LETTER

COVID-19 mortality increases with northerly latitude after adjustment for age suggesting a link with ultraviolet and vitamin D

Dear Editors,

We read with interest the review by Dr Kohlmeier in which he reported a correlation between COVID-19 mortality among African-Americans across the USA and northern latitude.[1] We previously reported a north–south gradient in global COVID-19 mortality but were conscious that lack of ultraviolet exposure and consequent vitamin D insufficiency was not the only possible explanation.[2] We have now investigated the relationships between latitude, age of population, population density and pollution with COVID-19 mortality.

COVID-19 mortality per million by country was downloaded from https://www.worldometers.info/coronavirus/ on 18 May 2020.[3] We included all 117 countries with population >1 million and ≥150 COVID-19 cases. Data by country for population %≥65 years, population density and air pollution (particles of matter <2.5 um diameter µg/m^3) were obtained from public sources.[4–6] Latitude was entered for each country's capital city. The hypothesis was that there was no relationship between mortality and latitude below a threshold and that thereafter mortality increased with latitude. Mortality data were log transformed, and piecewise linear modelling was used to explore the relationship with latitude. This was adjusted for %≥65, and pollution and population density were investigated to see if they further explained variability in mortality.

The analysis supported the hypothesis with a threshold of 28° north and a model of zero slope below the threshold, and a linear model above the threshold was fitted. The age adjustment was highly significant (p<0.0005), with an estimated mortality increase of 13.1% (95% CI 6.9% to 19.8%) for each 1% increase in %≥65. Latitude was also significant (p=0.015) with an estimated 4.9% (95% CI 1.0% to 9.0%) increase in mortality for each 1° further north (table 1, figure 1). Countries with higher pollution included many with younger populations, and pollution was negatively associated with mortality but added no significant explanatory power to a model containing latitude and age. Population density expressed per country was not significantly associated with mortality.

The proportion of older people in each country impacts greatly on COVID-19 mortality, but after adjustment for this, a strong association remains across the Northern hemisphere between latitude and higher COVID-19 mortality. This association exists above 28° north not far from the latitude, usually stated as 35° north, beyond which populations commonly get insufficient ultraviolet B to maintain normal vitamin D blood levels throughout winter. There are exceptions, but COVID-19 mortality correlates with reported vitamin D levels across Europe,[7] and in sunnier Brazil, where mortality is rising, 28% prevalence of vitamin D deficiency is reported.[8] An association between vitamin D insufficiency and COVID-19 severity is supported by substantial evidence of its impact on cytokine response to pathogens.[7] A direct effect of ultraviolet light on the environmental survival of severe acute respiratory syndrome coronavirus 2 is also possible but would not explain the association between mortality and ethnicity,[9] whereas people with dark skin need more ultraviolet exposure for equivalent vitamin D synthesis.

This analysis supports the link between latitude and COVID-19 mortality reported within the USA by Dr Kohlmeier.[1] Evidence linking vitamin D deficiency with COVID-19 severity is circumstantial but growing. Obtaining more direct evidence may be difficult as people could be reluctant to trial a placebo in place of a vitamin supplement. If the association between vitamin D deficiency and COVID-19 severity is causative, the disease should prove seasonal, since more severely affected individuals are infectious for longer. We agree that very high vitamin D doses >4000 IU/day should only be taken in the context of clinical trials[10] but urge that vitamin D supplementation at more moderate dose should be taken by all those at risk of deficiency, including people with darker skin or living in institutions.

Table 1 Associations between COVID-19 mortality by country, latitude and % of population ≥65 years

	Variable	Regression coefficient	SE	P value	% of variation explained	Effect size (95% CI)*
Univariate models						
	Latitude	0.1090	0.0139	<0.0005	18.4	11.5% (8.5% to 14.6%)
	%≥65	0.1766	0.0199	<0.0005	40.4	19.3% (14.8% to 24.1%)
Multivariate model						
	Latitude	0.0478	0.0194	0.015	42.1	4.9% (1.0% to 9.0%)
	%≥65	0.1235	0.0291	<0.0005		13.1% (6.9%19.8%)

*The effect size is, for latitude, the percentage increase in mortality from one location, situated at least 28° north, to another location 1° further north and, for %≥65, the percentage increase in mortality for each one % increase in %≥65.

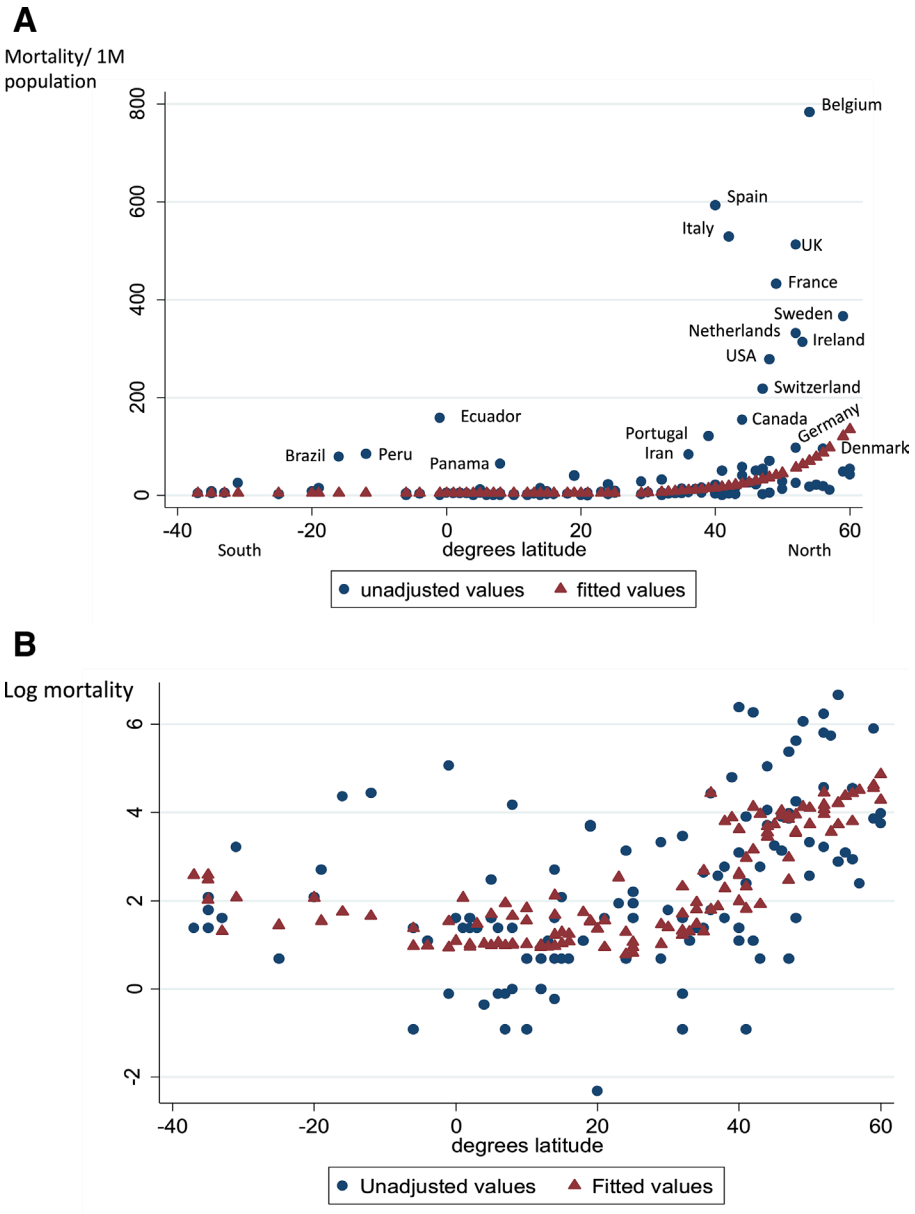

Figure 1 A. COVID-19 mortality per 1 million population by country compared with latitude of capital cities. Fitted values are derived from a piecewise linear model of the logarithm of mortality on latitude. This was based on a threshold of 28° north that explained the greatest amount of variation. B. Logarithm of COVID-19 mortality per 1 million compared with latitude with and without adjustment for age (%≥65 years).

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REFERENCES

1 Kohlmeier M. Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. *BMJNPH* 2020;322:bmjnph-2020-000096.
2 Rhodes JM, Subramanian S, Laird E, *et al*. Editorial: low population mortality from COVID-19 in countries South of latitude 35 degrees North supports vitamin D as a factor determining severity. *Aliment Pharmacol Ther* 2020;51:1434–7.
3 Coronavirus cases, 2020. Available: https://www.worldometers.info/coronavirus/ [Accessed 18 May 2020].
4 Population ages 65 and above (% of total population), 2020. Available: https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS [Accessed 18 May 2020].
5 List of countries and dependencies by population density, 2020. Available: https://en.wikipedia.org/wiki/List of countries and dependencies by population density [Accessed 18 May 2020].

6 Outdoor air pollution, 2020. Available: https://ourworldindata.org/outdoor-air-pollution [Accessed 18 May 2020].
7 Laird E, Rhodes J, Kenny RA, *et al*. Vitamin D and inflammation: potential implications for severity of COVID-19. *Irish Med J* 2020;113:P81.
8 Pereira-Santos M, Santos JYGD, Carvalho GQ, *et al*. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. *Crit Rev Food Sci Nutr* 2019;59:2102–9.
9 Coronavirus (COVID-19) related deaths by ethnic group, England and Wales: 2 March 2020 to 10 April 2020, 2020. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to10april2020 [Accessed 29 May 2020].
10 Lanham-New SA, Webb AR, Cashman KD, *et al*. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJNPH* 2020;8:bmjnph-2020-000089.