

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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 µm diameter µg/m<sup>3</sup>) were obtained from public sources.<sup>4–6</sup> 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

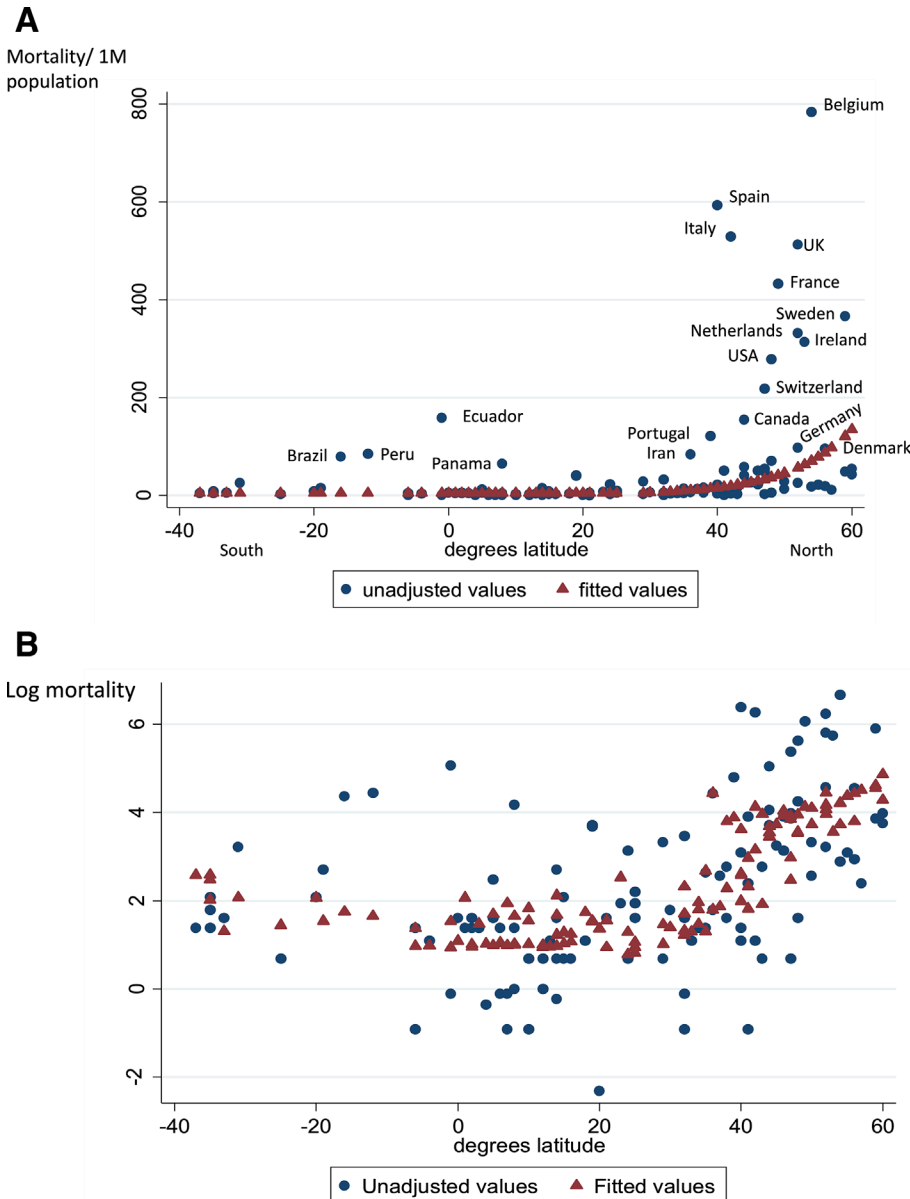
B to maintain normal vitamin D blood levels throughout winter. There are exceptions, but COVID-19 mortality correlates with reported vitamin D levels across Europe,<sup>7</sup> and in sunnier Brazil, where mortality is rising, 28% prevalence of vitamin D deficiency is reported.<sup>8</sup> An association between vitamin D insufficiency and COVID-19 severity is supported by substantial evidence of its impact on cytokine response to pathogens.<sup>7</sup> 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,<sup>9</sup> 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.<sup>1</sup> 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<sup>10</sup> 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% to 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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received speaker fees from MSD, Actavis, Abbvie, Dr Falk Pharmaceuticals and Shire and received educational grants from MSD, Abbvie and Actavis and is an advisory board member for Abbvie, Dr Falk Pharmaceuticals and Vifor pharmaceuticals. FD, EL and RAK have no conflicts to declare.

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