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Vitamin D and Inflammation: Potential Implications for Severity of Covid-19

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Abstract

Background
Recent research has indicated that vitamin D may have immune supporting properties through modulation of both the adaptive and innate immune system through cytokines and regulation of cell signalling pathways. We hypothesize that vitamin D status may influence the severity of responses to Covid-19 and that the prevalence of vitamin D deficiency in Europe will be closely aligned to Covid-19 mortality.

Methods
We conducted a literature search on PubMed (no language restriction) of vitamin D status (for older adults) in countries/areas of Europe affected by Covid-19 infection. Countries were selected by severity of infection (high and low) and were limited to national surveys or where not available, to geographic areas within the country affected by infection. Covid-19 infection and mortality data was gathered from the World Health Organisation.

Results
Counter-intuitively, lower latitude and typically 'sunny' countries such as Spain and Italy (particularly Northern Italy), had low mean concentrations of 25(OH)D and high rates of vitamin D deficiency. These countries have also been experiencing the highest infection and death rates in Europe. The northern latitude countries (Norway, Finland, Sweden) which receive less UVB sunlight than Southern Europe, actually had much higher mean 25(OH)D concentrations, low levels of deficiency and for Norway and Finland, lower infection and death rates. The correlation between 25(OH)D concentration and mortality rate reached conventional significance ($P=0.046$) by Spearman's Rank Correlation.

Conclusions
Optimising vitamin D status to recommendations by national and international public health agencies will certainly have benefits for bone health and potential benefits for Covid-19. There is a strong plausible biological hypothesis and evolving epidemiological data supporting a role for vitamin D in Covid-19.

Background

Vitamin D is a micronutrient which is essential to help maintain bone and musculoskeletal health[1]. However, recent research has highlighted a crucial supportive role for vitamin D in immune cell function, particularly in modulating the inflammatory response to viral infection[2,3]. At a cellular level, vitamin D modulates both the adaptive and innate immune system through cytokines and regulation of cell signalling pathways[4]. Vitamin D receptor (VDR) is present on both T and B immune cells; Vitamin D modulates the proliferation, inhibition and differentiation of these cells[5]. In experimental models of lipopolysaccharide-induced inflammation, vitamin D is associated with lower concentrations of the pro-inflammatory cytokine Interleukin- 6 (IL-6)[6], which plays a significant role in Covid-19 induced acute respiratory distress syndrome (ARDS)[7]. Vitamin D also reduces lipopolysaccharide-induced lung injury in mice by blocking effects on the Ang-2-Tie-2 and renin-angiotensin pathways that are highly relevant to Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2) pathogenicity[8]. A 'sufficient' vitamin D serum level is linked to a switch from a pro- to anti-inflammatory profiles in older adults[9]. This impact on the regulation of inflammation is of particular importance in older adults, the obese and those with chronic conditions as they may already be pre-set for a higher inflammatory response if exposed to Covid-19. A heightened immune response in people who are vitamin D deficient may therefore increase the potential for 'cytokine storm' and consequent ARDS[10].

In a recent large cross-sectional clinical trial (n = 18,883) lower vitamin D were associated with higher respiratory infection rates and the effect was more pronounced in those with underlying lung conditions[11]. Case-control studies have also reported associations between low vitamin D and increased risk of infection[12] and supplementation with vitamin D seems to help reduce both symptoms and antibiotic use[13]. Meta-analysis has also indicated a weak but reduced risk of acute respiratory infection with vitamin D supplementation[14] while a higher blood vitamin D status has been associated with a small reduction in risk of pneumonia[15]. Thus, although vitamin D deficiency probably increases risk of upper respiratory viral infections, the size of this effect is small. It is the impact of vitamin D deficiency on cytokine response, and potentially therefore on lung injury, that is potentially much more important in the context of Covid-19.

Common risk factors for vitamin D deficiency and Covid-19

Curiously, many of the risk factors for vitamin D deficiency (defined as a 25-hydroxyvitamin D (25(OH)D) <30nmol/L) are also risk factors for Covid-19 infection/worse outcomes. For instance older age, obesity, being male and having pre-existing chronic conditions are risk factors for deficiency[16,17] all of which can also make individuals particularly vulnerable to Covid-19 and complications from the virus[18,19]. Coincidentally, the mortality rate for Covid-19 is the highest for those aged >80 years e.g. >20% in Italy and typically this is the age group with the highest levels of deficiency regardless of country. Recent reports have indicated that those residing at higher latitudes, or with darker skin pigmentation (Black Asian Minority ethnics – BAME in UK) may be particularly affected by Covid-19[20]. BAME are also at higher risk of obesity, pre-existing chronic disease (such as heart disease or diabetes) and vitamin D deficiency[21,22]. Importantly, it is already evident that there is a world-wide association between northern latitude and increased Covid-19 mortality[23]. Whilst there could be various explanations for this, it supports the hypothesis that sunlight exposure and hence vitamin D status could be impacting on Covid-19 severity.

We hypothesize vitamin D plays a role in severity of responses to Covid-19 and the prevalence of vitamin D deficiency in Europe will be closely aligned to Covid-19 mortality.

Methods

We conducted a literature search on PubMed (no language restriction) of vitamin D status (for older adults) in countries/areas of Europe affected by Covid-19 infection. Countries were selected by severity of infection (high and low) and were limited to national surveys or where not available, to geographic areas within the country affected by infection (Italy, Spain, United Kingdom, France, Germany, Netherlands, Sweden, Ireland, Scotland, Portugal, Norway, Finland (22-38). Papers were selected from 1999 onwards, when most measurements in older adults were available in Europe. Covid-19 infection and mortality data was gathered from the World Health Organisation (for Scotland data was sourced from Public Health England and the National Records Office Scotland)

Results are presented in **Table 1** detailing for each country the total population (millions), the percentage aged >60 years and presence of vitamin D food fortification policy, vitamin D levels and Covid-19 mortality rates. As is the case for vitamin D research, the majority of the studies used different methodologies for assessing vitamin D status and many used different cut-points for deficiency status. Therefore, to standardise as much as possible we used the commonly accepted thresholds of <25 nmol/L and <30 nmol/L as deficient status and low status is denoted as <50 nmol/L. Winter and summer values are also widely reported across papers and we have tried to average as much as possible.

Results

Counter-intuitively, the lower latitude and typically 'sunny' countries such as Spain and Italy (particularly Northern Italy), had low mean concentrations of 25(OH)D and high rates of vitamin D deficiency. These countries have also been experiencing the highest infection and death rates in Europe. The northern latitude countries (Norway, Finland, Sweden) which receive less UVB sunlight than Southern Europe, actually had much higher mean 25(OH)D concentrations, low levels of deficiency and for Norway and Finland, lower infection and death rates. Across the mid-latitudes of Europe, mean 25(OH)D is similar but with slight deviations. For instance, the mean level is slightly higher in Ireland vs. Germany, UK or France and Ireland is also reporting lower rates of infection and deaths. Portugal appears to be an outlier with a lower vitamin D status but also with lower rates of infection and mortality.

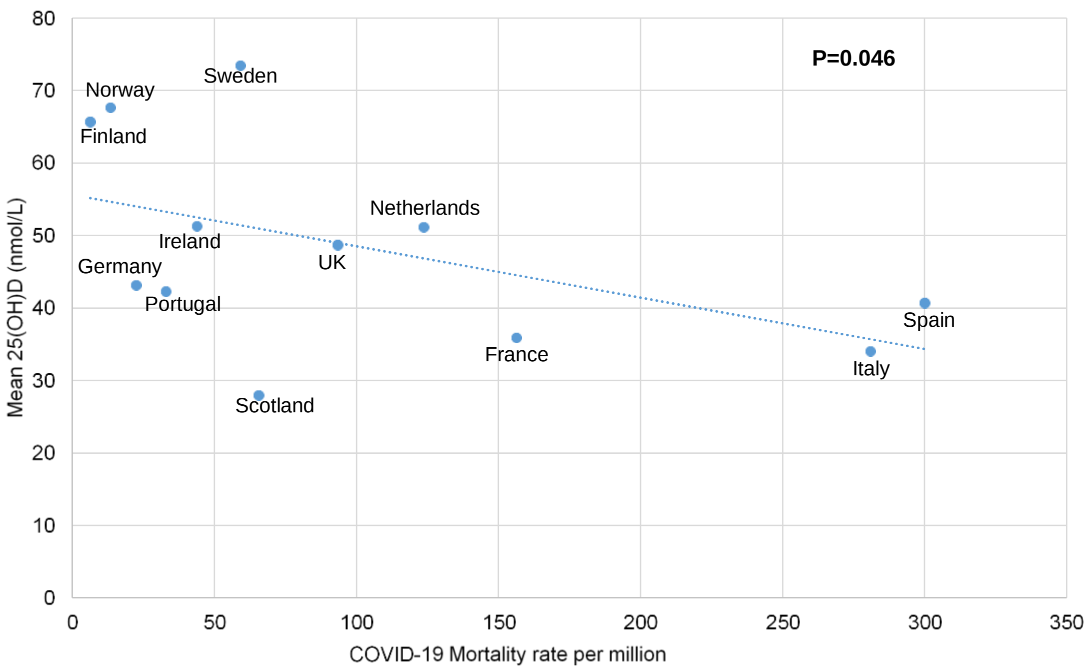
The calculated Covid-19 mortality rate (per million) from the selected countries was plotted against mean 25(OH)D concentrations in **Figure 1**. The correlation between 25(OH)D concentration and mortality rate reached conventional significance (P=0.046) by Spearman's Rank Correlation.

***Table 1**. Vitamin D status and Covid infection and mortality rates in UK and selected European countries*[1]

COVID Infection	COVID Deaths	COVID death rate	Country	Vitamin D policy	Area	Age (yrs)	n	Vitamin D	Notes	Pop millions	% >65
135,586	17,129	281	Italy (24)	No	Parma	>98	104	15 nmo/L	Vitamin D so low - undetectable in 95%	61	23
			Italy (25)	No	Tuscany/Chianti	>65	1,005	48.5 nmol/L	Vitamin D also associated with frailty		
			Italy (26)	No	Milan area	41-80	570	45.7 nmol/L	38.5% deficient		
			Italy (27)	No	Across Country	60-80	700	27.2 nmol/L	27% deficient		
140,510	13,798	300	Spain (28)	No	Madrid area	47-66	171	33.5 nmol/L	36% deficient	46	19
			Spain (29)	No	Sabadell, Barcelona	>64	237	43.0 nmol/L	86% low vitamin D (<50 nmol/l)		
			Spain (30)	No	Cantabria	>75	256	45.7 nmo/L	Deficiency worst with age		
7,693	591	59.1	Sweden (31)	Yes	Umea and Lulea	>65	363	73.5 nmo/L	Deficiency rates decreased with age	10	20
5,863	69	13.2	Norway (32)	No	Northern Norway	60-69	879	67.7 nmol/L	<2% Deficient	5.2	17
2,308	34	6.2	Finland (33)	Yes	Nationally	>65	1140	65.7 nmol/L	<1% Deficient	5.4	22
55,246	6,159	93	United Kingdom (34)	No	Nationally	>50	6004	48.7 nmol/L	32.0% deficient >80 years	66	18
5,709	210	43.7	Ireland (35)	No	Nationally	>50	5356	51.3 nmol/l	46% >85 yrs deficient	4.8	14
4,229	354	65.5	Scotland (36)	No	Aberdeen	>55	518	28.0 nmol/L	26% deficient on average	5.4	
103,228	1,861	22	Germany (37)	No	Nationally	60-79	1816	43.2 nmol/L	29.7% deficient on average	83	21
77,226	10,313	156	France (38)	No	Bordeaux, Dijon, Montpellier	>65	697	35.9 nmol/L	27.3% deficient on average	66	20
12,442	345	32.8	Portugal (39)	No	Nationwide cluster	>65	1500	42.3 nmol/L	39.6% deficient	10.5	22
19,580	2,101	124	Netherlands (40)	No	Nationally	>65	453	51.2 nmol/L	11% deficient on average	17	19

[1] Covid-19 infection and mortality data from the World Health Organisation (For Scotland data was sourced from Public Health England and the National Records Office Scotland). The population percentage aged >65 years was from the World Bank data resource. Due to the nature of vitamin D studies, 25(OH)D values have been measured by different methodologies and some have been measured winter/summer though averages have been tried to be taken where possible. Covid-19 death rate calculated from reported Covid deaths and country population

***Figure 1**. Calculated Covid-19 mortality rate and mean 25(OH)D concentration*



Discussion

In this short report we observed that low 25(OH)D concentrations appear to be associated with increased mortality from Covid-19. Countries with a formal vitamin D fortification policy appear to have the lowest rates of infection whilst countries with no policy and highest deficiency rates appear to be more adversely affected. This difference in Covid-19 mortality by country has also been observed to form a North-South latitude gradient[23]. Observational reports have also highlighted that Covid-19 infection and death rates appear to be higher in ethnic minority populations with darker skin[20] which research has shown to be at much higher risk of vitamin D deficiency[21,22].

Given the strong plausible hypothesis and evolving clinical studies supporting role for vitamin D and immune function for Covid-19, these observations are of concern. Optimising vitamin D status to public health recommendations could enhance immune response but will be a significant challenge for both the UK and Europe. Dietary intakes of the vitamin D are low across the continent / UK[41] and few countries (apart from Sweden or Finland) have any formal mandatory vitamin D food fortification policy. The Nordic countries also tend to have higher dietary intakes of vitamin D and their higher vitamin D status reflects intakes from all sources and not just mandatory fortification. Ireland currently has a 'voluntary vitamin D fortification policy' and the higher 25(OH)D concentration compared with the UK or Scotland could be reflective of this but again Ireland is much lower compared to the Nordic countries. However, introducing mandatory fortification of products (such as dairy) with vitamin D (as practiced in some Nordic countries) and promoting an increased dietary intake of vitamin D rich foods is considered safe and has the potential to help virtually eliminate deficiency in the population[33,42]. This new policy would require formal Government approval and careful modelling of the current level of vitamin D intake taking into account voluntary fortification and self-supplementation. However, it could have significant benefits in terms of bone and musculoskeletal health (economically and socially)[43-45] in addition to the suggested immune health benefits. Moreover this is particularly timely given current lock-down arrangements and government advice e.g. in UK to avoid sunbathing. In the interim strong public awareness campaigns regarding vitamin D sources and supplementation are recommended.

Official vitamin D intake policy

Recommendations for vitamin D intakes for older adults by various public health agencies (the Institute of Medicine (IOM) report (North American Health authority)[1], the Scientific Advisory Committee on Nutrition (SACN) (United Kingdom) report[46], the Nordic Nutritional Recommendations (NNR) report (Nordic countries)[47] and the European Food Safety Authority (EFSA) report)[48] are displayed in **Table 2**. For those with little sun exposure (housebound or confined) the recommended daily intake is 10 -20 ug (400-800 International units per day). Due to inadequate intake in the diet and lack of mandatory fortification in Europe and the United Kingdom (and confinement - lack of sunlight), a vitamin D supplement maybe required to achieve these recommendations. Currently there is insufficient evidence that suggests that higher intakes of vitamin D are required for extra-skeletal health. The optimum doses for Covid-19 protection are not known.

Table 2. Public health authority vitamin D intake recommendations

Report	**Country**	**25(OH)D cut-off for deficiency**	**Optimal 25(OH)D**	**Recommended intake for older adults with little or no sunlight exposure**
Institute of Medicine (IOM) 2011 report[1]	USA & Canada	<30 nmol/L	>50 nmol/L	20 µg daily
Scientific Advisory Committee on Nutrition (SACN) 2016 report[46]	UK	<25 nmol/L	Not stated	10 µg daily
Nordic Nutritional Recommendations (NNR) 2012 report[47]	Nordic countries	<25 nmol/L	>50 mmol/L	15 µg to 20 µg daily
EFSA 2016 report[48]	EU	not stated	>50 nmol/L	15 µg daily

Limitations

Interpretation of observational and cross-sectional data on vitamin D is hampered by the lack of formal set cut-off points which denote deficiency across different countries and the method of vitamin D measurement which can over or underestimate concentrations. Therefore some caution must be used in the interpretation of any analysis although this is typical in vitamin D cross-country comparisons and we have adhered to deficiency cut-points applied in similar analyses. Furthermore, there are also many more micronutrients which have been observed to have immunomodulation effects (such as zinc, selenium, vitamin B6 etc.) which may also have a role in immune function in Covid-19 infections which we did not examine as it was not the focus of this particular analysis. Moreover, the data on Covid-19 infection rates country by country are difficult to interpret because of variation in testing. Finally, this work is observational and maybe be confounded by a number of factors including the varied rate of infection in different countries, different approaches to screening which alters prevalence rates, differences in demographics ie ageing cohorts, and given the speed of the outbreak and infection, it is likely that other unknown factors will exist.

Conclusions

The circumstantial and experimental evidence suggests that vitamin D may have an important supportive role for the immune system, particularly in regulating cytokine response to pathogens. Vitamin D levels are low in countries in Europe which have high infection and mortality rates. Optimising vitamin D status to recommendations by national and international public health agencies will certainly have benefits for bone health and potential benefits for Covid-19. There is a strong plausible biological hypothesis and evolving epidemiological data supporting a role for vitamin D in Covid-19. Ideally, results from randomized controlled trials are required to fully investigate the association. However, these would have to be community-based, which would be impractical during lock-down, and there would also likely be difficulty in persuading participants to risk taking a placebo vitamin. Observational studies correlating vitamin D at time of hospital admission with subsequent outcome would be extremely valuable and should be urgently pursued. In the meantime we recommend that more publicity be given to current guidelines for vitamin D dietary intake and supplementation as denoted by the public health agencies in the USA, UK and Europe.

Declaration of Conflicts of Interest:
The authors have nothing to declare.

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