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/m³) 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 but 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 trials10 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

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

*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.
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