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Vitamin D in the time of the coronavirus (COVID-19) pandemic – a clinical review from a public health and public mental health perspective

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***Abstract*:** Individuals with serious mental disorders (SMD) may have a higher risk of vitamin D (VIT-D) deficiency. They also experience higher mortality because of coronavirus disease 2019 (COVID-19) infection. Therefore, we have conducted a comprehensive review to examine the significance of VIT-D for public health and public mental health during the ongoing COVID-19 pandemic. This review had three specific aims, from a global perspective to (a) create a profile of VIT-D and review the epidemiology of VIT-D deficiency, (b) explore VIT-D deficiency as risk factor for SMD and COVID-19 infections and (c) examine the effectiveness of VIT-D supplementation for both conditions. We found that, in terms of SMD, the evidence from laboratory and observational studies points towards some association between VIT-D deficiency and depression or schizophrenia. Mendelian randomisation studies, however, suggest no, or reverse, causality. The evidence from intervention studies is conflicting. Concerning COVID-19 infection, on proof of principle, VIT-D could provide a plausible defence against the infection itself and against an adverse clinical course. But data from observational studies and the first preliminary intervention studies remain conflicting, with stronger evidence that VIT-D may mitigate the clinical course of COVID-19 infection rather than the risk of infection in the first place. From a public health and public mental health point of view, based on the currently limited knowledge, for individuals with SMD, the benefits of VIT-D optimisation through supplementation seem to outweigh the risks. VIT-D supplementation, however, should not substitute for vaccination or medical care for COVID-19 infection.

Keywords: coronavirus, COVID-19, mental disorder, mental health, meta-analysis, public health, supplementation, vitamin D

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Introduction

In the ongoing coronavirus disease 2019 (COVID-19) pandemic, vitamin D (VIT-D) has emerged as a substance of potential public health importance in individuals with serious mental disorder (SMD). Individuals with SMD are one of the groups at higher risk of an adverse outcome from a COVID-19 [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] infection. Three large cohort studies have indicated an approximately two-fold increased risk of mortality.[1–3] It remains unclear whether this increased risk is due to the infection itself or due to a more adverse clinical course once infected.[1] Despite this higher mortality risk, individuals with SMD have been prioritised for vaccinations in only very few countries.[4] Therefore, it is even more important to identify other interventions that could help individuals with SMD, who are at risk of worse health outcomes during the ongoing COVID-19 pandemic, both in terms of physical and mental health.[1] VIT-D may be one substance that could improve both mental and physical health outcomes.

VIT-D deficiency has been associated with SMD, including psychosis and bipolar disorder and depression. At the same time, VIT-D may modify the risk of respiratory tract infections (RTIs).[5–8] The UK Scientific Advisory on Nutrition (SCAN), in a revision of its previous conclusion,[9] has suggested that low dose VIT-D supplementation between 10 µg (400 IU) and 25 µg (1000 IU) may be of some benefit in reducing the risk of acute respiratory tract infection (ARTI).[10] Because of this, VIT-D has increasingly been explored in the context of COVID-19 infections. The United Kingdom (UK) National Health Service (NHS) and the UK National Institute for Health and Care Excellence (NICE) currently recommend taking 10 µg (400 IU) per day for the general population between October and early March to compensate for lack of ultraviolet B (UVB) exposure.[11,12] At the same time, these recommendations point out that there currently is not enough evidence to support taking VIT-D to prevent or treat COVID-19 infections. The South London and Maudsley NHS Foundation Trust protocol for VIT-D prophylaxis during the COVID-19 pandemic, in acknowledgement of the special vulnerabilities of patients with SMD, has recommended that all patients of the hospital should be prescribed 100 µg (4000 IU) per day for 4 weeks.[13]

With the COVID-19 pandemic passing through various stages and waves with substantial global differences, the evidence regarding VIT-D is still evolving. Therefore, we have conducted a comprehensive review to examine the significance of VIT-D for public health and public mental health during the ongoing COVID-19 pandemic. This review had three specific aims, from a global perspective to (a) create a profile of VIT-D and review the epidemiology of VIT-D deficiency, (b) explore VIT-D deficiency as risk factor for severe mental disorder (SMD) and COVID-19 infections and (c) examine the effectiveness of VIT-D supplementation for both conditions.

Method

We conducted a narrative review with a profile of VIT-D and clinical and public health aspects of VIT-D deficiency as a starting point. We then explored the potential benefits of VIT-D regarding our two chosen outcomes: SMD and COVID-19 infections. In terms of proof of principle and association, we examined laboratory and observational studies. For causality, we examined Mendelian randomisation and intervention studies. For this narrative review, we performed a literature search using the PubMed/Medline database. For SMD, as most evidence is available for depression and schizophrenia, we explored these two conditions in more detail. Prevention of depressive and psychotic relapses is also a major public mental health concern during the current COVID-19 pandemic.

For the search for observational studies, we used 'vitamin D deficiency' AND ('depression' OR 'schizophrenia OR psychosis' OR 'COVID-19' OR 'coronavirus').

We complemented the presentation of observational data with studies using a Mendelian randomisation approach, as a method less affected by confounding and reverse causation. Mendelian randomisation studies use genetic variation to investigate causal relations and between potentially modifiable risk factors and health outcomes in observational studies.[14] For the search of Mendelian randomization studies, we used vitamin D AND (mental disorder OR depression OR schizophrenia OR psychosis).

For the search for intervention studies, we used 'vitamin D' AND ('depression' OR 'schizophrenia OR psychosis' OR 'COVID-19' OR 'coronavirus') AND ('trial OR meta-analysis'). Due to the large number of studies available, we focused on the available meta-analyses for the outcome depression. For outcomes related to COVID-19 infection, we reviewed the individual trials. We did not consider the only meta-analysis available at the time of writing. This meta-analysis only summarised three studies, all of which were heterogenous. Therefore, we judged the summary estimates as potentially unreliable.[15]

We included all relevant papers published between 1 January 2010 and 30 September 2020, and (b) at the time of the revision including relevant papers published between 1 September 2020 and 24 March 2021. We considered English language papers only. For intervention studies we excluded studies in which VIT-D was co-supplemented with other substances. We further excluded studies concerning children, pregnancy, post-natal conditions and specific somatic conditions. We complemented the literature review with references to national guidelines regarding VIT-D use from the UK, Australia, and the United States (US). We also used COVID-19 statistics regarding infection, testing and death rates published by Worldometer.[16] For assessing

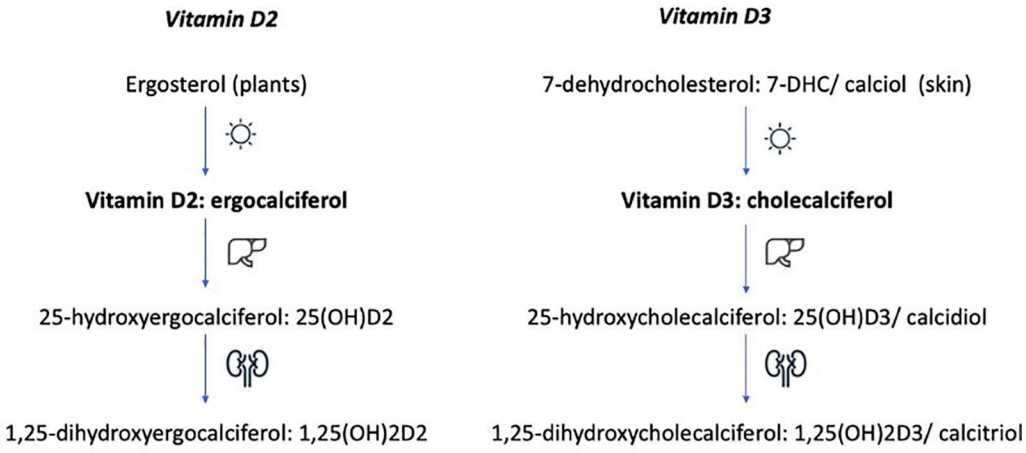

Figure 1. Vitamin D synthesis and hydroxylation.

the role of geographical latitude as a proxy of VIT-D exposure, we compared COVID-19 infection and mortality rates in the 13 countries that lie on the equator.

VIT-D: profile

Biochemistry

VIT-D is a fat-soluble vitamin. Chemically, it is a secosteroid that exists in two forms: VIT-D2 (ergocalciferol) and VIT-D3 (cholecalciferol).[17] VIT-D2 is synthesised by plants and fungi from ergosterol – a sterol found in the cell membranes. VIT-D3 is synthesised by humans under the influence of UVB light from 7-dehydrocholesterol (7-DHC) (calciol) – a sterol found in the skin.[18] VIT-D2 and D3 are not biologically active. Both forms need to undergo two steps of hydroxylation. The first step takes place in the liver to form 25(OH)D and the second in the kidneys to form 1,25(OH)2D (Figure 1).[17,19–21] 25(OH)D is the major circulating form of VIT-D through the body.[21] 1,25(OH)2D2 and 1,25(OH)2D3 are the biologically active forms of VIT-D (1,25(OH)2D). 25(OH)D has a half-life of about 15 days. 1,25(OH)2D has a much shorter half-life, measured in hours.[19] The longer half-life makes 25(OH)D the preferred serum marker to assess VIT-D status. Laboratory reference ranges vary. The normal range tends to lie between 20 and 100 ng/ml (50–250 nmol/l).

Function

Classically, VIT-D is associated with bone health. Jointly with the parathyroid hormone (PTH), VIT-D plays a major role in calcium and phosphate metabolism. PTH stimulates the conversion of 25(OH)D into the active form of VIT-D, 1,25(OH)2D. VIT-D provides negative feedback for PTH.[22] VIT-D contributes to the regulation of calcium and phosphate in three target organs, kidney, intestine and bones. In the kidney, VIT-D enhances tubular calcium reabsorption. The effects of VIT-D on renal phosphate transport, however, are poorly understood. In the intestine, VIT-D enhances absorption of calcium and phosphate. In the bones, the actions of VIT-D are complex. VIT-D can activate both osteoblasts and osteoclasts. Depending on the net result, VIT-D could promote bone formation, bone resorption or have a neutral effect on bone metabolism. By regulation of bone turnover, VIT-D also contributes to the regulation of plasma calcium levels.[22,23] But VIT-D has many other functions beyond bone metabolism. VIT-D receptors (VIT-DRs) are found in multiple tissues including brain, kidney, lung, cardiovascular system, breast, prostate, colon and immune cells, such as B and T lymphocytes.[24–26] We will discuss the effects of VIT-D on brain, lung and immune function in more detail during this review.

Source and daily intake

The extent of photochemically produced VIT-D depends on geographical latitude, season, time of day, skin type, age, actual duration sun exposure and amount of skin exposed.[18,27] At higher latitudes, more UVB radiation, of wavelength between 290 and 315 nm, is absorbed by the ozone layer of the atmosphere. Thus, the further

Table 1. Recommendation for daily VIT-D intake in US, Australia, UK and Europe.[11,19,30,31]

Age	Australia	Europe	UK	US
VIT-D intake µg/day[a]				
>1 year	5[b]	10[c]	8.5–10[d]	10[b]
1–18 years	5	15	10	15
18–50 years	5	15	10	15
51–70 years	10	15		15
>70 years	15	15		20

[a]Conversion factor from µg to IU = 40, 1 µg cholecalciferol = 0.2 µg 25(OH)D; 1 IU = 0.025 µg cholecalciferol or 0.005 µg 25(OH)D.
[b]Infants 0–12 months.
[c]Infants 7–11 months.
[d]Babies up to 1 year of age.
IU, international units; UK, United Kingdom; US, United States; VIT-D, vitamin D.

away from the equator, the less it is possible to rely on sunlight to produce VIT-D. During the winter months, very little, if any VIT-D can be produced photochemically in regions above 33° North (i.e. north of Los Angeles) or below 33° South (i.e. south of Cape Town).[27] In latitudes above about 50° (Canada and northern Europe), VIT-D can be produced in significant amounts only during the six summer months of the year. The amount of UVB light to be absorbed depends on melanin content in the skin.[27] Increased skin pigmentation can lead to a reduction of photochemical VIT-D synthesis of up to 50-fold.[28,29] Additionally, the amount of 7-DHC decreases with age, which reduces the capacity of the skin to synthesise VIT-D.[28] Life in institutionalised or homebound settings, clothes covering the whole body and use sunscreen may further reduce photochemical VIT-D synthesis.

VIT-D can also be taken up through foods. Recommendation of daily intake vary between countries, depending on age but not on gender (Table 1).[11,19,30,31] The requirements for pregnant and lactating women remain the same as the corresponding age group.[19,30]

Very few foods contain VIT-D. The best food sources of VIT-D include oily fish and fish oils. Liver, red meat, cheese and egg yolk also contain VIT-D. Mushrooms with enhanced VIT-D contents due to UVB exposure are a further option. Then, there are vitamin fortified foods such as some breakfast cereals, fat spreads, milk and dairy products and plant milk alternatives (Table 2).[26,32] The availability of VIT-D fortified foods varies between countries. For instance, in the US, milk is VIT-D fortified, in the UK it is not.[11,19]

VIT-D deficiency: clinical and public health aspects

Definition

There is no consensus of what a constitutes an optimal VIT-D level. Previously suggested ranges are higher than current recommendations (Table 3).[26,33] In older adults, the International Osteoporosis Foundation (IOF) suggests a VIT-D concentration of 30 ng/ml (75 mmol/l) for prevention of hip fractures.[34] For all the UK population, it is currently recommended that, in order to protect musculoskeletal health, the VIT-D concentration should not fall below 25 ng/ml (62.5 nmol/l) at any time of the year.[35] For the US, the National Institute of Health (NIH) suggests that VIT-D concentrations of less than 30 ng/ml constitute VIT-D deficiency leading to rickets in infants and osteomalacia in adults. Serum concentrations between 30 and 50 ng/ml may still bear some risk of VIT-D inadequacy.[19] An expert panel of the European Food Safety Agency considers a VIT-D concentration of 50 nmol/l (20 ng/ml) a suitable target value for all population groups.[31]

Clinical signs

Subclinical VIT-D deficiency can result in osteoporosis, increased falls and possibly fractures. Overt VIT-D deficiency results in hypocalcaemia and or hypophosphataemia. In children, overt VIT-D deficiency can lead to rickets and osteomalacia. In adults, overt VIT-D deficiency can lead to osteomalacia. VIT-D deficiency may lead to secondary hyperparathyroidism.[36] Many individuals with VIT-D insufficiency, however, may be asymptomatic.

Prevalence

The prevalence of VIT-D deficiency varies worldwide depending on UVB exposure and possibility to compensate with VIT-D containing foods (Table 4).[37–39] Although countries in lower latitudes have more access to UVB radiation, VIT-D deficiency may still be more common. This can occur if available UV light is not exploited, and VIT-D food sources are limited (populations at

Table 2. Some comparable foods with high and low VIT-D content.[26,32]

Food item	VIT-D content µg/ 100 g serving[a,b]	Food item	VIT-D content µg/ 100 g serving[a,b]
High		Low	
Herring, grilled	16.1	Prawns	Traces
Salmon farmed, grilled	7.8	Cod baked	Traces
Trout, grilled	8.2	Sea bass	Traces
Eggs, chicken, boiled[c]	3.2	Egg white raw	Traces
Beefburger grilled	1.9	Hamburger take-away	0.2
Fat spread, low fat, not polyunsaturated (26–39%)	8.4	Vegetable oil, average	Traces
Baking fat and margarine (75–90%)	8.8	Butter salted	0.9
Shiitake mushrooms sundried	4.0	Shiitake mushrooms fresh	0.25
Cornflakes, fortified	4.7	Cornflakes, unfortified	–
Dried skimmed milk fortified	2.7	Skimmed milk	0

[a]Conversion factor from µg to IU = 40, 1 µg cholecalciferol = 0.2 µg 25(OH)D; 1 IU = 0.025 µg cholecalciferol or 0.005 µg 25(OH)D.
[b]Conversion factor from g to ounce (oz) = 0.035.
[c]Medium egg weighs between 53 and 63 g.
IU, international units; VIT-D, vitamin D.

Table 3. Vitamin D status as measured by 25(OH)D serum concentration.

VIT-D status	Global consensus recommendations on prevention and management on nutritional rickets[33]		Recommendations Holick[26]	
	25(OH)D[a]			
	ng/ml	nmol/l	ng/ml	nmol/l
Sufficiency	>20	>50	30–60	75–150
Insufficiency	12–19	30–50	20–29	50–74
Deficiency	<12	<30	<20	<50
Intoxication	>100[b]	>250[b]	>150	375

[a]Conversion factor ng/ml to nmol/l = 2.5.
[b]With hypercalcaemia, hypercalciuria and suppressed PTH.
PTH, parathyroid hormone; VIT-D, vitamin D.

risk). Samples are often heterogenous. This can make comparison of prevalence rates difficult.

Factors associated with VIT-D deficiency

There are several factors associated with VIT-D deficiency. Association, however, does not necessarily imply causality, either in terms of the VIT-D deficiency itself, or in terms of risk of SMD or COVID-19 infection. We explore the limitation of such factors in more detail later, when examining the association between VIT-D deficiency, geographical latitude and death from COVID-19 infection.

Reduced sun exposure. VIT-D deficiency can occur when access to UVB radiation or nutritional sources are restricted (see section Source and daily intake). Migrants moving from lower to higher geographical latitudes and institutionalised populations have all been found to have an increased risk of VIT-D deficiency.[38,39] Women from countries where it is customary to cover large parts of the skin may also be at risk,[37] as may be individuals who avoid sun exposure for cultural or health reasons.[40] The Oslo Health Study (HUBRO) may serve as an example. In this cross-sectional study, VIT-D concentration taken between May 2000 and January 2001 were compared between individuals born in Norway (which is above 50° latitude) and individuals born in Pakistan (which is largely below 33° but where it is traditional to cover the body). Individuals born in Norway had a mean standardised 25(OH)D concentration of 28.4 (95% CI 26.9–29.9) ng/ml; 15% had a 25(OH)D concentration of less than 20 ng/ml and 0.1% of less than 10 ng/ml. Individuals born in Pakistan had a mean standardised 25(OH)D concentration of 11.0 (95% CI 9.1–13.0) ng/ml; 92% had a 25(OH)D concentration of less than 20 ng/ml and 52% of less than 10 ng/ml.[41] In the context of the ongoing COVID-19 outbreak, prolonged periods of quarantine are likely to increase the risk of VIT-D deficiency. This risk may be particularly higher in individuals with darker skin and/or older age. In consequence, populations living in, or originating from, countries in lower latitudes closer to the equator may be more affected by prolonged quarantines if they do not compensate through nutritional intake of VIT-D.[42] Additionally, older individuals run a higher risk of VIT-D deficiency, reducing the age-related decline of renal function may also impair conversion of VIT-D into its biological active forms, 1,25(OH)2D.[43] Finally, air pollution decreases the permeability for UVB radiation.[24]

Obesity. Obesity may also lead to VIT-D deficiency through a mechanism under genetic control. In a pooled analysis of 21 genetic studies with 42,024 participants, a higher body mass index (BMI) was associated with lower 25(OH)D serum concentrations. But, at the same time, lower 25(OH)D concentration did not seem to lead to higher BMI. In this study, a 10% higher BMI was associated with a 4.2% lower 25(OH)D concentration.[44] Two large American studies have shown that more than 40% of all patients admitted to hospital for a COVID-19 infection are obese.[45,46]

Age. There is an overlap between risk factors for VIT-D deficiency and need for hospital care for, or death from, COVID-19 infection. Older age has been identified as a major risk factor of death.[46]

Ethnicity. According to a preliminary report of the OpenSAFELY Collaborative in the UK, Black and Asian individuals have a two-fold higher risk of dying from a COVID-19 infection compared with White individuals.[47] These findings seem also hold true for individuals with psychotic disorders. A further retrospective cohort study of individuals treated with antipsychotics also found COVID-19 infection to be significantly associated with Black ethnicity, older age and obesity.[48] In the most recent retrospective cohort study at the time of writing, Black individuals with VIT-D serum concentrations of less than 40 ng/ml ran a higher risk of COVID-19 infection than black individuals with VIT-D serum concentrations of 40 ng/ml or greater. The risk of COVID-19 infection seemed to be VIT-D serum concentration dependent. For White individuals, no significant association was identified.[49]

Drug interactions. Orlistat is a slimming drug that reduces the absorption of fat and therefore VIT-D uptake. Enzyme induction and/or interference with the pregnane X receptor (PXR) can accelerate VIT-D metabolism. Enzyme induction and PXR activation can work in conjunction. PXR can bind to VIT-D responsive elements. Many drugs from various classes are PXR ligands.[50,51] From a psychiatric point of view, the PXR ligands most likely encountered in clinical practice are steroidal anti-inflammatory drugs, the antiepileptic carbamazepine, the herbal antidepressant St John's wort (*Hypericum perforatum*) and the herbal sedative Kava Kava (*Piper methysticum*).

Other risk factors. Smoking is a further risk factor for VIT-D deficiency.[52,53] This is possibly related to accelerated of skin aging in smokers with increased wrinkling and hyperpigmentation.[24,54] Adhering to a strict vegan diet may also increase the risk of VIT-D deficiency.[55] Some medical conditions can also increase the risk of VIT-D deficiency. These include (a) malabsorption syndromes such as irritable bowel syndrome or coeliac disease, (b) chronic kidney disease impairing the transformation of VIT-D from its biologically inactive form 25(OH)D to its biological active form 1,25(OH)2D and (c) taking medications that interfere with VIT-D uptake or accelerated VIT-D metabolism.

Table 4. Proportion of vitamin D insufficiency and deficiency in adults of varying age ranges between 18 and 99 years around the world collated from published reviews.

Country of originating study	Palacios and Gonzalez[37]						Lips *et al.*[38]/van Schoor and Lips[39]					
	% Insufficiency or deficiency											
	VIT-D ng/ml[a]											
	<12	<20	<12	<20	<12	<20	<10	<20	<10	<20	<10	<20
	All		Males		Females		All		Males		Females	
Africa												
Egypt											72	
Egypt[b]											40–77	
Morroco[c]											52	
Nigeria				5		34					52	
Tanzania		1										
America North/Central												
Canada	2	20					2–21					
Canada[d]							2	64				
Canada[e]							7	89				
Mexico			0.2	10	2	10	2	44				
Puerto Rico		32										
US	6	34–37					2–9	18–54				
America South												
Brazil		28										
Brazil[b]							14	41–58				
Chile					13	27		27–60				
Ecuador								22				
Guatemala[b]								46				
Asia												
Bangladesh					36	80						
Bahrain							50	86				
India		66										
Israel			9–12	41–50	15–23	51–60	14–27	28–78				
Iran		51					19–34	85				
Jordan				2		14	cf. Palacios and Gonzalez[37]					

(Continued)

Table 4. (Continued)

Country of originating study	Palacios and Gonzalez[37]						Lips *et al.*[38]/van Schoor and Lips[39]					
	% Insufficiency or deficiency											
	VIT-D ng/ml[a]											
	<12	<20	<12	<20	<12	<20	<10	<20	<10	<20	<10	<20
	All		Males		Females		All		Males		Females	
Korea	8	62										
Lebanon									40–58	60–63		
Lebanon[b]									37	94	56	95
Malaysia		70										
Pakistan		58										
Saudi Arabia							42–53	84–90				
Sri Lanka			0	34	6	59						
Syria							61					
Thailand		6%										
Vietnam				1		3						
Australia/Oceania												
Australia	4	31										
Fiji					3	11						
New Zealand			0–2	42–54	2–6	51–52						
Europe												
Belgium							7	51				
Croatia[c]											14	63
Denmark	14	52					0	24				
Estonia[d]	1	29					cf. Palacios and Gonzalez[37]					
Estonia[e]	8	73					cf. Palacios and Gonzalez[37]					
Finland	15	65					0.2	7				
Finland[b]							7	60				
France							6	35				
Germany			16	57	17	58	4	55				
Great Britain[d]	3	15										
Great Britain[e]	16	47										
Greece								29				
Hungary												57

(Continued)

Table 4. (Continued)

Country of originating study	Palacios and Gonzalez[37]						Lips *et al.*[38]/van Schoor and Lips[39]					
	% Insufficiency or deficiency											
	VIT-D ng/ml[a]											
	<12	<20	<12	<20	<12	<20	<10	<20	<10	<20	<10	<20
	All		Males		Females		All		Males		Females	
Iceland							4	34				
Ireland							6	45				
Italy[b]								76				
Netherlands							2	29				
Netherlands[b]							4	33				
Norway		40					0.1	19				
Poland[c]											25	92
Scotland	35	78										
Russia[b]								47				
Russia, Northern Indigenous							2–53	8–84				
Slovakia												15
Slovenia							31	66				
Spain		34										
Sweden[b]									0.8	17	0	16
Switzerland		38					6	>50				
Turkey										66		79
UK										21		

Studies including hospital patients, pregnant women and children excluded.
[a]Conversion factor ng/ml to nmol/l = 2.5.
[b]Older individuals with varying age ranges from 60+ years.
[c]Postmenopausal women.
[d]Summer.
[e]Winter.
UK, United Kingdom; US, United States; VIT-D, vitamin D.

Vitamin D supplements

Dietary supplements exist in two forms, VIT-D2 and VIT-D3. VIT-D2 supplements are plant-based, originating from UV-irradiated ergosterol in yeast. VIT-D3 supplements are animal-based, originating from UV-irradiated 7-dehydrocholesterol in lanolin (sheep wool grease).[26] As an animal product, VIT-D3 supplements are not suitable for vegans.[56] In the UK, VIT-3 formulations are most common. Many over-the-counter available formulations also contain calcium-carbonate. Different VIT-D preparations may vary in pharmacokinetic properties depending on mode of administration (intramuscular *versus* oral) and type of VIT-D.[57] VIT-D2 has been suggested to be inferior to VIT-3 in terms of pharmacokinetic properties, including affinity to VIT-D binding protein, speed of deactivation and clearance.[57–59] However, differences in

Table 5. Safe upper level for daily VIT-D intake in AUS and the US.[19,30]

Age	Males	Females	Males	Females	
	AUS		US		
	Vitamin D intake µg/day[a]				
0–12 months	25	25	25	25	0–6 months
			38	38	7–12 months
1–18 years	80	80	73	73	1–3 years
			75	75	4–8 years
			100	100	9–13 years
18+ years	80	80	100	100	
Pregnancy	80	80			
Lactation	80	80			

[a]Conversion factor from µg to IU = 40, 1 µg cholecalciferol = 0.2 µg 25(OH)D; 1 IU = 0.025 µg cholecalciferol or 0.005 µg 25(OH)D.
AUS, Australia; IU, international units; VIT-D, vitamin D.

clearance performance between VIT-D3 and VIT-D2 may diminish with higher baseline concentrations and increasing doses.[57] One meta-analysis of seven intervention studies has suggested that VIT-D3 was more effecting raising 25(OH)D concentrations than VIT-D2, when given intramuscularly but not when given orally.[60]

The UK Food Standard Agency suggests that long-term exposure to doses of 25 µg (1000 IU) may be well tolerated. Higher exposures such as 45 µg (1800 IU) may be tolerated short-term under medical supervision.[23] US recommendations suggest a toxicity threshold of daily intakes between 250 µg (10,000 IU) and 1000 µg (40,000 IU)/day.[19] Both the US and Australia provide more detailed recommendations for safe upper levels for daily VIT-D intake (Table 5).[19,30]

Adverse effects

Excess VIT-D may result in hypercalcemia and hypercalciuria. Excessive use can lead to renal and cardiovascular toxicity due to tissue calcification in the heart, blood vessels and kidney. The evidence, however, remains conflicting. A Cochrane systematic review reported a 3.2-fold increased risk of hypercalcaemia with active forms of VIT-D, 1,25(OH)2D or alfacalcidiol – a VIT-D analogue. However, there was no statistically increased risk of hypercalcaemia with supplemental VIT-D2 or VIT-D3. VIT-D combined with calcium increased the risk of nephrolithiasis by 20%.[61] A more recent meta-analysis also found that long-term VIT-D use was associated with hypercalcaemia and hypercalciuria, but not with nephrolithiasis. These findings were irrespective of VIT-D dose and calcium co-administration.[62] An update of this meta-analysis concerning monthly high dose VIT-D supplementation did not either show any increased risk of nephrolithiasis, although there was a trend towards hypercalcaemia.[63] A randomised controlled trial (RCT) from the same research group with 5110 participants in New Zealand concluded that monthly supplementation of 100,000 international units (IU) VIT-D over a median of 3.3 years did not affect the incidence rate of hypercalcaemia or nephrolithiasis.[64] VIT-D remains, however, contraindicated in conditions associated with hypercalcaemia and nephrolithiasis. VIT-D should be used only with caution in patients with sarcoidosis because of increased conversion of 25(OH)D to 1,25(OH)2D.[65] Finally, there are several drugs that can increase calcium serum concentrations. Such include thiazide diuretics and theophylline.[65] Lithium has also been associated with hypercalcaemia and hyperparathyroidism.[66] Varying prevalence rates have been reported. One Swedish study of patients with bipolar disorder estimated that 26% patients treated with lithium had hypercalcaemia, compared with 1.5% not

treated with lithium and 3% in a control population.[67] Routine monitoring of calcium concentrations is already standard for patients treated with lithium. Monitoring of serum calcium concentrations could be extended to other individuals with SMD, if excessive VIT-D use was suspected, or if there was deterioration in mental status without any obvious reason.

Vitamin D and serious mental disorders

VIT-D deficiency has been linked to several severe mental and neurodevelopmental disorders, including depression and schizophrenia, autism and ADHD.[68–70] However, it remains unclear whether the link between VIT-D deficiency and such disorders is causal or just associative.

Proof of principle

Laboratory findings. A role for VIT-D in the brain was suggested when both 25(OH)D and 1,25(OH)2D were found in the cerebrospinal fluid of 46 patients with no endocrine disorders, who had undergone lumbar puncture for a suspected or confirmed disk prolapse.[71] A year later, it was demonstrated in a rodent model that 25(OH)D and 1,25(OH)2D could cross the blood brain area, albeit in small amounts.[72] An immunohistochemical study performed on human brain tissue showed that the VIT-D3 receptor (VIT-DR) was present in the brain; 1α-hydroxylase (1α-OHase), required to convert VIT-D into its active form, was also found. For both, immunoreactivity was present in varying amounts in the prefrontal cortex, cingulate gyrus, hippocampus, caudate, putamen, amygdala, thalamus, substantia nigra, lateral geniculate nuclei, hypothalamus and cerebellum. Additionally, 1α-OHase immunoreactivity was present in the basal forebrain. The wide distribution of the VIT-DR and 1α-OHase suggested a diverse role for VIT-D for cerebral functions.[73] VIT-D seems to play a crucial role for the developing, adult and aging brain.[74] Yet many functions are still not well understood. Studying inborn errors of VIT-D metabolism is one way to explore the role of VIT-D in the central nervous system (CNS). VIT-D 1α-OHase deficiency, formerly called pseudo VIT-D deficiency rickets, is caused by a mutation affecting CYP27B1 that converts 25(OH)D to 1,25(OH)2D leading to hypocalcaemic rickets. However, the impact of VIT-D 1α-OHase deficiency on the CNS has been described mainly in terms of symptoms associated with hypocalcaemia, seizures, depression and anxiety.[75]

Neurodevelopment. Nutritional deficits including VIT-D deficiency can interfere with these neurodevelopmental processes. Timing, degree, and duration of VIT-D deficiency are all factors that are poorly understood.[76] Rodent experiments have shown that VIT-D deficiency can affect brain morphology. This can result in increase of volume of the lateral ventricles and decrease of cortical thickness – two morphological changes associated with psychosis.[77,78] Further changes observed in rodent experiments include increase of mitosis in some brain areas, decrease of apoptosis and reduction of neurotrophic factors such as glia-derived neurotrophic factor (GDNF) and nerve growth factor (NGF).[77] VIT-D deficiency may also adversely affect the development of the dopaminergic system possibly through modulation of dopamine turnover and GDNF activity.[77] L-Type voltage gated Ca 2+ channels (L-VSCC), mediating a range of neuronal processes, including excitability, gene expression, long-term potentiation and depression, have been identified as a target for VIT-D.[79,80] L-VSCC have been linked to brain aging, neuronal vulnerability and schizophrenia.[80,81] Rodent experiments have further shown that pre-natal VIT-D deficiency can affect dopamine neurotransmission in adult life and lead to an enhanced response to pro-psychotic agents.[77,82,83] Further rodent experiments have shown that 1,25(OH)2D2 can partially protect against neurotoxic damage from 6-hydroxydopamine (6OHDA) when given over a longer time,[77,84] or against serotonin and dopamine depletion caused by toxic doses of methamphetamine.[85] Both effects may be GDNF mediated.[84,85] Besides, VIT-D can also mediate the synthesis of various neurotransmitters such as acetylcholine, noradrenalin, serotonin and dopamine.[79,86,87]

Neurodegeneration. VIT-D has neuroprotective properties. In consequence, VIT-D deficiency may lead to neurodegeneration. The neuroprotective properties of VIT-D seem related to anti-inflammatory and antioxidant properties.[88] In one *in vitro* experiment, primary cortical glial cultures were exposes to a bacterial endotoxin. This led to an accommodation of nitrite, reactive oxygen species (ROS), interleukin-6 (IL-6) and macrophage inflammatory protein-2 (MIP-2). It was found that 1,25(OH)2D3 reduced the production of these pro-inflammatory substances.[89] Downregulation of L-VSCC protects against 6-hydroxydopamine-

mediated neurotoxicity. Protection from glutamate-induced neurotoxicity is a further option.[79,90,91] Finally, as outlined previously, VIT-D modulates GDNF and NGF. GDNF acts on the basal ganglia, whereas NGF acts on the cholinergic neurons in the basal forebrain. *Via* these pathways, VIT-D could potentially reduce the risk of Parkinson disease and cognitive impairment.[79]

Observational studies

Depression. The suspicion of a link between depression and VIT-D deficiency stems from studies of seasonal affective disorder (SAD). SAD is characterised by seasonal mood swings with decreases in mood in the autumn and winter months.[17] It has also been shown that sunlight affects serotonin turnover in the brain, that serotonin turnover is lowest in winter and serotonin production is directly related to bright sunlight exposure.[92] Three meta-analyses have examined the association between VIT-D concentrations and depression.[93–95] All three analyses identified an inverse association between VIT-D concentration and depression. However, it proved difficult to pool studies, and two meta-analyses reported heterogeneity.[93,95] One meta-analysis reported publication bias,[93] and another meta-analysis could not rule out publication bias.[94] Cut-off points for VIT-D insufficiency and deficiency varied somewhat.

Three observational studies have been published since the most recent meta-analysis.[96–98] In these studies, the relationship between depression and VIT-D deficiency was less clear. One study failed to find a significant difference in participants with non-psychotic depression and controls.[97] Another study, following older adults with a depressive disorder over 2 years, found that an increase in VIT-D concentrations was significantly associated with improved frailty scores when adjusted for depression, but not independently with improvement of depression.[98]

Schizophrenia. The risk of schizophrenia has been linked to factors also associated with VIT-D deficiency. These concern individuals (a) born during winter or spring, (b) born in higher latitudes of either hemisphere, (c) living in urban areas and (d) with darker skin living in colder climates.[77,79]

Five meta-analyses have examined the association between VIT-D concentrations and schizophrenia or psychosis.[99–103] All five meta-analyses identified an inverse association between VIT-D concentration and schizophrenia. However, four meta-analyses reported heterogeneity.[99–102] One meta-analysis did not test for heterogeneity.[103] Three meta-analyses did not find any evidence for publication bias.[99–101] The remaining two meta-analyses had not tested for publication bias.[102,103] As for the meta-analyses concerning depression, the cut-off points for VIT-D insufficiency and deficiency varied somewhat. There have been six observational studies published since the most recent meta-analysis.[96,97,104–107] Four studies found a low VIT-D concentration in individuals with psychosis or schizophrenia,[96,105–107] two of which concerned first episode psychosis.[105,106] Two studies failed to find such an association.[97,104] One of these studies was substantially larger than all other observational studies.[97] There were no intervention studies testing the use of VIT-D in individuals with schizophrenia.

Mendelian randomisation studies

A recent genome-wide association study (GWAS) of 417,580 European UK biobank participants, using a Mendelian randomisation approach, explored the relationship between VIT-D concentrations and several phenotypes including several mental disorders. There were several candidate phenotypes, including major depression, bipolar, disorder or schizophrenia, with causal (direct or indirect) effects on VIT-D concentration. The findings suggested that SMDs were associated with behaviours leading to reduced production of VIT-D rather than VIT-D deficiency leading to SMD.[108] Another recent study exploring the causality between 25(OH)D and depression reported similar findings. Depression led to lower 25(OH)D concentrations, but lower 25(OH)D did not lead to depression.[109] Previous Mendelian randomisation studies had failed to find shared genetic effects between 25(OH)D and major depressive disorder.[110–114] However, all studies have some limitations. Findings from populations with predominant European ancestry cannot be generalised to populations with non-European ancestry. Statistical power can become a problem, when investigating the impact of either extremely high or low 25(OH)D concentrations.[113] Potential antenatal adverse effects of VIT-D deficiency on the risk of SMD in offspring cannot be determined.[108] A life-time perspective for both risk factors and outcomes under study cannot inform on the impact of risk factors on outcomes during a specific sensitive period.[112] A potential impact of

VIT-D deficiency in childhood on the risk of SMD later in life can therefore not be explored with this approach. Finally, all studies used data from a few major genetic databanks with overlap and partly duplication of results.

Intervention studies

Depression. Eight meta-analyses investigated the effect of VIT-D supplementation on depression (Supplemental Table S1).[115–122] Three meta-analyses found VIT-D to be effective as judged by the reduction of depression scores. VIT-D doses and routes of administration differed. However, most studies used oral VIT-D administration. Five meta-analyses reported heterogeneity[115,118,119,121,122] One study did not assess heterogeneity.[120] Publication bias was present in two studies.[118,122] Two studies did not assess publication bias.[119,120]

Two more clinical trials have been published subsequent to the latest meta-analysis.[123,124] The first study assessed the effect of oral VIT-D supplementation with 40 µg on depression and anxiety in 158 Chinese patients with low 25(OH)D concentrations over a period of 6 months. Whereas symptoms of anxiety improved significantly, symptoms of depression did not.[123] However, the findings of this study are difficult to interpret, since information on blinding and placebo use in the control group is not given. The second study was conducted as a randomised controlled trial in 46 Indian patients with major depression and concurrent VIT-D deficiency over 12 weeks. The intervention group received 75,000 µg single parenteral dose of VIT-D in addition to treatment as usual. At the end of follow-up, the intervention had significantly improved symptoms of depression, severity of illness and quality of life.[124]

Summary of findings

The laboratory evidence suggests that VIT-D may have a role in the pathophysiology of SMD.

Most of the evidence from observational studies points towards some association between VIT-D deficiency and depression and VIT-D and schizophrenia. Mendelian randomisation studies suggest no or reverse causality; VIT-D deficiency is more likely consequence but not a cause of SMD, possibly related to social withdrawal and isolation indoors.[17] The evidence from intervention studies is conflicting; the effect of VIT-D may be most prominent when correcting an underlying VIT-D deficiency.

Vitamin D and COVID-19 infections

Proof of principle

The precise mechanism by which VIT-D exerts any protective effect against infection is unknown. Vitamin-D is nonetheless known to play a role in the immune system. As demonstrated for brain cells, immune cells also express 1α- hydroxylase (1α-OHase) and VIT-DR.[69]

Several pathways have been suggested by which VIT-D could reduce the risk of viral infections: (a) actions on the innate and adaptive immune system, (b) antioxidant actions and (c) renin-angiotensin system (RAS) inhibition in the context of COVID 19 infection.[69,125–127] The actions of VIT-D on these pathways are not completely understood.

Actions on the immune system

Vit-D can exert actions on both the innate and the adaptive part of the immune system (Figure 2).[125,128–134]

Innate immune system. The innate immune system is the first line of defence with a rapid response to invading pathogens. It is non specific. The innate immune system has both cell and humoral components. The innate immune system aims at rapidly recognising and eliminating pathogens, thereby limiting the infection. Cellular physical barriers prevent pathogens from entry.[125,126,133] VIT-D is involved in the upregulation of genes that encode proteins required to maintain cellular barriers and junction integrity.[133] Innate immune mediators include human cathelicidin (leucine-leucine-37/LL-37) and human α and β defensins. These 'alarmins' are peptides with antimicrobial activity against bacteria and fungi as well as viruses[125,135] VIT-D can induce human cathelicidin and defensins as part of the rapid (innate) response system. This can reduce viral replication and pro-inflammatory cytokines. VIT-D may reduce the generation of pro-inflammatory cytokines, such as TNF-α, INF-γ, IL-6, IL-12p70; IL-17 and IL-21.[134,136–142] At the same time, VIT-D may also increase the generation of anti-inflammatory cytokines, such as IL-10.[137,140,143] VIT-D may also act synergistically with IL-2 to stimulate other proteins that regulate the immune response.[134] The net effect of shifting the balance towards anti-inflammatory cytokine activity may

decrease the probability of a cytokine storm. This could then also decrease the likelihood of a potentially lethal cytokine storm, which can result from alarmins being released in excess during severe injuries or maximal stimulation.[144] Specifically, VIT-D may be able to reduce the pro-inflammatory IL-6.[145] This is particularly relevant since IL-6 may have a key role in the generation of cytokine storms and therefore in the pathophysiology of a COVID-19 infection. This assumption is supported by studies that have shown that higher IL-6 concentrations are associated with higher COVID-19 disease severity and mortality.[146,147] One study investigated inflammatory markers in 154 patients with COVID-19 in relation to VIT-D deficiency. VIT-D deficient patients had significantly higher concentrations of IL-6 and a significantly higher mortality.[148]

Adaptive immune system. The adaptive (acquired) immune system is the second line of defence with a protracted response to invading pathogens. It is highly specific to particular pathogens. The adaptive immune system has antibody response and a cell-mediated response. The antibody response involves B lymphocytes and T1-helper cells (Th1). The cell-mediated response involves cytotoxic T lymphocytes and T2 helper cells (TH2). The adaptive immune system aims at eliminating a specific pathogen and creating longer-lasting immunity. The actions of VIT-D seem directed mainly at T cells.[125,130,134]

Antioxidant properties

VIT-D may also have some antioxidant properties.[125] In rodent experiments, it has been shown that VIT-D can increase the expression of glutathione reductase (GR). GR facilitates the conversion of glutathione disulphide to glutathione. Glutathione reduces oxidative stress by scavenging hydroxyl radicals, ROS and other electrophiles.[149]

Renin-angiotensin inhibition

RAS is an essential regulator of lung function. The angiotensin converting enzyme-2 (ACE-2) plays an essential role. ACE-2 converts angiotensin-2 into angiotensin.[150] Whereas angiotensin-2 is a vasoconstrictor, angiotensin is a vasodilator. Therefore, altered ACE-2 function plays a role in the development of hypertension. ACE-2 deficiency is associated with hypertension. ACE-2 overexpression is associated with attenuation of hypertension.[150] ACE-2 is also expressed highly in the lungs. Already in the early 2000s, ACE-2 was implicated as a functional receptor for SARS-CoV.[151] Coronavirus mediated acute respiratory distress syndrome (ARDS) may result from down-regulation of ACE-2. This results in upregulation of angiotensin-2. Actions of angiotensin-2 on the angiotensin-2 type 1a (AT1a) receptor leads to pulmonary oedema and impaired lung function. Actions of angiotensin-2 on the AT2 receptor, however, may be lung-protective.[152] SARS-CoV-2 is closely related to SARS-CoV. Like SARS-CoV, SARS CoV-2 also binds with high affinity to ACE-2. The virus uses ACE-2 to enter target cells in the lung and may affect lung function in the same way.[153,154] Based on animal models, it has been suggested that VIT-D can suppress RAS and angiotensin-2 activity. In humans, this has been put to the test in 184 normotensive individuals. In this study, lower VIT-D levels were associated with (a) higher angiotensin-2 concentrations and (b) a blunted renal plasma flow response to exogenous angiotensin-2 infusion.[155]

Evidence from observational studies regarding COVID-19 infections

Since the beginning of 2020, a multitude of observational studies have been published, examining the relationship between vitamin status and risk of COVID-19 infection or adverse clinical course, including death. These studies have been summarised in five meta-analyses (Supplemental Table S2).[156–160] The results regarding an association between VIT-D deficiency and risk of COVID-19 infection were conflicting.[156–158,160] Two meta-analyses found an increased risk of COVID-19 infection associated with lower 25(OH)D concentrations.[156,158] For the third meta-analysis, the result was ambiguous; the lower confidence interval (CI) was 1.[157] The fourth meta-analysis did not find any significant association.[160] Three meta-analyses explored the severity of COVID-19 infection in relation to VIT-D status.[156,159,160] All three studies found that lower 25(OH)D concentrations were associated with a more severe clinical course. Two meta-analyses reported on risk of death with COVID-19 infection.[156,160] One meta-analysis reported a significant association with VIT-D deficiency.[160] The other meta-analysis had conflicting results, depending on regression model used.[156] All five meta-analyses reported heterogeneity. One meta-analyses reported publication bias.[157] Another meta-analysis reported publication bias for the subgroup analysis regarding risk of infection.[158] No Mendelian randomisation

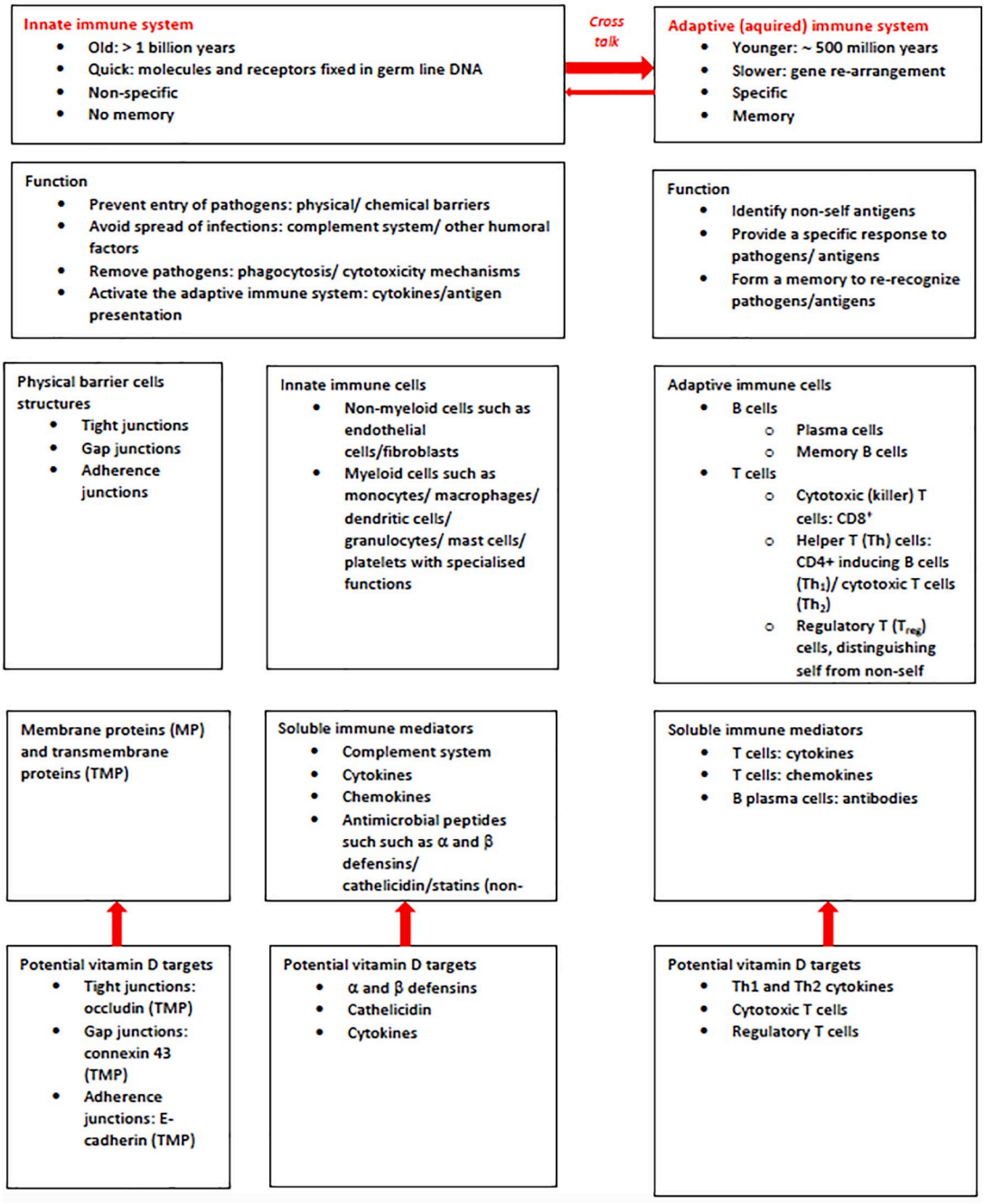

Figure 2. Immune system: schematic overview and potential vitamin D targets.

studies have been published assessing the relationship between VIT-D status and risk of COVID-19 infection or adverse clinical course.

Country/region comparisons. Several studies have related COVID-19 infections or deaths in a country or region to the assumed VIT-D status in that country or region.[42,161–168] However, such studies are difficult to interpret. Reporting of COVID-19 infections and deaths varies between countries.[169] Reporting of VIT-D deficiency also varies, rendering population-based mean or median VIT-D concentrations unreliable. A Mendelian randomisation analysis from the US indicated a relationship between geographical latitude as a proxy for VIT-D status and COVID-19 associated mortality. The

Table 6. COVID-19 cases and death in the 13 countries through which the equator passes.

Country[a]	Latitude	COVID-19 as of 24 March 2021[16] (Worldometer: Coronavirus https://www.worldometers.info/coronavirus/) last updated 13.07 GMT					
		N tests/ 1 M pop	*N* cases/ 1 M pop	*N* deaths/ 1 M pop	Ratio *n* cases/ *n* deaths/ 1 M pop	World ranking *n* cases	World ranking *n* deaths
Ecuador	2°N–5°S	61,951	17,580	925	19.0	98	42
Colombia	12°N–4°S	240,726	45,777	1215	37.7	54	28
Brazil	6°N–34°S	133,861	56,805	1399	40.6	39	23
Sao Tome and Principe	0°	52,194	9721	153	63.5	123	108
Gabon	3°N–4°S	267,214	7987	48	166.4	126	144
Republic of Congo	4°N–5°S	16,472	1703	24	71.0	160	160
Democratic Republic of Congo	6°N–14°S						
Uganda	4°N–2°S	19,717	871	7	124.4	181	184
Kenya	5°N–5°S	26,094	2255	37	60.9	151	147
Somalia	12°N–2°S		640	28	22.9	188	154
Maldives	8°N–1°S	1,128,428	41,632	121	344.1	61	116
Indonesia	6°N–11°S	44,519	5357	154		145	113
Kiribati	3°N–11°S	No data available					

[a]Countries listed geographically from West to East.
1 M pop, 1 million population; COVID-19, coronavirus disease 2019.

relationship was most prominent in Afro-Americans and less so in others. The mortality excess was related to geographical latitude with the steepest gradient at 44° north.[170]

Still, latitude and VIT-D deficiency may correlate less well than often assumed. VIT-D status is dependent not only on exposure to sunlight but also on compensatory dietary intake, including access to VIT-D fortified foods and ethnicity.[37–39,49,171] COVID-19 infections or deaths in the Southern hemisphere[165] may just reflect the much smaller landmass and population in the Southern hemisphere. Also, in the Southern hemisphere, the COVID-19 pandemic began during the summer months. Seasonal VIT-D fluctuations may not necessarily account for seasonal fluctuations of COVID-19 infection. Temperature and humidity are factors to influence the survival of many respiratory viruses including SARS-CoV, Middle Eastern respiratory syndrome (MERS)-CoV and influenza. This may also apply to COVID-19.[169] Finally, underreporting may play a role. Exploring the 13 countries through which the equator passes shows that latitude *per se* is a poor measure for the risk of or death from COVID-19 infection. There was a considerable variation in COVID-19 cases and deaths between countries. For reasons still unknown, the COVID-19 infection and mortality rates are much more unfavourable in the South American than for most African equatorial countries. Variations in country size and test availability cannot fully account for this observation (Table 6).

Evidence from intervention studies regarding COVID-19 infection

We identified seven studies examining VIT-D as an intervention.[172–178] Three studies were intervention trials,[172,173,175] two studies used mixed methods and two studies were observational (Table 7).[174,176,177,178] The results were mixed. Doses and modes of administration varied. Five studies explored COVID-19 associated mortality.[172,173,176–178] Of these, two studies found a decreased risk of death,[176,177] whereas

Table 7. Vitamin D supplementation and COVID-19. Evidence from intervention studies.

Study	Type of study	Sample	Age (years)	Sex	Intervention	Control	Follow up	Results
Ma *et al.*,[174] UK	Prospective study of an intervention	8297 adults with COVID-19 test results in the UK biobank I: 363 VIT-D users C: 7934 VIT-D non-users	I: 59.1 SD 8.1 C: 57.4 SD 8.6 ($p < 0.001$)	I: M 39% F 61% C: M 50% F 50%	Habitual use of VIT-D	No VIT-D use	COVID-19 test results for ca. 4 months	Risk of COVID 19 infection I: 13.5%, C: 16.8% Unadjusted OR 0.78 CI 0.57, 1.05) ($p = 0.105$) Adjusted OR 0.67 CI 0.46, 0.98 ($p = 0.038$)
Murai *et al.*[173]	Multi-centre RCT, double blind	237 of 240 randomised pts hospitalised with moderate to severe COVID-19 infection I: 119 C: 118	Mean I: 56.5 SD 13.8 C: 56.0 SD 15.0 (NS)	I: M 59%, F 41% C: M 53% F 55% (NS)	5000 µg VIT-D3 as a single dose	Placebo	Ca. 4 months	Median LOS I: 7 IQR 4, 10 days C: 7 IQR 5, 13 days HR 1.07 CI 0.82, 1.39 ($p = 0.59$) In-hospital mortality I: 7.6%, C: 5.1% Δ 2,5 CI −4.1, 9.2% ($p = 0.43$) Admission to ICU I: 16.0%, C: 21.2% Δ −5.2 CI −15.1, 4.7% ($p = 0.30$)
Annweiler *et al.*,[176] France [a]	*Post hoc* open label intervention study	66 pts, nursing home residents I: 57 C: 9	Mean I: 87.7 SD 9.3 C: 87.4 SD 7.2 (NS)	I: M 23% F 77% C: M33% F 67% (NS)	2000 µg VIT-D3 Bolus VIT-D in the week following a suspected or confirmed COVID-19 infection or in the preceding month	None	Mean 36 SD 17 days	Death I: 17.5%, C: 55.6%) Adjusted HR 0.11 CI 0.03, 0.48 ($p = 0.003$) Survival time I: Longer survival ($p = 0.002$) Severity of COVID-19 I: Inverse OS CI ($p = 0.001$)
Annweiler *et al.*,[177] France	*Post hoc* open label intervention study	77 pts hospitalised in a geriatric unit I_1: 29 I_2: 16 C: 32	I_1: 88 IQR 87, 93 I_2: 85 IQR 84–89 C: 88 IQR 84–92 (NS)[b]	I_1: M 31% F 69% I_2: M 69% F 31% C: M 59% F 41% ($p = 0.02$)	I_1: Bolus VIT-D3 po taken regularly during the year before the COVID-19 pandemic, either 1250 µg VIT-D3 every month or 2000–2500 µg VIT-D3 every 2–3 months I_2: Bolus VIT 3 po 2000 µg VIT-D3 within a few hours after COVD-19 diagnosis and no previous VIT-D supplements	None	14 days (from hospitalisation)	*Death* I_1: 6.9%, I_2: 18.8%, C 31.3% Adjusted HR I_1 versus C 0.07 CI 0.01, 0.61 (p = 0.017) Adjusted HR I_2 versus C 0.37 CI 0.06, 2.21 (0.28) Survival time I_1 versus C: longer survival (p = 0.015) I_2 versus C: no difference in survival time (p = 0.32) I_1 versus I_2: no difference in survival time (p = 0.32) Severity of COVID-19 I_1 versus C: fewer pts with severe COVI-19 (p = 0.033) I_2 versus C: no difference (p = 0.40)

(Continued)

Table 7. (Continued)

Study	Type of study	Sample	Age (years)	Sex	Intervention	Control	Follow up	Results
Entrenas Castillo *et al.*,[172] Spain	Open label trial, blinded at the point of analysis	76 pts hospitalised with COVID-19 infection I: 50 C: 26	Mean I: 53.1 SD 10.8 C: 52.8 SD 9.4 (NS)	I: M 54% F 46% C: M 69% F 31% (NS)	532 µg 25(OH)D3 (=2660 µg VIT D3) on admission, 266 µg 25(OH)D3 (=1330 µg VIT D3) on day 3 and 7 and then weekly until ICU admission or discharge	None	Until ICU admission, death, or hospital discharge	Admission to ICU I: 2%, C: 50%, Adjusted OR 0.03 CI 0.003, 0.25 Death in ICU I: 0%, C: 15.4%[c] ($p = 0.894$)[d]
Rastogi *et al.*,[175] India	RCT (SHADE study)	40 pts with mild or asymptomatic COVID-19 infection with VIT-D deficiency, i.e., 25(OH)D conc <20 ng/ml I: 16 C: 24	Median I: 50 IQR 36, 51 C: 47.5 IQR 39.3, 49.2 (NS)	I: M 38% F 62% C: M 58% F 42% (NS)	1500 µg VIT D3 for 7 days with a serum conc of >50 ng/ml 25(OH)D as therapeutic target If after 7 days 25(OH)D <50 ng/ml 1500 µg VIT D3 for a further 7 days until day 14	Placebo	21 days	COVID-19 RNA –ve after 21 days I: 62.5%, C: 20.8% ($p < 0.018$) No difference in mean duration to COVID-19 –ve ↓ fibrinogen I: more ↓ ($p < 0.01$) Other inflammatory parameters: No difference regarding D-dimer, CRP, ferritin, procalcitonin
Hernandez *et al.*,[178] Spain	Retrospective study of an intervention (case control)	216 pts hospitalised with COVID-19 infection I: 19 C: 197	Median I: 60 IQR 59, 75 C: 61 IQR 47.5, 70 (NS)	I: M 37% F 63% C: M 62% F 38% ($p = 0.03$)	Oral vitamin D supplements >3 months	No VIT-D use	21 days	Median LOS I: 8 IQR 6, 14 days C: 12 IQR 8.0, 16.0 days ($p = 1.07$) ICU admission I: 5.3%, C: 25.4% ($p = 0.05$) Death I: 10.5%, C: 10.4% ($p = 0.999$)

[a]Conversion factor from µg to IU = 40, 1 µg cholecalciferol = 0.2 µg 25(OH)D.
[b]Not specified by authors whether mean or median, in view of IQR use most likely median.
[c]Of all ICU patients.
[d]Own calculation.
1 IU = 0.025 µg cholecalciferol or 0.005 µg 25(OH)D.
C, control; CI, 95% confidence interval; conc, concentration; COVID-19, coronavirus disease 2019; F, female; HR, hazard ratio; I, intervention; ICU, intensive care unit; IU, international units; LOS, length of stay; M, male; NS, not significant; OR, odds ratio; po, per os; pts, participants; RCT, randomised controlled trial; re, regarding; SD, standard deviation; VIT-D: vitamin D; –ve, negative; Δ, difference.

two did not.[173,178] One study reported fewer deaths in the intensive care unit (ICU), but the result was not significant.[172] Three studies explored admission to ICU.[172,173,178] Of these, one study found a significant association with decreased ICU admissions.[172] Another trial bordered on significance.[178] Two trials explored length of stay. Both did not find any association with VIT-D treatment.[173,178] One study examined the time to recovery from COVID-19 infection in terms of negative RNA serology.[175] Significantly more patients receiving VIT-D became seronegative within 21 days. However, there was no difference in mean time to seronegativity.[175] One observational study explored the risk of COVID-19 infection with habitual VIT-D use in 8297 biobank patients. A significant association became only evident after adjustment for confounders.[174] The results from these studies can be considered as only preliminary. The studies are heterogenous and vary in mode of VIT-D administration. Only two studies used a placebo as a comparator.[173,175] Lack of power and blinding are further concerns.

Summary. The laboratory evidence suggests that VIT-D in principle could provide a defence against COVID-19 infection and against an adverse clinical course. The potential ability of VIT-D to reduce anti-inflammatory cytokines mitigate a cytokine storm and inhibit RAS may be particularly important. The evidence from observational studies does not point consistently towards some association between VIT-D deficiency and risk of COVID-19 infection. There is stronger, but not unanimous, evidence for an association between VIT-D deficiency and an adverse clinical course from COVID-19 infection. Inferences from geographical latitude seem unreliable. The available intervention studies provide conflicting results. Methodological flaws and lack of statistical power limits the validity of several studies. Larger and more methodical trials are required to assess the effectiveness in the prevention and treatment of COVID-19 infection as well as VIT-D dosing and mode of administration. Three larger trials are currently in preparation. The CARED trial will examine whether a single high dose of oral cholecalciferol improves the respiratory outcomes as compared with placebo among 1264 adult COVID-19 patients at moderate risk of clinical complications.[179] The VIVID trial will evaluate the efficacy of daily Vit-D3 supplementation for 4 weeks to reduce disease severity in persons with newly diagnosed COVID-19 infection and to prevent infection in their closest household members. This trial plans to recruit 2700 participants.[180] The COVIT-TRIAL will compare the effect of a single oral high dose of cholecalciferol *versus* a single oral standard dose of cholecalciferol on 14-day all-cause mortality rate in 260 older adults infected with SARS-CoV-2 at higher risk of deterioration.[181]

Conclusion

VIT-D deficiency seem associated with mental disorders such as depression and schizophrenia. But VIT-D deficiency is more likely consequence than a cause of SMD. On proof of principle, VIT-D in could provide a plausible defence against COVID-19 infection and against an adverse clinical course. But data from observational studies and the first preliminary intervention studies remain conflicting, with stronger evidence that VIT-D may mitigate the clinical course of COVID-19 infection rather than the risk of infection in the first place.

Individuals with SMD may have a higher risk of VIT-D deficiency. They also experience higher mortality COVID-19 infection.[1–3] Therefore, it is not unreasonable to assume that individuals with SMD may also experience more adverse effects from COVID-19 infection. VIT-D is relatively cheap, widely available, and easy to administer as an oral supplement. Within the recommended dose-range, adverse effects seem rare. From a public health and public mental health point of view, based on the currently limited knowledge, for individuals with SMD, the benefits of VIT-D optimisation through supplementation seem to outweigh the risks. At the same time, it is important to medically supervise VIT-D supplementation to prevent inappropriate VIT-D use in high doses that could lead to toxicity. VIT-D supplementation should not substitute for vaccination or medical care for COVID-19 infection.

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Conflict of interest statement

UW received funding for educational activities on behalf of Norrbotten Region (Masterclass Psychiatry Programme 2014-2018 and EAPM 2016, Luleå, Sweden): Astra Zeneca, Eli Lilly, Janssen, Novartis, Otsuka/Lundbeck, Servier, Shire, and Sunovion. UW has received a lecture

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Supplemental material

Supplemental material for this article is available online.

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