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'Scientific Strabismus' or Two Related Pandemics: COVID-19 & Vitamin D Deficiency

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Abstract

World Health Organization announced the novel coronavirus disease (COVID-19) outbreak to be a global pandemic. The distribution of community outbreaks shows seasonal patterns along certain latitude, temperature, and humidity i.e. similar to the behavior of seasonal viral respiratory tract infections. COVID-19 displays significant spread in northern midlatitude countries with an average temperature of 5-11 °C and low humidity. Vitamin D deficiency has also been described as pandemic, especially in the Europe. Regardless of age, ethnicity, and latitude; recent data showed that 40% of the Europeans are vitamin D deficient (25(OH)D levels <50 nmol/L), and 13% are severely deficient (25(OH)D <30 nmol/L).A quadratic relationship was found between the prevalences of vitamin D deficiency in most commonly affected countries by COVID-19 and the latitudes. Vitamin D deficiency is more common in the subtropical and midlatitude countries than the tropical and high latitude countries. The most commonly affected countries with severe vitamin D deficiency are from the subtropical (Saudi Arabia; 46%, Qatar; 46%, Iran; 33.4%, Chile; 26.4%) and midlatitude (France; 27.3%, Portugal; 21.2% and Austria; 19.3%) regions. Severe vitamin D deficiency was found to be nearly 0% in some high latitude countries (e.g. Norway, Finland, Sweden, Denmark and Netherlands).

Accordingly, we would like to call attention to the possible association between severe vitamin D deficiency and mortality pertaining to COVID-19. Given its rare side effects and relatively wide safety, prophylactic vitamin D supplementation and/or food fortification might reasonably serve as a very convenient adjuvant therapy for these two worldwide public health problems alike.

Key words: Coronavirus; death; insufficiency; Europe, acute respiratory syndrome

On 11 March 2020, The World Health Organization announced the novel coronavirus disease (COVID-19) outbreak to be a global pandemic.[1] The spread of COVID-19 is becoming unstoppable and as of May 4, more than 3.500.000 people has been infected and about 250.000 people died (Fig. 1).[1] The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is the pathogen of COVID-19. SARS-CoV-2, classified to β coronaviruses, is an enveloped, positive-sense, and single-stranded RNA virus of ~30 kb. The life cycle of the virus with the host comprises mainly five steps as follows: attachment, penetration, biosynthesis, maturation and release. Once SARS-CoV-2 attaches to the host receptors, it penetrates the cells via endocytosis/membrane fusion. Herein, angiotensin converting enzyme 2 (ACE2) is the entry and functional receptor of SARS-CoV-2. It has been shown that the spike for SARS-CoV-2, structural membrane proteins formed by the transmembrane trimetric glycoprotein protruding from the viral surface, also binds to ACE2. After the viral contents are released inside the host cells, viral RNA enters the nucleus to replicate. As for the biosynthesis, viral mRNA is used to make viral proteins. The new viral particles are formed in the maturation step and then released. [2]

The ACE2 plays an important role for the interaction between the classical and non-classical pathway of the renin angiotensin system (RAS). The former acts through the angiotensin II type 1 receptors (AT1) and its increased activity leads to fibrosis, inflammation and angiogenesis. The latter acts through the Mas receptors and has opposing effects to the AT1 receptors [3] ACE2 is expressed by the epithelial cells of lungs, intestines, kidneys, and blood vessels; therefore the aforementioned tissues/organs are vulnerable to SARS-CoV-2 infection.[4] Additionally, activation of the RAS is significantly associated with increased morbidity and mortality as in hypertension.[3]

On the other hand, vitamin D deficiency has also been described as pandemic and a global public health problem, especially in the Europe (Table 1).[5-44] Regardless of age, ethnicity, and latitude; recent data showed that 40% of the Europeans are vitamin D deficient (25(OH)D levels <50 nmol/L), and 13% are severely deficient (25(OH)D <30 nmol/L).[44] According to regression analyses; a quadratic relationship was found between the prevalences of vitamin D deficiency in most commonly affected countries by COVID-19 and the latitudes (Fig. 2). Interestingly, vitamin D deficiency is more common in the subtropical and mid-latitude countries than the tropical and high latitude countries. Contrary to the expectation, the most commonly affected countries with severe vitamin D deficiency are from the subtropical (Saudi Arabia; 46%, Qatar; 46%, Iran; 33.4%, Chile; 26.4%) and mid-latitude (France; 27.3%, Portugal; 21.2% and Austria; 19.3%) regions. On the other hand, severe vitamin D deficiency was found to be nearly 0% in some high latitude countries (e.g. Norway, Finland, Sweden, Denmark and Netherlands). The low prevalences of severe vitamin D deficiencies in high-latitude countries (except for the United Kingdom; 23.7%) can possibly be attributed to the high awareness of vitamin D deficiency, high amount of vitamin D supplementation, food fortification and health policies as well.[44] Indeed, as the main source of vitamin D is exposure of the skin to sun (UVB), it has long been supposed that living in a sunny country guarantees sufficient vitamin D levels. However, there is increasing evidence that vitamin D deficiency may have been underestimated/ignored in low latitude, even in tropical countries. [45]

The risks for vitamin D deficiency encompass obesity, elderly, lack of proper sun (UV-B) exposure, dark skin, smoking, living with air pollution, and the presence of comorbid diseases such as infection, cancer, cardiovascular disease, chronic respiratory disease, osteoporosis, sarcopenia and diabetes mellitus.[46,47] Further, it is known that severe vitamin D deficiency dramatically increases the risk of mortality, infections, and many other diseases. As such, it should indisputably be prevented whenever detected/possible.[46]

Vitamin D hormone has important functions - including immunomodulant, anti-inflammatory and anti-infective roles.[47] It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production, and cytokine synthesis.[48] Human lung cells are able to intracellularly convert the inactive 25(OH)D to its active form 1,25(OH)D which reduces proinflammatory cytokines and increases peptides (e.g. the innate antimicrobial peptide cathelicidin).[48] Cathelicidin has direct antiviral activity against enveloped respiratory viruses such as hepatitis B, influenza, respiratory syncytial virus, and possibly the COVID-19 as well.[48] Other than the above-mentioned functions, vitamin D has also anti-fibrotic effects. The renin-inhibiting activity and downregulation of the RAS activity seem to be the beneficial effects of vitamin D. Moreover, vitamin D has been shown to suppress angiotensinogen and regulate its expression.[49]

The distribution of community outbreaks shows seasonal patterns along certain latitude, temperature, and humidity i.e. similar to the behavior of seasonal viral respiratory tract infections. It has been reported that COVID-19 displays significant spread in mid-latitude (35-50° N') regions and/or in those with an average temperature of 5-11 °C and low humidity (Fig. 1).[1, 50] Coronaviruses are very stable at 4°C (viable for up to three days) and can survive at -20°C (for up to two years).[1] Depending on some parameters (e.g. temperature, humidity and sunlight), they can live on different surfaces for a few days. They are thermolabile; decreased sunlight, low temperatures, and less humidity seem to be favorable for COVID-19.[1] Although natural ultraviolet (UV-C) from the sunlight may not be strong enough to kill COVID-19, its antimicrobial efficacy has long been shown to inactivate, thus prevent the transmission of airborne-mediated infections such as influenza and tuberculosis.[51] Further, UV-B from the sun can induce endogenous synthesis of vitamin D in the skin - being the main source of vitamin D other than the dietary intake or supplementation. These factors might possibly be explanatory as regards the low prevalence of COVID-19 in subtropical and southern countries.

Patients infected with COVID-19 have higher mortality rates if they are older i.e. 8.0% (70-79 years) and 14.8% (>80 years). The similar rates for comorbid conditions are as 10.5% (cardiovascular disease), 7.3% (diabetes mellitus), 6.3% (chronic respiratory disease), 6.0% (hypertension) and 5.6% (cancer).[52] Older adults with any of these comorbid diseases are at high risk for COVID-19 infection - especially in the presence of severe vitamin D deficiency.[53] To this end, since there is positive/strong evidence concerning the effects of vitamin D against viral respiratory infections; it would not be unsound to say that vitamin D supplementation may decrease viral induction and inflammatory genes, and incidence/severity of respiratory tract infections.[48] In this sense, a meta-analysis of 25 randomized controlled trials showed that vitamin D supplementation has a preventive effect against acute respiratory tract infections and that the benefit is higher in those subjects receiving daily or weekly vitamin D without additional bolus doses, and in those having severe vitamin D deficiency at baseline.[54]

Although vitamin D was primarily recognized for bone metabolism, increasing evidence indicates its proper function for nearly every tissue in the body including brain, heart, lung, muscle, immune system and skin. [55] Therefore, the treatment of vitamin D deficiency would be vital for several diseases including cardiovascular and neurological disorders, cancers, autoimmune diseases, and infections as well.[55] Likewise, a recent review recommended that in people at risk of influenza/Covid-19 infection, 10.000 IU/d of vitamin D3 for a few weeks (or a month) i.e. to rapidly increase the 25(OH)D concentrations and then 5.000 IU/d in the follow up can be considered.[47] The target should be to raise its value above 40-60 ng/mL. Additionally, the authors also suggested higher vitamin D3 doses for infected patients with COVID-19. For sure, attention should be paid not to take high calcium supplementation for potential risk of hypercalcemia while taking high doses of vitamin D3. Needless to say; as vitamin D is synthesized mainly in the skin, sun (UV-B) exposure (15-20 min daily) inducing the light pink color of minimal erythema would be the natural way of production and activation of vitamin D by keratinocytes.[55]

Accordingly, presenting this paper, we would like to call attention to the possible association between severe vitamin D deficiency and mortality pertaining to COVID-19. Given its rare side effects and relatively wide safety, prophylactic vitamin D supplementation and/or food fortification might reasonably serve as a very convenient and incomparable/invaluable adjuvant therapy for these two worldwide public health problems alike.

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Figure Legends

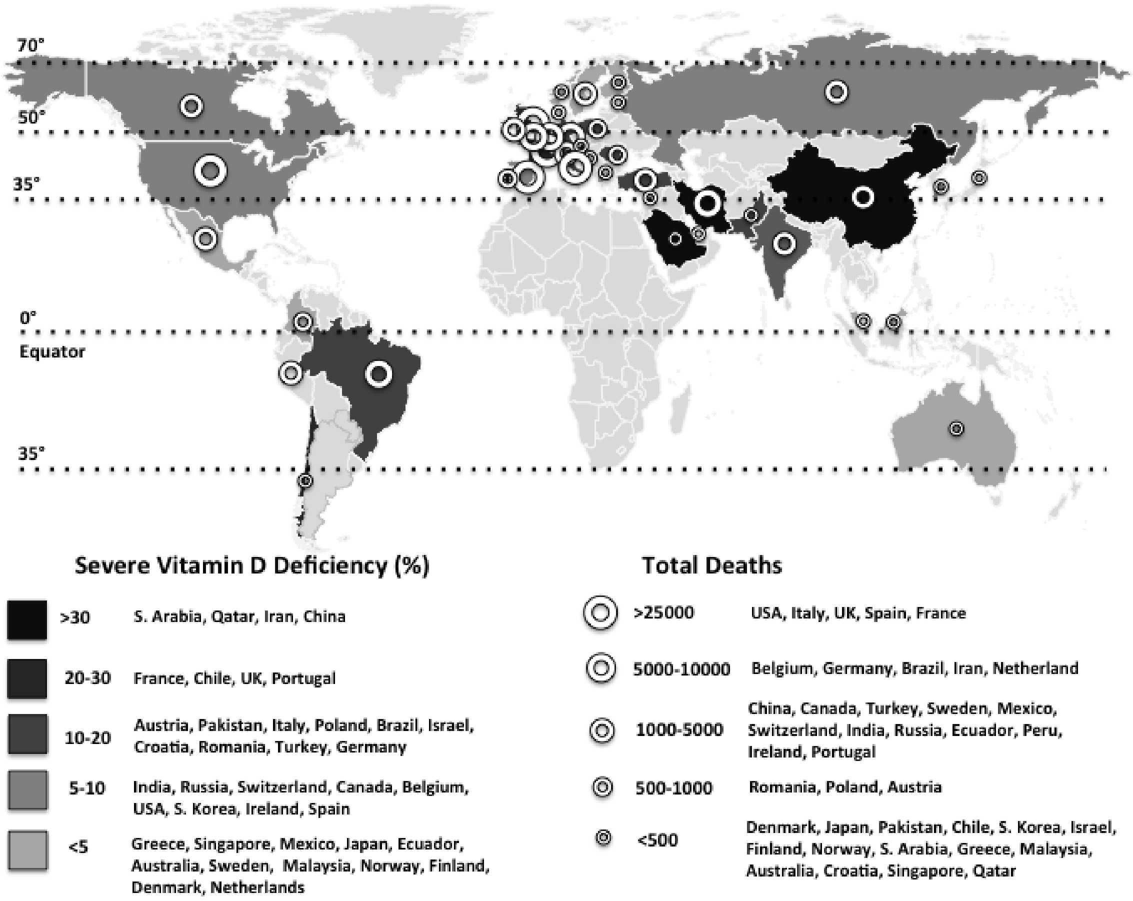

Figure 1: The world map illustrates the total deaths and percentage of severe vitamin D deficiency in countries most commonly affected by COVID-19 [1,5-43]

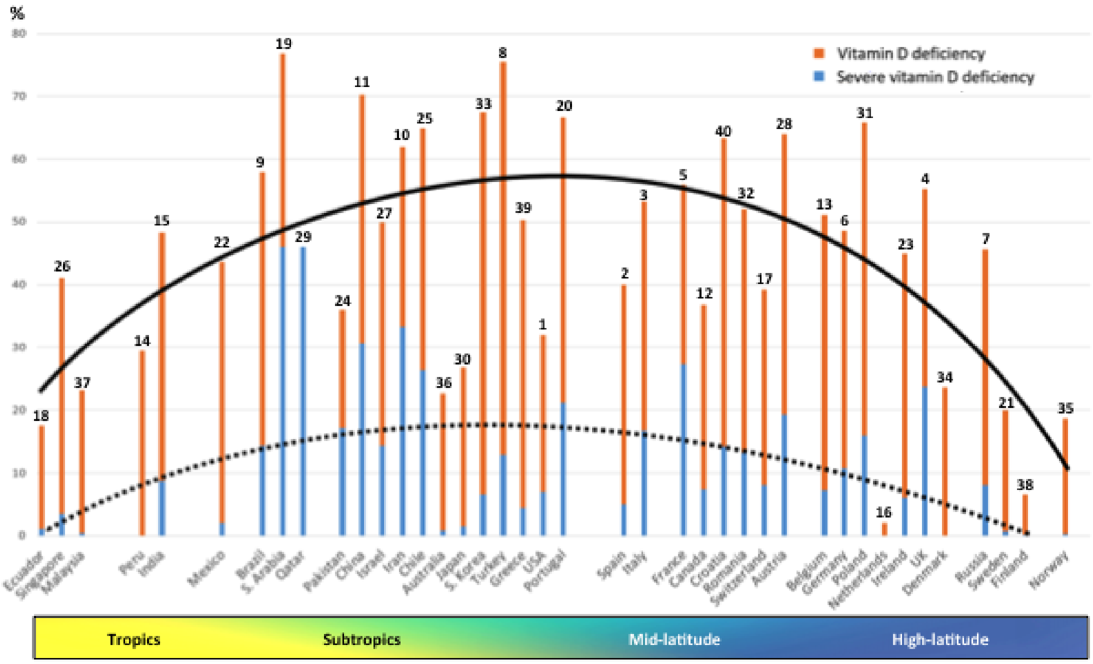

Figure 2: The histogram shows the prevalence of vitamin D deficiency (<50 nmol/L) and severe deficiency (<25 nmol/L) among the 40 countries most commonly affected by the COVID-19. The number above each column represents the country's position in the world ranking concerning the number of total cases of infections. The color band is a graphical representation of the four main climatic areas in the world.

Regression lines show the prevalence of overall *(solid black line)* and severe *(dotted line)* vitamin D deficiencies.

Table 1. Available data for vitamin D deficiency among older adults (if available) in countries most commonly affected by COVID-19.^{x}

Rank*	Country	Latitude	N	Age	25(OH)D deficiency (%)		Reference
					<25 nmol/L	<50 nmol/L	
Region of the Americas							
1	**USA**	Midlatitude (38°)	4363	76±5	**7 (≤30)**	32	Eymundsdottir et al.[5] 2020
9	**Brazil**	Subtropics (23°)	908	73±5	**14.4**	58.0	Lopes et al.[6] 2014
12	**Canada**	Midlatitude (45°)	11336	3-79	**7.4 (<30)**	36.8	Sarafin et al.[7] 2015
14	**Peru**	Tropics (12°)	204	39±11	**N/A**	29.4	Pastor et al.[8] 2019
18	**Ecuador**	Tropics (0°)	2374	71±8	**N/A**	21.6	Orces et al.[9] 2015
22	**Mexico**	Tropics (19°)	585	41±15	**2.0**	43.6	Clark et al.[10] 2015
25	**Chile**	Subtropics (33°)	686	≥65	**26.4 (<30)**	64.9	Solis-Urra et al.[11] 2019
European Region							
2	**Spain**	Midlatitude (41°)	312	≥85	**14.4**	N/A	Formiga et al.[12] 2014
3	**Italy**	Midlatitude (41°)	2640	65-98	**10.6**	21.6	Veronese et al.[13] 2014
4	**UK**	High latitude (54°)	6004	<50	**23.7 (<30)**	55.3	Aspell et al.[14] 2019
5	**France**	Midlatitude (44°)	697	73±4	**27.3**	55.9	Cougnard-Gregoire et al.[15] 2015
6	**Germany**	High latitude (51°)	1671	60-85	**10.7**	48.6	Vetter et al.[16] 2020
7	**Russia**	High latitude (59°)	1664	3-75	**8.0 (<30)**	45.7	Karonova et al.[17] 2016
8	**Turkey**	Midlatitude (37°)	1161	18-90	**12.9**	75.5	Ozturk et al.[18] 2017

13	**Belgium**	High latitude (50°)	697	32-53	**7.3**	51.1	Hoge et al.[19] 2015
16	**Netherlands**	High latitude (52°)	450	65-93	**0.0**	2.0	Ten Haff et al.[20] 2019
17	**Switzerland**	Midlatitude (47°)	1291	≥60	**8.0**	39.2	Sakem et al.[21] 2013
20	**Portugal**	Midlatitude (38°)	3092	≥18	**21.2**	66.6	Duarte et al.[22] 2020
21	**Sweden**	High latitude (56°)	995 (W)	80-81	**0.0**	16.0	Buchebner et al.[23] 2014
23	**Ireland**	High latitude (53°)	1118	18-84	**6.0**	45.0	Cashman et al.[24] 2013
28	**Austria**	Midlatitude (47°)	161	65-80	**19.3**	64.0	Elmadfa et al.[25] 2017
31	**Poland**	High latitude (51°)	5775	16-90	**16.0**	65.8	Pludowski et al.[26] 2016
32	**Romania**	Midlatitude (46°)	14052	37-62	**13.2**	52.0	Niculescu et al.[27] 2017
34	**Denmark**	High latitude (56°)	3409	19-72	**0.0**	23.6	Cashman et al.[28]2015
35	**Norway**	High latitude (69°)	12817	30-87	**0.3**	18.6	Cashman et al.[29] 2016
38	**Finland**	High latitude (64°)	4102	29-77	**0.2**	6.6	Cashman et al.[28] 2015
39	**Greece**	Midlatitude (37°)	181 (M)	20-50	**4.4**	50.3	Kassi et al.[30] 2015
40	**Croatia**	Midlatitude (45°)	120 (W)	61±9	**14.2 (<30)**	63.3	Laktasic et al.[31] 2010
Western Pacific Region							
11	**China**	Subtropics (31°)	2180	>65	**30.6 (<30)**	70.3	Wei et al.[32] 2019
26	**Singapore**	Tropics (1°)	504	45-74	**N/A**	14.0	Robien et al.[33] 2013
30	**Japan**	Midlatitude (38°)	9084	40-74	**N/A**	53.6	Nakamura et al.[34] 2015
33	**S. Korea**	Midlatitude (36°)	4107 (W)	50-79	**6.6 (<37.5)**	67.4	Shin et al.[35] 2015

36	**Australia**	Subtropics (34°)	2413	51±17	**0.9**	22.7	Gill et al.[36] 2014
37	**Malaysia**	Tropics (3°)	63 (M)	≥60	**0.0**	17.5	Chin et al.[37] 2014
Eastern Mediterranean Region							
10	**Iran**	Subtropics (30°)	370	≥35	**33.4**	61.9	Khosravi-Boroujeni et al.[38] 2017
19	**Saudi Arabia**	Subtropics (24°)	3475	47±16	**46.0**	76.8	Alfawaz et al.[39] 2014
24	**Pakistan**	Subtropics (30°)	858	18-60	**N/A**	58.4	Mehboobali et al.[40] 2015
27	**Israel**	Subtropics (31°)	198834	60 (median)	**14.4**	49.9	Saliba et al.[41] 2012
29	**Qatar**	Subtropics (25°)	547	49±13	**46.0**	N/A	El-Menyar et al.[42] 2012
South-East Asia Region							
15	**India**	Tropics (12°)	149	≥46	**8.7 (<30)**	48.3	Mechenro et al.[43] 2018

* The most commonly infected countries and regions with COVID-19 in descending order.

N; number, N/A; not applicable, M; men, W; women, USA; United States of America. UK; United Kingdom, S; South

Percentages (%) of severe vitamin D deficiency are given in bold.