some have noted that groups at risk of severe COVID-19 overlap with groups at risk of vitamin D deficiency – for example, people with chronic disease, ethnic minorities and the elderly. If vitamin D does have a role in preventing or mitigating the effects of COVID-19 infection, supplementation would be a cheap and low risk intervention.

Vitamin D is known to play a role in many of the body's processes including modulating the inflammatory and immune responses. Additionally, previous science has reported links between vitamin D deficiency and the prevalence and severity of respiratory disease, as well as evaluating its use in an anti-viral context.

Studies that investigate links between vitamin D status and COVID-19 progression, and evaluate if vitamin D is useful for treatment and/or prevention of COVID-19, are therefore warranted. Several pre-print publications and expert opinion letters are publicly available on this topic and some clinical trials are registered. These are summarised below.

Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-19)[16]

This preprint paper (not yet peer-reviewed) is a retrospective statistical analysis of clinical outcomes of COVID-19 patients and their vitamin D status. Vitamin D status was determined by serum 25D concentration from samples that were obtained after illness onset**.** The study looked at 212 cases across three hospitals in South Asian countries.

The study found that:

- 25.9% of the cases were vitamin D normal (serum 25D ≥ 30 ng/mL). These cases were predominantly mild (85%).
- 37.7% of the cases were vitamin D insufficient (serum 25D of 21–29 ng/mL). Most of these cases were ordinary (confirmed pneumonia with fever and other respiratory symptoms) but reasonably high numbers were severe (hypoxia/respiratory distress) or critical (respiratory failure requiring intensive care).
- 36.3% of the cases were vitamin D deficient. Most of these cases were severe but there were also reasonably high numbers of critical and ordinary cases.

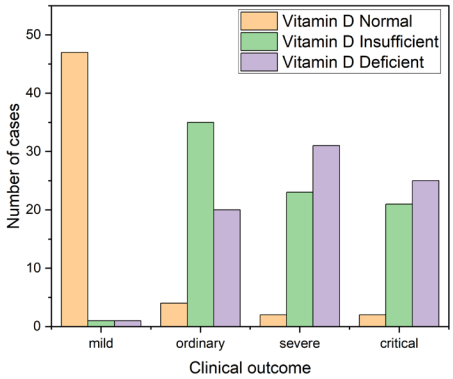

Figure 4: adapted from Table 3 in paper by Alipio.[16]

Results of the analysis were consistent with the hypothesis that vitamin D decreases severity of COVID-19. The author concluded:

- The odds of having a mild clinical outcome increase when Vitamin D status is normal.
- The odds of having a critical outcome increase with a vitamin D deficiency.
- Increased serum 25D either improves clinical outcomes or mitigates the worst clinical outcomes.
- Vitamin D supplementation could possibly improve clinical outcomes of patients infected with SARS-CoV-2 based on increasing the odds of a mild clinical outcome. Further research to evaluate this hypothesis is recommended.

However, this study is limited by confounding factors. We know that older people and those with obesity, diabetes and hypertension all have lower 25D levels, but also increased risk of severe COVID-19.

Even if these variables are adjusted for, the presence of residual uncontrolled confounding factors could still explain this inverse association.

Do latitude and ozone concentration predict COVID-2019 cases in 34 countries?[17]

In a second paper, the same author of the research outlined above examines the effects of latitude and ozone on the number of COVID-19 cases.

There was no statistical association found between latitude and COVID-19 prevalence, but there was a significant positive link between ozone concentration and COVID-19 cases.

The author suggests that because ozone concentration is inversely related to transmission and lower UV exposure is correlated with vitamin D deficiency, it is possible that COVID-19 cases are higher in vitamin D deficient populations. However, this as an ecological study it is only able to generate hypotheses for further study, not test them.

Patterns of COVID-19 mortality and vitamin D: An Indonesian study[18]

This paper is a retrospective statistical analysis of COVID-19 patient mortality and vitamin D status. For 780 cases across hospitals in Indonesia, age, sex, comorbidities, vitamin D status and disease outcome (mortality) were evaluated.

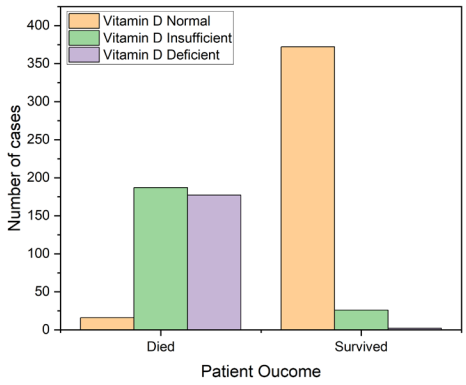

Figure 5: adapted from data in Table 1 by Raharusuna *et al.*[18]

The majority of cases were vitamin D normal (49.7%). Most of these cases (96%) survived the disease. 27.3% of the cases were vitamin D insufficient and a large number of these did not survive the disease (87.8%). 23% of the cases were vitamin D deficient. Almost all of these patients died (99%)

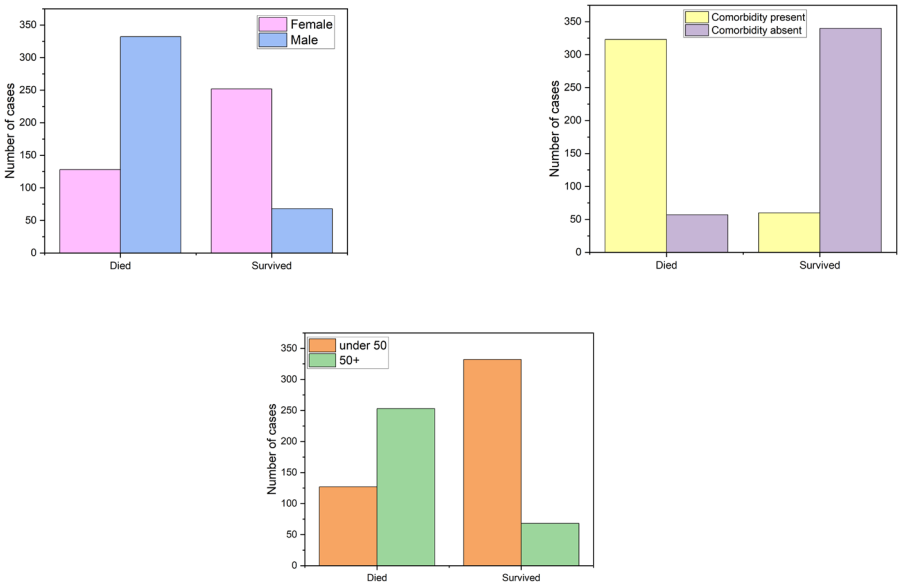

Figure 6: adapted from data in Table 1 in Raharusuna *et al.*[18]

In this patient population:

- A greater proportion of men died of disease (66.3%) compared to women (32%).
- A greater proportion of patients with a pre-existing condition died (84.3%) compared to previously healthy patients (14.4%).
- A greater proportion of the patients over the age of 50 died (78.8%) compared to younger patients (27.7%).

From these data and considering only one variable at a time the authors calculated that

- Older cases were *ca.* 10.45 times more likely to die than younger cases
- Male cases were *ca.* 5.73 times more likely to die than women
- Patients with pre-existing conditions were 11.24 times more likely to die compared to previously healthy patients
- Compared to Vitamin D normal patients Vitamin D insufficient patients were 12.55 times more likely to die and Vitamin D deficient cases were 19.12 times more likely to die.

Controlling for these confounding factors, the authors calculated that vitamin D deficient patients were 7.63 times more likely to die compared to vitamin D normal patients, while vitamin D deficient patients were 10.12 times more likely to die. However, even with some factors controlled for, there may be residual uncontrolled factors that explain this apparent link between vitamin D status and COVID-19 mortality.

Letter: COVID-19 and vitamin D[11]

In this letter to the editors of the journal *Alimentary Pharmacology and Therapeutics*, Panarese *et al*. argue that vitamin D treatment may contribute to reducing the severity of illness caused by SARS-CoV-2 – particularly in settings where vitamin D deficiency is frequent.

The authors looked for a correlation between mortality from COVID-19 (per million population) and the latitude of the country's capital city.

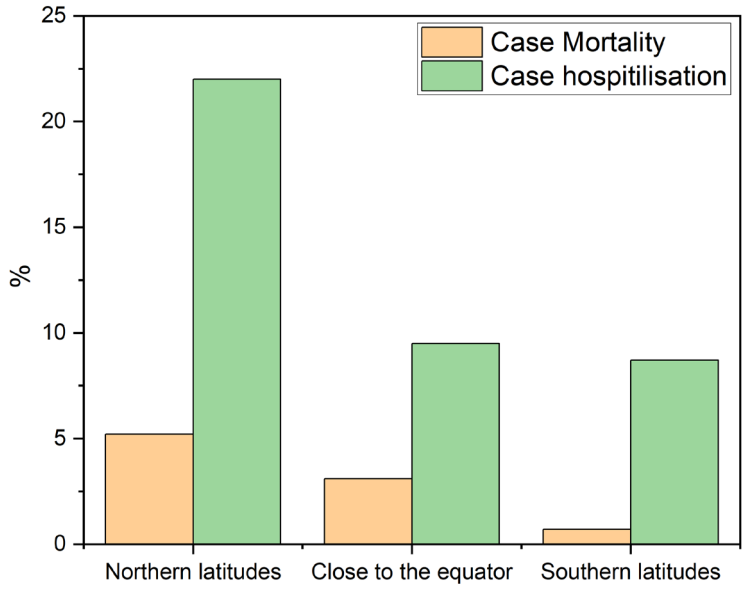

Figure 7: adapted from the text in Panarese *et al.*[11]

The authors speculate that the observed higher incidences of case mortality and hospitalisation could be attributed to either:

- The higher prevalence of older people in northern Europe, predisposing the population to higher probability of cardio-pulmonary and metabolic comorbidities that are linked to more severe COVID-19 cases; or
- vitamin D deficiency due to lower sunlight exposure, leading to increased inflammatory response and thus greater disease severity.

As an ecological study, the results here can only generate these hypotheses. Further research is needed to test the idea that vitamin D status has an impact on COVID-19 severity and outcomes.

Editorial: Low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity[20]

In this editorial, the authors propose that vitamin D could play a role in preventing the cytokine storm and subsequent acute respiratory distress syndrome that commonly causes mortality during SARS-CoV-2 infections. Like the above letter from Panarese *et al*., this analysis examines COVID-19 mortality data (per million population) and the latitude of a country's capital city.

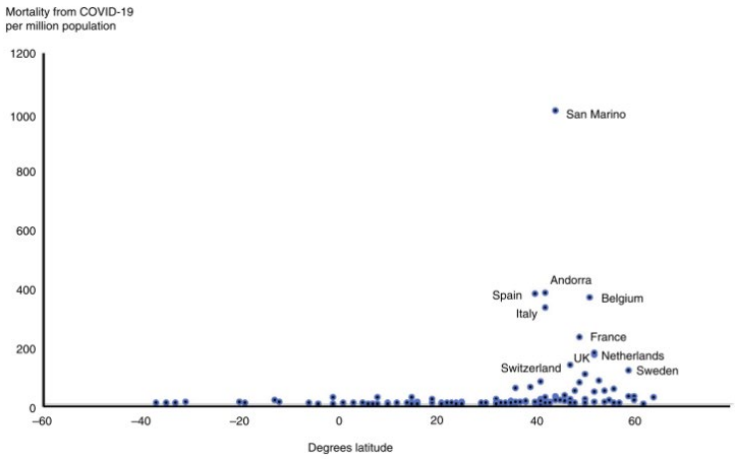

Figure 8: COVID-19 mortality vs. latitude of country's capital city.

The analysis showed that countries in the southern hemisphere were experiencing lower mortality. This may be because:

- the virus spread to the southern hemisphere later (but as time goes by, this reasoning becomes weaker),
- the southern hemisphere was in summer/autumn, with more warmth and sunlight exposure, or
- a substantial proportion of the population in the Northern Hemisphere will currently be vitamin D deficient as a result of winter.

Meanwhile, countries that lie above 35° north displayed higher mortality rates. These countries also do not receive sufficient sunlight in the winter months for normal vitamin D status. The outliers to this observed trend are Nordic countries. However, vitamin D deficiency in these countries is typically low due to widespread use of supplements. Italy and Spain are below 35° north but have high mortality. The authors claim these two countries have "surprisingly high prevalence of vitamin D deficiency" without citation.

While the authors argue that the evidence is "very suggestive" that there is a protective effect of vitamin D against severe disease, as an ecological study this analysis is purely hypothesis-generating. Further research is needed to assess any link between vitamin D status and COVID-19 severity.

Does vitamin D status impact mortality from SARS-CoV-2 infection?[21]

This research evaluates the correlation between case fatality rates (number of deaths per reported number of confirmed cases) for each of the 50 states in the US, along with the latitude.

The authors assumed that the difference of test methods and statistics of all states are statistically insignificant; this assumption may not be entirely correct.

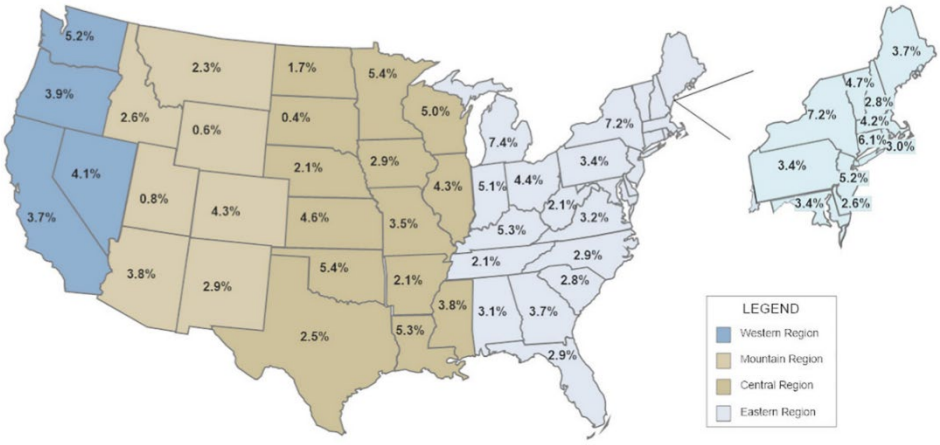

Figure 9: case fatality rate by state in the US.

The authors report that their results show:

- An increasing mortality with increasing latitude, and
- Cumulative summary case fatality rate greater for northern states (> 40^{o} latitude) as compared to southern states (6.0% vs. 3.5%, P< 0.001).

Exceptions to this trend were Wyoming and South Dakota, northern states with low case fatality, and Louisiana, a southern state with a high case fatality rate.

The differences in testing and reporting across the states, as well as population demographics, adherence to social distancing, access to quality medical care etc. will likely contribute to the geographical variations in case fatality rates.

As an ecological study, this research again hypothesises that COVID-19 severity correlates with latitude, which in turn is linked to vitamin D deficiency. The authors suggest that vitamin D deficiency at least partially explains the geographical variations in the reported case fatality rate of COVID-19.

Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19[23]

This rapid review includes discussion of previous literature around vitamin D's role in the immune system and acute respiratory distress syndrome (ARDS), drawing heavily on the 2017 meta-analysis by Martineau *et al.*[44] that has since been updated in 2019.[6]

The authors conclude that there is currently no clinical evidence that vitamin D supplements are beneficial in preventing or treating COVID-19. They do note that there is some evidence that vitamin D plays a role in preventing other respiratory tract infections, and advise that people at risk of vitamin D deficiency should take supplements in line with current guidance.

Selected clinical trials

Vitamin D as a treatment

CoVitTrial – COVID-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (recruiting)

This is a phase III, randomized controlled trial comparing a single high dose (400,000 IU) of oral vitamin D to a lower dose (50,000 IU) of vitamin D. The trial involves 260 participants with COVID-19 at a single centre and aims to assess whether the vitamin D treatments have any effect on severity or outcome. The design of the study is such that it is likely to show no effect. Completion of the study is expected in July 2020.

ZnD3 CoVici – Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19

In this study, 3140 participants in aged care are randomised to either receive a zinc + vitamin D3 supplement or no intervention. They are then monitored for two months for development of COVID-19 and survival rate. The intervention does not use native vitamin D3 as produced through sun exposure, but rather its metabolite, 25-hydroxyvitamin D3.

The study is listed as 'not yet recruiting' but also lists an expected completion date of July 2020. If any beneficial effect is seen, it will not be possible to discern whether it is due to vitamin D alone, zinc alone, or the synergistic combination of the two micronutrients.

COVITD-19 – Vitamin D on Prevention and Treatment of COVID-19

This interventional study will examine the effect of vitamin D supplementation on the progression of COVID-19 disease severity. Two hundred participants aged 40–70 will be randomised to receive either usual care, or usual care plus a daily vitamin D dose equating to 25,000 IU over ten weeks. While this study is well-designed, the vitamin D dose is low and may no show any effect.

Vitamin D as a prophylactic

VITACOV – Vitamin D Polymorphisms and Severity of COVID-19 Infection

In this observational study, 500 participants are split into two groups: those displaying mild to severe symptoms of COVID-19, and those with critical status requiring intensive care. Blood samples will be taken from both cohorts to investigate whether vitamin D status and different genetic variants in vitamin D-related genes contribute to COVID 19 symptoms, severity and mortality.

Further reading

Should people take vitamin D to ward off the new coronavirus? *Medical News Today*

Vitamin D *Ministry of Health – Manatū Hauora*

It is time to take seriously the link between vitamin D deficiency and more serious COVID-19 symptoms *The Telegraph*

Vitamin D levels appear to play a role in COVID-19 mortality rates *Science Daily*

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