



PROFESSOR JONATHAN M RHODES (Orcid ID : 0000-0002-1302-260X)

DR SREEDAR SUBRAMANIAN (Orcid ID : 0000-0002-6483-1730)

Article type : Invited Editorial

**Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees  
North – supports vitamin D as a factor determining severity**

**Jonathan M Rhodes<sup>1</sup>, Sreedhar Subramanian<sup>1</sup>, Eamon Laird<sup>2</sup> and Rose Anne Kenny<sup>3</sup>**

Correspondence to:

Jonathan M Rhodes

Emeritus Professor of Medicine

Department of Cellular and Molecular Physiology

Institute of Translational Medicine

University of Liverpool

Nuffield Building

Crown Street

Liverpool L69 3GE

UK

rhodesjm@liverpool.ac.uk

Tel 07889649862

Sreedhar Subramanian

Department of Cellular and Molecular Physiology

Institute of Translational Medicine

University of Liverpool

Nuffield Building

Crown Street

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/apt.15777](https://doi.org/10.1111/apt.15777)

This article is protected by copyright. All rights reserved

Liverpool L69 3GE

UK

Eamon Laird

The Irish Longitudinal Study on Ageing,

School of Medicine,

Trinity College Dublin,

Ireland

Prof Rose Anne Kenny

Department of Medical Gerontology,

6<sup>th</sup> floor, Mercers Institute for Ageing,

St James Hospital,

Dublin 8, Ireland

Email: rkenny@tcd.ie

The excellent review by Al-Ani et al reflects a consensus approach to management of inflammatory bowel disease during the SARS-CoV-2 pandemic that has been established remarkably rapidly by very effective international collaboration.<sup>1</sup> Much of the focus has appropriately been on the potential impact of immuno-modulating therapies. We would also like to highlight the potential importance of nutrition and particularly vitamin D as raised by Panarese and Shahini.<sup>2</sup>

There are marked variations in mortality from COVID-19 between different countries. It is becoming clear that countries in the Southern Hemisphere are seeing a relatively low mortality (Figure and Table).<sup>2,3</sup> It could be argued that the virus spread later to the Southern Hemisphere and that countries there are simply behind those in the Northern Hemisphere but as time goes

by this argument looks increasingly weak. In Australia 100 cases were reported by 10<sup>th</sup> March, 1000 by 21<sup>st</sup> March; in the UK the first 100 had been reported by 5<sup>th</sup> March and the first 1000 by 14<sup>th</sup> March, just one week earlier. If one compares the mortality (68 per million) in the UK by 3<sup>rd</sup> April with the mortality (2 per million) in Australia by 10<sup>th</sup> April there is still a huge discrepancy.

When mortality per million is plotted against latitude it can be seen that all countries that lie below 35 degrees North have relatively low mortality. Thirty-five degrees North also happens to be the latitude above which people do not receive sufficient sunlight to retain adequate vitamin D levels during winter. This suggests a possible role for vitamin D in determining outcomes from COVID-19. There are outliers of course – mortality is relatively low in Nordic countries – but there vitamin D deficiency is relatively uncommon, probably due to widespread use of supplements.<sup>4</sup> Italy and Spain, perhaps surprisingly, have relatively high prevalences of vitamin D deficiency. Vitamin D deficiency has also been shown to correlate with hypertension,<sup>5</sup> diabetes,<sup>6</sup> obesity,<sup>7</sup> and ethnicity<sup>8</sup> – all features associated with increased risk of severe COVID-19.

There are considerable experimental data showing that vitamin D is important in regulating and suppressing the inflammatory cytokine response of respiratory epithelial cells and macrophages to various pathogens including respiratory viruses.<sup>9</sup> Evidence that vitamin D might protect against infection is modest but it is important to note that the hypothesis is not that vitamin D would protect against SARS-CoV-2 infection but that it could be very important in preventing the cytokine storm and subsequent Acute Respiratory Distress Syndrome that is commonly the cause of mortality.<sup>10</sup>

Research is urgently needed to assess whether there may be a correlation between vitamin D status and severity of COVID-19 disease. Meanwhile the evidence supporting a protective effect of vitamin D against severe COVID-19 disease is very suggestive, a substantial proportion of the population in the Northern Hemisphere will currently be vitamin D deficient, and supplements eg 1000 units per day are very safe. It is time for governments to strengthen recommendations for vitamin D intake and supplementation, particularly when under lock-down.

#### Authorship:

All authors contributed to writing and revision and approved the final version.

#### Declaration of interests:

JMR is Co-Editor of *Alimentary Pharmacology and Therapeutics* and with the University of Liverpool and Provenir UK, holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent for its use in antibiotic-associated diarrhoea. Patent also held with the University of Liverpool and others in relation to use of modified heparins in cancer therapy.

SS has received speaker fees from MSD, Actavis, Abbvie, Dr Falk pharmaceuticals, Shire and received educational grants from MSD, Abbvie, Actavis and is an advisory board member for Abbvie, Dr Falk pharmaceuticals and Vifor pharmaceuticals.

EL and RAK have no conflicts to declare.

Funding: None

#### References

1. Al-Ani A, Rentsch C, Prentice R, Johnson D, Ardalan Z, Heerasing N, Garg M, Campbell S, Sasadeusz J, Macrae F, Ng SC, Rubin DT, Christensen B. Review Article: Prevention, diagnosis and management of COVID-19 in the inflammatory bowel disease patient *Aliment Pharmacol Ther* 2020; in press.
2. Panarese A, Shahini E. COVID-19 and vitamin D. (letter) *Aliment Pharmacol Therap*. 2020 DOI: 10.1111/apt.15752
3. <https://www.worldometers.info/coronavirus/>
4. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol*. 2019;180:P23-P54.
5. Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. *Eur J Epidemiol* 2013;28:205-21.

6. Mauss D, Jarczok MN, Hoffmann K, Thomas GN, Joachim E, Fischer JE. Association of Vitamin D Levels with Type 2 Diabetes in Older Working Adults. *Internat J Med Sci* 2015; 12:362-368.
7. Yao Y, Zhu L, He L, et al. A meta-analysis of the relationship between vitamin D deficiency and obesity. *Int J Clin Exp Med* 2015;8:14977-84.
8. Herrick KA, Storandt RJ, Afful J, et al. Vitamin D status in the United States, 2011-2014. *Am J Clin Nutr* 2019;110:150-157.
9. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* 2015;7:4240-70.
10. Laird E, Kenny RA. Vitamin D deficiency in Ireland: Implications for COVID-19. Results from the Irish longitudinal study on ageing. April 4 2020.  
<https://www.doi.org/10.38018/TildaRe.2020-05>

Legend to Figure:

Correlation between mortality from COVID-19 per million by country and latitude. All countries with >150 cases included. Data are from <https://www.worldometers.info/coronavirus/><sup>3</sup> accessed 15<sup>th</sup> April 2020. Latitude is for capital city. It can be seen that mortality is relatively low at latitudes less than 35 degrees North, the point below which adequate sunlight is likely to have been received to maintain vitamin D levels during the winter. Correlation between mortality and latitude  $r=0.53$ ,  $P<0.0001$  by Spearman's rank correlation.

Table:

Comparison between latitude (of capital city in each country) and mortality from COVID-19 per million population - as per Panarese et al,<sup>2</sup> with further analysis and updated 15th April 2020 from <https://www.worldometers.info/coronavirus/><sup>3</sup>

<b>Countries</b>	<b>Latitude degrees</b>	<b>Total cases (N)</b>	<b>Total deaths (N)</b>	<b>Deaths/ Million population</b>
Iceland	64	1720	8	23
Faeroe	62	184	0	0
Norway	60	6740	145	27
Finland	60	3237	64	12
Sweden	59	11927	1203	119
Estonia	59	1400	35	26
Latvia	57	666	5	3
Russia	56	24490	198	1
Denmark	56	6681	309	53
Lithuania	55	1091	29	11
Belarus	54	3728	36	4
Isle of Man	54	256	4	47
Ireland	53	11479	406	82
Germany	52	132321	3502	42
UK	52	93873	12107	178
Netherlands	52	28153	3134	183
Poland	52	7408	268	7
Belgium	51	33573	4440	383
Czechia	50	6151	163	15
Luxembourg	50	3307	67	107
Ukraine	50	3764	108	2
France	49	143303	15729	241
Channel Islands	49	445	13	75
Austria	48	14321	393	44
Slovakia	48	863	6	1
Switzerland	47	26336	1221	141
Moldova	47	1934	43	11

Hungary	47	1579	134	14
Kazakhstan	47	1290	16	0.9
Croatia	46	1741	34	8
Slovenia	46	1248	61	29
Serbia	45	4873	99	11
Canada	44	27063	903	24
Romania	44	7216	362	19
Bosnia and Herzegovina	44	1110	41	12
San Marino	44	372	36	1061
Bulgaria	43	735	36	5
Kyrgyzstan	43	449	5	0.8
Italy	42	162488	21067	348
North Macedonia	42	974	45	22
Andorra	42	659	31	401
Montenegro	42	288	4	6
Georgia	42	306	3	0.8
USA	41	614246	26064	79
Turkey	41	65111	1403	17
Uzbekistan	41	1275	4	0.1
Albania	41	494	25	9
Spain	40	177633	18579	397
China	40	82295	3342	2
Azerbaijan	40	1253	13	1
Armenia	40	1111	17	6
Portugal	39	18091	599	59
S. Korea	38	10591	225	4
Greece	38	2170	101	10
Algeria	37	2070	326	7

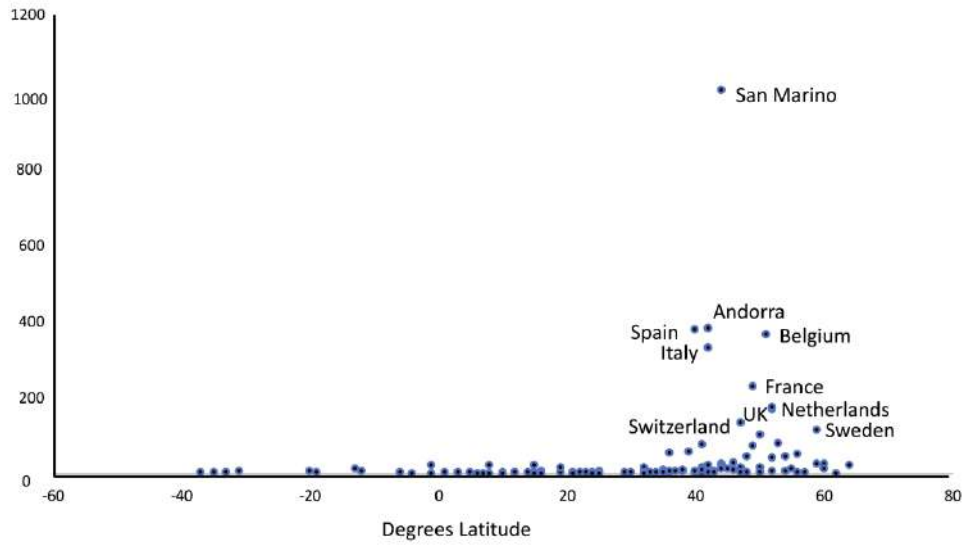
Iran	36	76389	4777	57
Japan	36	8100	146	1
Malta	36	399	3	7
Cyprus	35	695	12	10
Afghanistan	35	784	25	0.6
Pakistan	34	5988	107	0.5
Tunisia	34	747	34	3
Lebanon	34	658	21	3
Iraq	33	1400	78	2
Israel	32	12200	126	15
Morocco	32	1988	127	3
Jordan	32	397	7	0.7
Palestine	32	308	2	0.4
Egypt	30	2350	178	2
India	29	11555	396	0.3
Kuwait	29	1405	3	0.7
Saudi Arabia	25	5862	79	2
Qatar	25	3711	7	2
Bahrain	25	1671	7	4
Taiwan	25	395	6	0.3
UAE	24	4933	28	3
Bangladesh	24	1231	50	0.3
Cuba	23	766	21	2
Hong Kong	22	1017	4	0.5
Oman	21	910	4	0.8
Reunion	21	391	0	0
Vietnam	21	297	0	0
Mexico	19	5399	406	3



Dominican Republic	19	3286	183	17
Brazil	16	25758	1557	7
Guatemala	16	180	5	0.3
Philippines	15	5453	349	3
Senegal	15	314	2	0.1
Martinique	15	158	8	21
Thailand	14	2643	43	0.6
Niger	14	570	14	0.6
Honduras	14	419	31	3
Burkina Faso	12	528	30	1
Djibouti	12	363	2	2
Costa Rica	10	618	3	0.6
Guinea	10	404	1	0.1
Venezuela	10	197	9	0.3
Panama	8	3574	95	22
Ivory Coast	8	638	6	0.2
Nigeria	7	373	11	0.05
Sri Lanka	7	235	7	0.3
Ghana	6	636	8	0.3
Colombia	5	2979	127	2
Cameroon	5	848	17	0.6
Malaysia	3	5072	83	3
Singapore	1	3252	10	2
Ecuador	-1	7603	369	21
Kenya	-1	225	10	0.2
DRC	-4	241	20	0.2
Indonesia	-6	5136	469	2
Peru	-12	10303	230	7
Mayotte	-13	217	3	11

Bolivia	-19	397	28	2
Mauritius	-20	324	9	7
Chile	-31	7917	92	5
South Africa	-33	2415	27	0.5
Australia	-35	6447	63	2
Argentina	-35	2443	108	2
Uruguay	-35	492	8	2
New Zealand	-37	1386	9	2

Mortality from COVID-19  
per million population



apt\_15777\_f1.jpg