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# BMJ Open

## Number of International Arrivals Is Associated with the Severity of the first Global Wave of the COVID-19 Pandemic

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3 **Number of International Arrivals Is Associated with the Severity of the first Global**  
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5 **Wave of the COVID-19 Pandemic**  
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## ABSTRACT

**Objective:** We aimed to derive a measure of COVID-related death rates that is comparable across countries and identify its country-level determinants.

**Design:** An ecological study design of publicly available data was employed.

Countries reporting >25 COVID-related deaths until 08/06/2020 were included. The outcome was log mean mortality rate from COVID-19, an estimate of the country-level daily increase in reported deaths during the ascending phase of the epidemic curve. Potential determinants assessed were most recently published demographic parameters (population and population density, percentage population living in urban areas, median age, average body mass index, smoking prevalence), Economic parameters (Gross Domestic Product per capita); environmental parameters: pollution levels, mean temperature (January-April), co-morbidities (prevalence of diabetes, hypertension and cancer), health system parameters (WHO Health Index and hospital beds per 10,000 population); international arrivals and the stringency index, as a measure of country-level response to COVID-19. Multivariable linear regression was used to analyse the data.

**Primary Outcome:** Country-level mean mortality rate: the mean slope of the COVID-19 mortality curve during its ascending phase.

**Participants:** Thirty-seven countries were included: Algeria, Argentina, Austria, Belgium, Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Egypt, Finland, France, Germany, Hungary, India, Indonesia, Ireland, Italy, Japan, Mexico, the Netherlands, Peru, the Philippines, Poland, Portugal, Romania, the Russian Federation, Saudi

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3 Arabia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom  
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5 and the United States.  
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8 **Results:** Of all country-level predictors included in the multivariable model, only total  
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10 number of international arrivals was significantly associated with the mean death  
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12 rate: Beta 0.040 (95% Confidence Interval 0.017, 0.063),  $P < 0.001$ .  
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16 **Conclusions:** International travel was directly associated with the mortality slope and  
17  
18 thus potentially the spread of COVID-19. Very early restrictions on international  
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20 travel may be a very effective strategy to control COVID outbreak and prevent  
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22 related deaths.  
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## ARTICLE SUMMARY

### Strengths and limitations

- A comparable and relevant outcome variable quantifying country-level increases in the COVID-19 death rate was derived which is largely independent of different testing policies adopted by each country
- Our multivariable regression models accounted for public health and economic measures which were adopted by each country in response to the COVID-19 pandemic by adjusting for the Stringency Index
- The main limitation of the study stems from the ecological study design which does not allow for conclusions to be drawn for individual COVID-19 patients
- Only countries that had reported at least 25 daily deaths over the analysed period were included, which reduced our sample and consequently the power.

## INTRODUCTION

The atypical pneumonia caused by SARS-CoV 2 has spread rapidly. As of the 8<sup>th</sup> of June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.<sup>1</sup> The estimated overall case fatality rate is ~7%, with country-level estimates ranging between 0.5-14%.<sup>2</sup> Nevertheless, there is wide variation in the reported country-specific death rates which may be attributed to variation in testing rates, underreporting or real differences in environmental, sociodemographic and health system parameters.

Country-level determinants of the pandemic severity are largely unknown. The only previous ecological study to date assessing country-level predictors of the severity of the COVID-19 pandemic including data on 65 countries<sup>3</sup> has found that the cumulative number of infected patients in each country was directly associated with the case fatality rate, whilst testing intensity was inversely associated with case fatality rate. This study found no association between health expenditure and case fatality rate. However, other important country-level determinants were not evaluated and thus their relationship with pandemic severity remains unknown.

Several risk factors for COVID-related mortality have been proposed, including older population,<sup>4</sup> higher population co-morbid burden,<sup>5</sup> smoking,<sup>6</sup> obesity,<sup>7</sup> pollution levels<sup>8</sup> and healthcare system performance.<sup>9</sup> Furthermore, countries outside China most severely hit by the pandemic were those with a high income, high GDP per capita and well-established healthcare systems, such as Italy, Spain, France, the United Kingdom and the United States.<sup>10</sup> In contrast, lower- and middle-income countries reported much lower COVID-19 incidence and mortality rates.<sup>10</sup> Whilst these differences may be attributable to case under-reporting and infrequent testing in these countries, other factors may also be involved.

In this study, we aimed to derive a comparable measure of COVID related death rates. In addition, we aimed to assess the determinants for this measure by examining the



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3 association between potential country level determinants driven by hypothesis based on  
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5 currently available evidence using country level publicly available data and an ecological  
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7 study design.  
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## **METHODS**

### ***Patient and Public Involvement***

There was no patient or public involvement in designing the study given the urgent nature of the COVID-19 pandemic and the usage of publicly available data.

### ***Study Design***

An ecological study design was used. The outcome was the steepness of the ascending curve of country specific daily reports of COVID-19 related deaths between 31/12/2019-08/06/2020. The following determinants were assessed: demographic predictors (population and population density, percentage population living in urban areas, median age, average body mass index (BMI), smoking prevalence), economic predictors (gross Domestic Product (GDP) per capita), environmental predictors (pollution levels, mean temperature (January-April) [2010-2016] ), prevalent co-morbidities (diabetes, hypertension and cancer), health systems predictors (WHO Health Index and hospital beds per 10, 000 population), international arrivals (as a proxy measure of the globalisation status of each country) and the stringency index (as measure of country level response to the pandemic).<sup>11</sup>

### ***Ethics Committee Approval***

Given the study design and the use of publicly available data, no ethical approval was considered necessary.

### ***Selection criteria***

Countries reporting at least 25 daily deaths up to the 8<sup>th</sup> of June 2020 with available data for all chosen determinants were included. A total of 37 countries were included in the analysis: Algeria, Argentina, Austria, Belgium, Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Egypt, Finland, France, Germany, Hungary, India, Indonesia, Ireland, Italy, Japan, Mexico, the Netherlands, Peru, the Philippines, Poland, Portugal, Romania, the Russian Federation, Saudi Arabia, South Africa, Spain, Sweden, Switzerland,

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3 Turkey, Ukraine, the United Kingdom and the United States. China was not included in the  
4 analysis due to potential inaccuracies in the number of daily reported deaths which may have  
5 occurred subsequent to 1290 deaths which were retrospectively reported on the 17<sup>th</sup> of  
6 April.<sup>12</sup>  
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### 14 ***Data Sources***

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17 Country-level parameters were obtained from freely accessible data sources. The  
18 daily reported number of COVID-19 cases and deaths between 31/12/2019-08/06/2020 as  
19 well as the 2018 population data were extracted from the European Centre for Disease  
20 Control.<sup>13</sup>  
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26 The data regarding the median population age and population density were extracted  
27 from the United Nations World Population Prospects<sup>14</sup> and United Nations Statistics  
28 Division, respectively.<sup>15</sup> The data regarding the percentage of the population living in urban  
29 areas were extracted from the World Urbanisation Prospects, issued by the United Nations  
30 Population Division.<sup>16</sup> Temperature data were extracted from the Climate Change Knowledge  
31 Portal from the World Bank Group.<sup>17</sup> Prevalent diabetes, gross domestic product,  
32 international arrivals in 2018, and current health expenditure data were extracted from the  
33 World Development Indicators (WDI) database, provided by the World Bank Group.<sup>18</sup>  
34 Prevalent cancers data were extracted from the Our World in Data and the Sustainable  
35 Development Goals (SDG) tracker,<sup>19</sup> an open-access publication tracking global progress to  
36 the United Nations Sustainable Development Goals for global development, adopted in  
37 September 2015. Prevalent hypertension, body mass index (BMI), cigarette smoking and  
38 ambient air pollution data were obtained from the Global Health Observatory (GHO) data  
39 repository of the World Health Organization.<sup>20</sup> The world health organisation health index  
40 was extracted from the WHO Global Partnership for Education (GPE) paper series published  
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3 in 2000.<sup>21</sup> Country-level total hospital beds per 10,000 population data were extracted from  
4 the World Bank Dataset “World Bank Indicators of Interest to the COVID-19 Outbreak”.<sup>22</sup>  
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6 Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020 were extracted  
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8 from the Oxford COVID-19 Government Response Tacker (OxCGRT).<sup>11</sup>  
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### 14 ***Definition of outcome and predictors***

#### 15 *Outcome*

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19 Whilst previous ecological studies of other epidemics have utilised case or death  
20 counts as outcome,<sup>23</sup> this may be prone to bias due to variations in country-level testing  
21 strategies,<sup>24</sup> variations in population movement controls and differences in secondary attack  
22 rates within community cohorts<sup>25</sup>. The mean mortality rate was thus chosen as outcome  
23 instead, since it is independent of these parameters and may thus represent a more reliable  
24 indicator of the country-level severity of the COVID-19 pandemic  
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33 Mean mortality rate was defined as the mean slope of the mortality curve (Figure 1),  
34 measured from the first day when more than 2 COVID-19 deaths were reported until either  
35 the mortality curve reached a peak value or the 8<sup>th</sup> of June 2020, whichever occurred first.  
36  
37 Before slope calculation, the mortality curve in each country was smoothed using a locally  
38 weighted (Lowess) regression using a bandwidth of 0.4. In order to ensure a good fit of the  
39 Lowess regression line, only countries having reported at least 25 daily deaths until the 8<sup>th</sup> of  
40 June 2020 were included. The mean mortality rate thus represents an estimate of the country-  
41 level daily increase in reported deaths during the ascending phase of the epidemic curve.  
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#### 51 *Determinants*

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53 Data on population density were extracted as the country-level population per square  
54 kilometre in 2019.<sup>26</sup> Data on ambient air pollution were extracted as the country-level mean  
55 concentration of fine particulate matter (PM2.5) measured in 2016.<sup>27</sup> Temperature data were  
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3 extracted as the mean temperature recorded in each country between January and April  
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5 between 2010 and 2016.<sup>17</sup> Data on International Arrivals were extracted as the total number  
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7 of country-level international arrivals in 2018.<sup>28</sup>  
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10 Data on prevalent diabetes were extracted as the percentage of the population aged 20  
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12 to 79 years in 2019.<sup>18</sup> Data on prevalent cancers were extracted as the age-standardized  
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14 cancer prevalence among both sexes in 2017, expressed as percentages.<sup>29</sup> Data on prevalent  
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16 hypertension were extracted as the age-standardised percentage of the population over 18  
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18 years of age with systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg  
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20 in 2015.<sup>30</sup> Data on BMI were extracted as the age-standardised mean body mass index trend  
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22 estimates for both sexes amongst adults ( $\geq 18$  years) in 2016.<sup>31</sup> Data on daily cigarette  
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24 smoking were extracted as the age-standardised rate on both sexes amongst adults ( $\geq 18$   
25  
26 years) in 2013.<sup>32</sup> Whilst the definition of “daily cigarette smoking” varies across surveys, it  
27  
28 habitually refers to current smoking of cigarettes at least once a day.<sup>32</sup>  
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33 Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in  
34  
35 current international dollars in 2018.<sup>33</sup> The percentage of population living in urban areas was  
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37 defined as the percentage of de facto population living in areas classified as urban according  
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39 to the criteria used by each area or country.<sup>16</sup> The World Health Organisation (WHO) health  
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41 index is a composite index that aims to evaluate a given countries healthcare system  
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43 performance relative to the maximum it could achieve given its level of resources and non-  
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45 healthcare system determinants. It was calculated in the year 2000. The index uses five  
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47 weighted parameters: overall or average disability-adjusted life expectancy (25%),  
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49 distribution or equality of disability-adjusted life expectancy (25%), overall or average  
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51 healthcare system responsiveness (including speed of provision and quality of amenities;  
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53 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare  
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55 expenditure (25%). Data on hospital beds per 10,000 population were defined by the World  
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3 Bank as including “inpatient beds available in public, private, general, and specialized  
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5 hospitals and rehabilitation centres. The published data for countries included was from 2000  
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7 to 2017. In most cases beds for both acute and chronic care are included.<sup>22</sup> The SI is an  
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9 overall indicator of public health measures adopted by each country in response to the  
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11 COVID-19 pandemic and includes containment and closure indicators, economic response  
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13 indicators as well as health systems indicators.<sup>11</sup> The mean SI was calculated for each country  
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15 between 31/12/2019 and until either the mortality curve reached a peak value or the 8<sup>th</sup> of  
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17 June 2020, whichever occurred first.

### 21 ***Statistical analysis***

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24 All analyses were performed in Stata 15.1SE, Stata Statistical Software. A 5%  
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26 threshold of statistical significance was utilised for all analyses ( $P < 0.05$ ). Linear regression  
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28 was performed to assess the univariable relationship between each country-level predictor  
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30 and the calculated mean mortality rate for each country. The following predictors were  
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32 included in the univariable analyses: population in 2018 (natural logarithm), median age,  
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34 pollution levels, mean temperature (January-May), international arrivals, population density,  
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36 prevalent diabetes, prevalent neoplasms, median BMI, prevalent hypertension, smoking  
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38 prevalence, hospital beds (per 10,000 population), WHO health index, percentage population  
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40 living in urban areas, GDP per capita (PPP) and the Stringency Index. Predictors reaching a  
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42  $P$ -value  $< 0.3$  at univariable level were then included in a multivariable logistic regression  
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44 model with the natural logarithm of the mean mortality rate as outcome: median age,  
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46 pollution levels, international arrivals, prevalent neoplasms, median BMI, prevalent  
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48 hypertension, WHO health index, percentage of population living in urban areas and GDP per  
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## RESULTS

Table 1 and Supplementary File 1 detail the analysed data for the 37 included countries, including the calculated mean mortality rates. The mean mortality rates ranged between 0.22 (Chile) and 43.74 (the United States) new daily deaths. Only five included countries had a high mean mortality rate (>10): the United States (43.74), Spain (29.23), the United Kingdom (24.05), France (22.13), Italy (18.79) and Brazil (13.09).

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**Table 1.** Observed mean mortality rate and number of international arrivals in 2018 (millions) for each country included in the analyses. Countries were categorised in 3 groups: high mean mortality rate group (>20 additional daily deaths), medium mean mortality rate group (2-20 additional daily deaths) and low mean mortality rate group (<2 additional daily deaths).

Country Name	Mean Mortality Rate (daily increase in deaths) [up to 01/05/20]	International Arrivals (millions) [2018]
<b>High Mean Mortality Rate</b>		
United States of America	43.74	79.75
Spain	29.23	82.77
United Kingdom	24.05	36.32
France	22.13	89.32
Italy	18.79	61.57
Brazil	13.09	6.62
<b>Medium Mean Mortality Rate</b>		
Belgium	7.86	9.12
Mexico	7.15	41.31
Germany	6.58	38.88
Netherlands	5.40	18.78
Turkey	3.48	45.77
India	3.48	17.42
Canada	3.27	21.13
Sweden	2.59	7.44
Russian Federation	2.52	24.55
Peru	2.05	4.42
<b>Low Mean Mortality Rate</b>		
Switzerland	1.60	10.36
Ireland	1.58	10.93
Portugal	1.03	16.19
Algeria	0.88	2.66
South Africa	0.84	10.47
Ecuador	0.81	2.54
Poland	0.79	19.62
Indonesia	0.72	15.81
Austria	0.70	30.82
Romania	0.60	11.72
Egypt	0.50	11.20
Japan	0.48	31.19
Saudi Arabia	0.48	15.33
Philippines	0.46	7.17
Colombia	0.42	3.90



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Hungary	0.38	17.55
Ukraine	0.31	14.10
Dominican Republic	0.28	6.57
Finland	0.26	3.22
Argentina	0.25	6.94
Chile	0.22	5.72

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3 Table 2 details the results of the linear regression analyses. The following country-  
4 level predictors showed a statistically significant relationship with log mean mortality rate at  
5 univariable level: international arrivals in 2018 (coefficient (95% confidence interval) =  
6 0.049 (0.033, 0.064),  $P < 0.001$ ), prevalent neoplasms (0.614 (0.209, 1.019),  $P = 0.005$ ) and  
7 prevalent hypertension (-0.150 (-0.254, -0.045),  $P = 0.008$ ) . The multivariable model  
8 included the following predictors, which were selected from univariable models: median age,  
9 pollution levels, mean temperature, international arrivals, prevalent neoplasms, prevalent  
10 hypertension, WHO health index, percentage of population living in urban areas, GDP per  
11 capita and the stringency index. International arrivals in 2018, as a marker of global  
12 connection, was the only statistically significant predictor of log mean mortality rate (0.040  
13 (0.017 ,0.063) for 1 million increase in international arrivals,  $P = 0.002$ ). Figures 2 and 3  
14 detail the relationship between the country-level log mean mortality rate (predicted and  
15 observed) and each country-level predictor included in the multivariable regression model.  
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**Table 2.** Results of the linear regression assessing the country-level predictors of the daily increase in deaths. The predictors achieving a 30% statistical significance level at univariable levels ( $P < 0.3$ ) were included in the multivariable model.

Predictor	Univariable		Multivariable	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Population (10 million increase) [2018]	0.432 (-0.050, 0.814)	0.033	0.317 (0.163, 0.798)	0.186
Median age	0.063 (-0.006, 0.132)	0.82	0.037 (-0.079, 0.154)	0.512
Pollution levels	-0.017 (-0.044, 0.11)	0.247	-0.007 (-0.036, 0.021)	0.605
Mean Temperature (January-April) [2010-2016]	-0.031 (-0.078, 0.017)	0.218	0.005 (-0.061, 0.072)	0.869
International Arrivals (1 million increase) [2018]	<b>0.049 (0.033, 0.064)</b>	<b>&lt;0.001</b>	<b>0.040 (0.017, 0.063)</b>	<b>0.002</b>
Population Density	-0.002 (-0.006, 0.002)	0.268	0.001 (-0.002, 0.005)	0.377
Diabetes prevalence (% of population ages 20 to 79) [2019]	-0.0031 (-0.189, 0.126)	0.700	-	-
Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017]	<b>0.614 (0.209, 1.019)</b>	<b>0.005</b>	-0.301 (-1.062, 0.461)	0.423
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	<b>-0.150 (-0.254, -0.045)</b>	<b>0.008</b>	0.118 (-0.250, 0.014)	0.078
Smoking prevalence, 2016 total (ages 15+)	0.002 (-0.058, 0.062)	0.952	-	-
Hospital beds (per 10, 000 population)	-0.004 (-0.022, 0.014)	0.632	-	-
WHO health index, [2000]	2.259 (-0.920, 5.439)	0.173	-3.465 (-7.455, 0.526)	0.086
Population living in urban areas (%)	0.023 (-0.011, 0.58)	0.193	0.004 (-0.029, 0.038)	0.804
GDP per capita, PPP (\$1000 increase), [2018]	0.280(0.037, 0.524)	0.030	0.303 (-0.051, 0.657)	0.009
Mean Daily Stringency Index	-0.036 (-0.072, -0.000)	0.057	0.000 (-0.035, 0.035)	0.99

R<sup>2</sup> for multivariable linear regression = 0.7565

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity;

## DISCUSSION

### Principal findings

In this ecological study including data from 37 countries which were most severely affected by COVID-19 in the first wave of current Global pandemic, we assessed 16 country-level socioeconomic, environmental, health and healthcare system, and globalisation parameters as potential predictors of variation in death rates from COVID 19 infection. In the multivariable linear regression model, the only predictor that reached statistical significance was international arrivals, a proxy of global connection.

### Comparison with literature.

A previous ecological study analysed the country-level predictors of the COVID-19 case fatality rate including 65 countries.<sup>3</sup> This study found that upon adjustment for epidemic age, health expenditure and world region, the case fatality rate was significantly associated with increasing cumulative number of COVID-19 cases and decreasing testing intensity.<sup>3</sup> Nevertheless, no other country-level predictors were included in this study.

Further comparisons can be made with data from previous pandemics. A negative association has been reported between health expenditure and death rates from the 2009 influenza pandemic in 30 European countries.<sup>23</sup> Associations have also been reported between airline travel and spread of the H1N1 influenza virus infection.<sup>34</sup>

Comorbidities may account for mortality rate differences between countries. A study among laboratory-confirmed cases of COVID-19 in China showed that patients with any comorbidity, including diabetes, malignancy and hypertension, had poorer clinical outcomes than those without.<sup>5</sup> We thus accounted for country-level data on a selection of key comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI  $\geq 40\text{kg/m}^2$  has been identified as an independent risk factor for severe COVID-19 illness.<sup>7</sup>

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3 Finally, a recent systematic review on 5 studies from China showed that smoking is likely  
4 associated with negative outcomes and progression of COVID-19.<sup>6</sup>  
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### 10 **Interpretation of findings.**

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12 In our multivariate model, the only significant determinant of mortality was  
13 international arrivals. Travel restrictions and their effectiveness in containing respiratory  
14 virus pandemics remains a contentious subject. In 2007 the WHO published a protocol on  
15 'rapid operations to contain the initial emergence of pandemic influenza', which included  
16 recommendations on travel restrictions.<sup>35</sup> However, subsequent guidance advises such  
17 restrictions are not recommended once a virus has spread significantly.<sup>36</sup> A recent systematic  
18 review of 23 studies that demonstrated limited impact of travel restrictions in the containment  
19 of influenza: internal travel restrictions delayed pandemic peak by approximately 1.5 weeks,  
20 while 90% air travel restriction delayed the spread of pandemics by approximately 3–4 weeks  
21 but only reduced attack rates by less than 0.02%.<sup>37</sup> However, another systematic review of  
22 combination strategies for pandemic influenza response showed that combination strategies  
23 including travel restrictions increased the effectiveness of individual policies.<sup>38</sup>  
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40 The WHO recommendations for pandemic preparedness and resilience recommends  
41 that points of entry into the country should be monitored by focussing on surveillance and  
42 risk communication to travellers but falls short of closing down international travel.<sup>39</sup>  
43  
44 Interestingly, during the COVID-19 pandemic, some countries such as Thailand have adopted  
45 aggressive international travel screening and isolation policies, which may have led to lower  
46 infection rates.<sup>40</sup> Our study suggests that travel restrictions have the potential to influence the  
47 impact of the COVID-19 pandemic and should be part of a structured and rapidly instigated  
48 pandemic preparedness plan. Furthermore, the mean stringency index, which also accounts  
49 for international travel restrictions amongst other measures, was not associated with the mean  
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3 mortality rate in the multivariable model. This suggests that international travel restrictions  
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5 and other containment measures may have been imposed too late to influence the steepness  
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7 of the mortality curve and that the level of global connectivity of each country may influence  
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9 the course of the epidemic mortality curve before the number of COVID-19 related cases and  
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11 deaths reaches worrying levels.  
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### 19 **Strengths and Limitations.**

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21 The main strength of this study lies in its use of comparable and relevant outcome data  
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23 derived from contemporary death reporting from countries affected by COVID-19. As testing  
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25 rates for the virus vary across countries, the incidence or prevalence of the disease cannot be  
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27 compared between countries. While death from the disease is a hard outcome, the  
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29 denominator information to calculate death rates make between-country comparisons  
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31 difficult. In addition, the deaths in the community, particularly in the elderly living in care  
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33 homes, often go untested and thus firm diagnosis remains impossible. Therefore, in this  
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35 study we have adopted an outcome that is comparable in terms of the increase in the rate of  
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37 death, rather than death rates *per se*. Therefore, this may better represent the spread and  
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39 seriousness of pandemic in individual countries when comparing countries at different stages  
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41 of the pandemic. The country-level parameters assessed as potential predictors have all been  
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43 implicated at some point to be associated with severity and consequently mortality. We  
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45 however found that the only significant predictor to be total number of international arrivals  
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47 in the country (2018 figures), signifying transmission of the infection through travel.  
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49 Although the data was from 2018, there is no reason to believe that international travel  
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51 figures between countries would be different in early 2020. Furthermore, our multivariable  
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3 model also accounts for country-level international travel restrictions adopted in response to  
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5 the spread of COVID-19,  
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8 The main limitation of the study stems from the ecological study design. Despite the  
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10 fact that we did not find any association between comorbidities such as diabetes, cancer and  
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12 hypertension and the mean death rates at country level, it is possible for an individual with  
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14 any or all of these comorbid conditions to be more susceptible to the infection and  
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16 consequently at increased risk of dying. Only including countries that had reported at least 25  
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18 deaths reduced our sample and consequently the power. This may also result in the regression  
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20 model overfitting the data. Other explanatory variables associated with COVID-19 related  
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22 mortality may have been missed and some of the covariate data used in our model predate the  
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24 COVID outbreak and may not be relevant at this time point. Furthermore, as new countries  
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26 are affected by the epidemic, the virulence of the virus and resistance of the human body may  
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28 have changed over time which was not accounted for in our model. Lastly, it is possible that  
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30 the quality of data, especially underreporting of deaths, may have been associated with some  
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32 of the predictors in our model and thus biased our results.  
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## 40 **CONCLUSION**

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42 Out of all the country-level parameters assessed, international travel was the only  
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44 significant predictor of the severity of the first global wave of the COVID-19 pandemic.  
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46 Given that many of world middle and lower-income countries are showing signs of continued  
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48 rise in infection rates, international travel restrictions applied very early in the pandemic  
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50 course may be an effective measure to avoid rapidly increasing infection and death rates  
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52 globally.  
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## **CONTRIBUTORSHIP**

PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP collected data and performed literature search. TAP, PKM, DJM and SB developed analysis plan. TAP analysed the data under supervision of DJM. TAP and SB drafted the paper. All authors contributed to the interpretation of results and in making an important intellectual contribution to the manuscript. All authors read and approved the final manuscript.

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## **CONFLICTS OF INTEREST**

None.

## **FUNDING**

None.

## **DATA SHARING STATEMENT**

All data relevant to the study have been submitted to the journal as supplementary materials.



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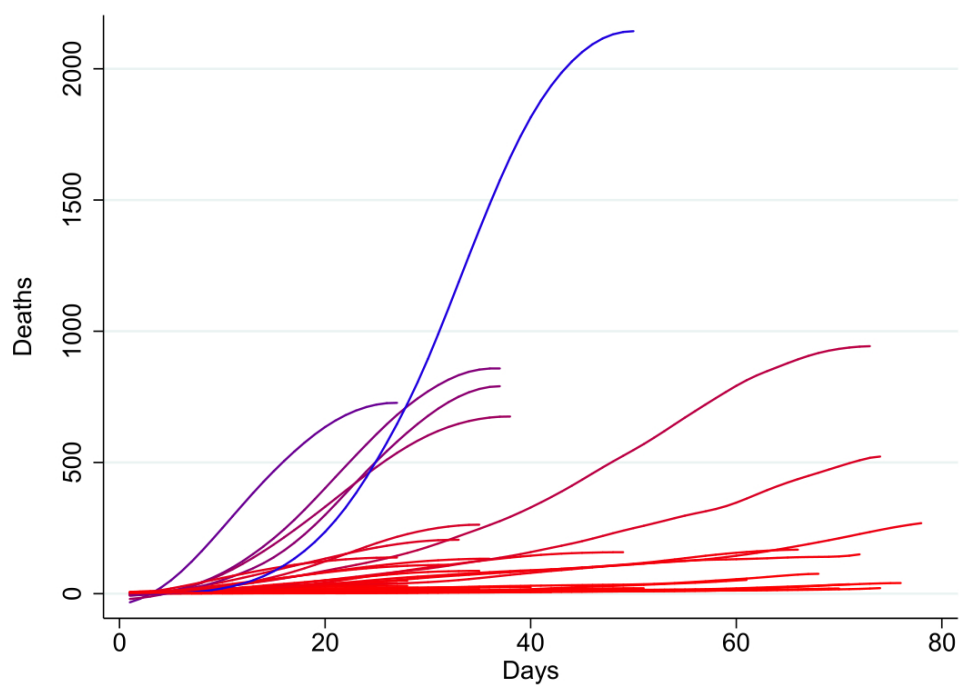
## FIGURE LEGENDS

**Figure 1.** Graphical representation of the smoothed\* number of daily deaths of each country (before reaching mortality peak, if applicable) as a function of the number of days passed since the first day when an excess of 3 deaths were reported. Countries with higher mortality rates are depicted in blue, while those with lower mortality rates are depicted in red.

\*smoothed using a local regression (lowess) function with a bandwidth of 0.4

**Figure 2.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions).

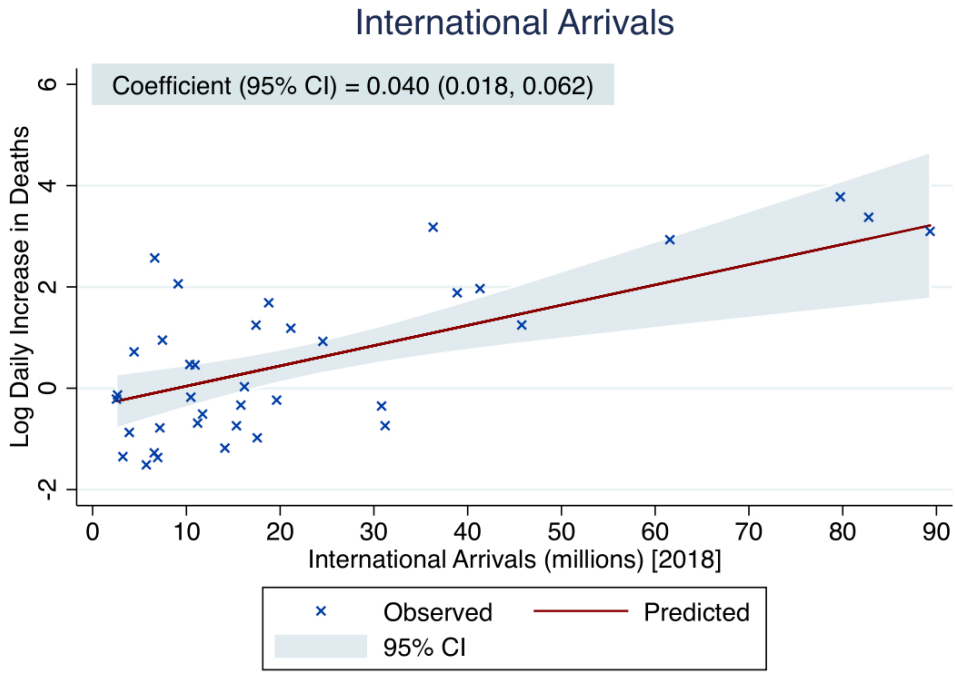
**Figure 3.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of each country-level predictor included in the multivariable model.

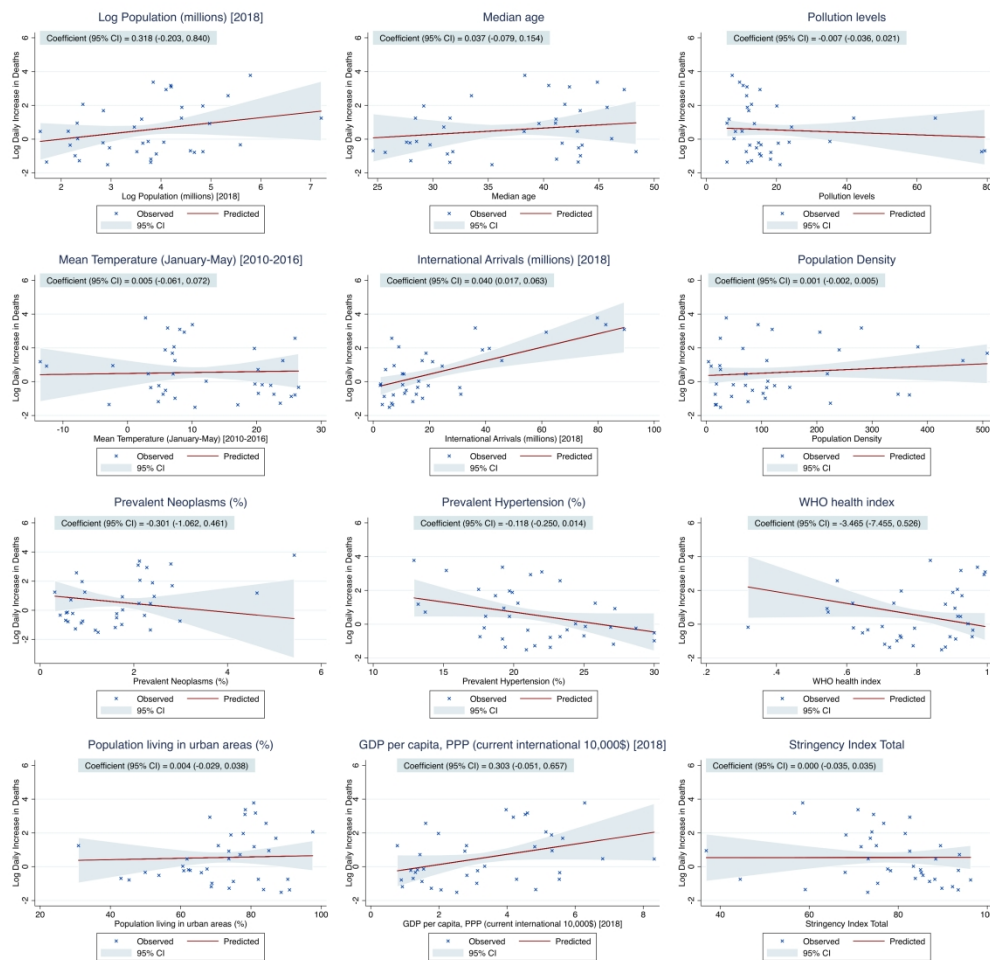


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Country Name	Country ISO3	Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]
Algeria	DZA	0.874736667
Argentina	ARG	0.254453868
Austria	AUT	0.70305109
Belgium	BEL	7.861977577
Brazil	BRA	13.08982944
Canada	CAN	3.267152071
Chile	CHL	0.220118642
Colombia	COL	0.417602718
Dominican Republic (the)	DOM	0.279192001
Ecuador	ECU	0.805740535
Egypt	EGY	0.501979768
Finland	FIN	0.258884579
France	FRA	22.12519836
Germany	DEU	6.579157352
Hungary	HUN	0.375261575
India	IND	3.476038218
Indonesia	IDN	0.716477156
Ireland	IRL	1.581101656
Italy	ITA	18.78667641
Japan	JPN	0.476880431
Mexico	MEX	7.145730972
Netherlands (the)	NLD	5.404974937
Peru	PER	2.04847312
Philippines (the)	PHL	0.457063943
Poland	POL	0.789834261
Portugal	PRT	1.029355645
Romania	ROU	0.599669456
Russian Federation (the)	RUS	2.520816803
Saudi Arabia	SAU	0.476594448
South Africa	ZAF	0.836880863
Spain	ESP	29.23356628
Sweden	SWE	2.585143805
Switzerland	CHE	1.598400593
Turkey	TUR	3.484348059
Ukraine	UKR	0.30672127
United Kingdom of Great Britain and Northern Ireland (the)	GBR	24.04783058
United States of America (the)	USA	43.73626709

<b>Log Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]</b>	<b>Population (millions) [2018]</b>	<b>Log Population (millions) [2018]</b>	<b>Median age</b>	<b>Pollution levels</b>
-0.133832395	42.228429	3.743093729	28.521	35.2
-1.368635774	44.494502	3.795365572	31.532	11.8
-0.352325708	8.847037	2.18008256	43.483	12.4
2.062038183	11.422068	2.435547352	41.928	12.9
2.571835518	209.469333	5.344577312	33.481	11.5
1.183918715	37.058856	3.612507343	41.124	6.5
-1.513588548	18.72916	2.930081606	35.339	21
-0.873224735	49.648685	3.904971838	31.307	15.2
-1.275855541	10.627165	2.363413572	28.002	12.9
-0.215993509	17.084357	2.838163137	27.93	14.9
-0.689195454	98.423595	4.589280605	24.606	79.3
-1.351372957	5.51805	1.708024502	43.128	5.9
3.096717119	66.987244	4.204502106	42.338	11.6
1.883906722	82.927922	4.417971611	45.744	11.7
-0.980131984	9.768785	2.279192209	43.336	15.6
1.24589324	1352.617328	7.209796906	28.426	65.2
-0.333408922	267.663435	5.589730263	29.744	15.6
0.458121866	4.853506	1.579701304	38.246	8.3
2.933147907	60.431283	4.10150671	47.288	15.3
-0.740489483	126.5291	4.840472221	48.358	11.4
1.966515064	126.190788	4.837794781	29.171	20.1
1.687319756	17.231017	2.846711159	43.314	12.1
0.717094719	31.989256	3.465399981	30.984	24.3
-0.782931983	106.651922	4.669570446	25.687	18.4
-0.235932156	37.978548	3.637021542	41.678	20.5
0.028933018	10.281762	2.330371618	46.158	7.9
-0.511376679	19.473936	2.969076872	43.171	14.3
0.924582958	144.47805	4.973127365	39.586	13.7
-0.741089344	33.699947	3.517496347	31.797	78.4
-0.178073555	57.779622	4.056636333	27.621	23.6
3.375317574	46.723749	3.844252586	44.858	9.5
0.94978112	10.183175	2.320736885	41.078	5.9
0.469003499	8.516543	2.14201045	43.053	10.2
1.248281002	82.319724	4.410610676	31.549	42
-1.181815863	44.622516	3.798238516	41.178	18.3
3.180044889	66.488991	4.197036266	40.467	10.5
3.778177738	327.167434	5.790472031	38.308	7.4

Mean Temperature (January-May) [2010-2016]	International Arrivals (millions) [2018]	Population Density	Diabetes prevalence (% of population ages 20 to 79) [2019]	Prevalence - Neoplasms - Sex: Both - Age-standardized (Percent) (%) [2017]
19.73687172	2.657	18.41134759	6.7	0.581716794
17.08312035	6.942	16.51475944	5.9	1.176868831
3.60226965	30.816	109.289034	6.6	2.228314728
7.198050499	9.119	382.7482166	4.6	2.129967521
25.94433403	6.621	25.43142481	10.4	0.775327051
-13.5369606	21.134	4.150449826	7.6	4.629727772
10.44359493	5.723	25.71000172	8.6	1.237788506
25.36407089	3.904	45.86109419	7.4	0.875953763
23.65955734	6.569	224.5013245	8.6	0.753248307
22.18272591	2.535	71.03825093	5.5	0.693830173
20.25822067	11.196	102.8021528	17.2	0.543731123
-2.867335558	3.224	18.23264339	5.6	2.353037036
8.096049309	89.322	119.2086157	4.8	2.091774092
5.824878693	38.881	240.3716577	10.4	2.398478606
7.352726936	17.552	106.7088258	6.9	1.7429261
24.05548096	17.423	464.1494102	10.4	0.312306273
26.49332619	15.81	150.987056	6.3	0.426835825
7.058465958	10.926	71.6765278	3.2	2.354530107
8.776521683	61.5672	205.5545931	5	2.277105536
5.503757954	31.192	346.9338179	5.6	2.985185404
19.65898323	41.313	66.32513851	13.5	0.894715491
6.944470882	18.78	508.1516311	5.4	2.818549509
20.21702194	4.419	25.75925469	6.6	0.655925982
25.9392662	7.168	367.5121072	7.1	0.593539368
4.848646641	19.622	123.5888221	6.1	1.635208395
12.17464447	16.186	111.3299159	9.8	1.761483237
5.888294697	11.72	83.58031889	6.9	1.633056952
-12.54715347	24.551	8.911010468	6.1	1.754436206
22.67894936	15.334	16.19483135	15.8	0.908721275
20.85716248	10.472	48.89059344	12.7	0.556269555
10.04498005	82.773	93.73452887	6.9	2.119853473
-2.283463001	7.44	24.61195594	4.8	2.433869445
3.199521542	10.362	219.015538	5.7	2.110949955
7.340251446	45.768	109.583913	11.1	0.95246871
4.765891075	14.104	75.49154008	6.1	1.602203378
6.205169678	36.316	280.6018435	3.9	2.791155517
2.793249846	79.74592	36.18535576	10.8	5.42440701

Median BMI	Prevalent Hypertension (%)	Smoking prevalence, 2016 total (ages 15+)	Hospital beds (per 10, 000 pop)	WHO health index
25.5	25.1	15.6	19	0.701
27.7	22.6	21.8	50	0.722
25.6	21	29.6	76	0.959
26.1	17.5	28.2	62	0.915
26.6	23.3	13.9	22	0.573
26.9	13.2	14.3	27	0.881
28	20.9	37.8	22	0.87
26.2	19.2	9	15	0.91
26.5	21.5	13.7	16	0.789
27.3	17.9	7.1	15	0.619
29.6	25	25.2	16	0.752
25.9	19.4	20.4	44	0.881
25	22	32.7	65	0.994
26.6	19.9	30.6	83	0.902
27.3	30	30.6	70	0.743
21.8	25.8	11.5	7	0.617
23.1	23.8	39.4	12	0.66
27.5	19.7	24.3	28	0.924
25.6	21.2	23.7	34	0.991
22.7	17.6	22.1	134	0.957
28	19.7	14	15	0.755
25.6	18.7	25.8	47	0.928
26.7	13.7	4.8	16	0.547
23.2	22.6	24.3	5	0.755
26.7	28.7	28	65	0.793
25.6	24.4	22.7	34	0.945
26.9	30	29.7	63	0.645
26.2	27.2	39.3	82	0.544
28.5	23.3	15.6	27	0.894
27.3	26.9	20.3	28	0.319
25.9	19.2	29.3	30	0.972
26	19.3	18.8	26	0.908
25.2	18	25.7	47	0.916
27.9	20.3	27.2	27	0.734
26.6	27.1	28.9	88	0.708
27.1	15.2	22.3	28	0.925
28.9	12.9	21.8	29	0.838

<b>Population living in urban areas (%)</b>	<b>GDP per capita, PPP (current international 10,000\$) [2018]</b>	<b>Mean Stringency Index</b>
67.5	1.548178762	77.63316345
91	2.061056855	93.48109436
65.9	5.545468929	85.19000244
97.6	5.140799834	74.07343292
84.3	1.609640096	76.73246765
80.9	4.813025597	71.65020752
88.6	2.522252778	73.15000153
75	1.501293027	87.03500366
73.8	1.774818532	89.80999756
62.7	1.173438739	93.51999664
43	1.24123094	83.8278656
83.6	4.841693603	59.09785461
78.3	4.534239574	74.44837952
74.3	5.307454012	68.25333405
68.9	3.110250275	75.38137817
30.9	0.776288177	89.49436188
49.9	1.30796193	68.05999756
61.8	8.320339468	88.42713928
68.3	4.183042633	82.60578918
90.5	4.279745852	44.48974991
77.8	1.984464567	81.5681839
87.1	5.632894114	73.73036957
76.9	1.441807067	93.75784302
45.3	0.895108565	96.26882172
60.9	3.13366035	78.28689575
60.6	3.34154379	83.40107727
53.8	2.820635705	85.55750275
73.7	2.758812544	82.5987854
82.1	5.533567959	88.22161865
62.2	1.368688236	85
78.4	3.971543906	70.95444489
85.1	5.320888436	36.85228729
73.7	6.806094105	73.24888611
70.7	2.806885941	75.08468628
68.7	0.924946213	92.20458221
81.3	4.59735735	56.70891953
80.8	6.279458565	58.52120209

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A

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<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	12-13
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-20
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Country-level Determinants of the Severity of the First Global Wave of the COVID-19 Pandemic: An Ecological Study

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# Country-level Determinants of the Severity of the First Global Wave of the COVID-19

## Pandemic: An Ecological Study

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Tables 3, Figures 3

Word count: 3929

Abstract word count: 300

## 1 ABSTRACT

2 **Objective:** We aimed to identify the country-level determinants of the severity of the  
3 first wave of the COVID-19 pandemic.

4 **Design:** An ecological study design of publicly available data was employed. Countries  
5 reporting >25 COVID-related deaths until 08/06/2020 were included. The outcome  
6 was log mean mortality rate from COVID-19, an estimate of the country-level daily  
7 increase in reported deaths during the ascending phase of the epidemic curve. Potential  
8 determinants assessed were most recently published demographic parameters  
9 (population and population density, percentage population living in urban areas,  
10 median age, average body mass index, smoking prevalence), Economic parameters  
11 (Gross Domestic Product per capita); environmental parameters: pollution levels, mean  
12 temperature (January-May)), co- morbidities (prevalence of diabetes, hypertension and  
13 cancer), health system parameters (WHO Health Index and hospital beds per 10,000  
14 population); international arrivals, the stringency index, as a measure of country-level  
15 response to COVID-19, BCG vaccination coverage, UV radiation exposure and testing  
16 capacity. Multivariable linear regression was used to analyse the data.

17 **Primary Outcome:** Country-level mean mortality rate: the mean slope of the COVID-19  
18 mortality curve during its ascending phase.

19 **Participants:** Thirty-seven countries were included: Algeria, Argentina, Austria, Belgium,  
20 Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Egypt, Finland, France,  
21 Germany, Hungary, India, Indonesia, Ireland, Italy, Japan, Mexico, the Netherlands, Peru, the  
22 Philippines, Poland, Portugal, Romania, the Russian Federation, Saudi Arabia, South Africa,  
23 Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom and the United States.

24 **Results:** Of all country-level predictors included in the multivariable model, total  
25 number of international arrivals (beta 0.033 (95% Confidence Interval 0.012,0.054))

1 and BCG vaccination coverage (-0.018 (-0.034,-0.002)), were significantly associated  
2 with the mean death rate.

3 **Conclusions:** International travel was directly associated with the mortality slope and  
4 thus potentially the spread of COVID-19. Very early restrictions on international travel  
5 should be considered to control COVID outbreak and prevent related deaths.

6

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# 1 ARTICLE SUMMARY

## 2 Strengths and limitations

- 3 • A comparable and relevant outcome variable quantifying country-level increases in  
4 the COVID-19 death rate was derived which is largely independent of different  
5 testing policies adopted by each country
- 6 • Our multivariable regression models accounted for public health and economic  
7 measures which were adopted by each country in response to the COVID-19  
8 pandemic by adjusting for the Stringency Index
- 9 • The main limitation of the study stems from the ecological study design which does  
10 not allow for conclusions to be drawn for individual COVID-19 patients
- 11 • Only countries that had reported at least 25 daily deaths over the analysed period were  
12 included, which reduced our sample and consequently the power.

## 1 INTRODUCTION

2 The atypical pneumonia caused by SARS-CoV 2 has spread rapidly. As of the 8<sup>th</sup> of  
3 June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.<sup>1</sup>  
4 The estimated overall case fatality rate is ~7%, with country-level estimates ranging between  
5 0.5-14%.<sup>2</sup> Nevertheless, there is wide variation in the reported country-specific death rates  
6 which may be attributed to variation in testing rates, underreporting or real differences in  
7 environmental, sociodemographic and health system parameters.

8 Country-level determinants of the pandemic severity are largely unknown. The only  
9 previous ecological study to date assessing country-level predictors of the severity of the  
10 COVID-19 pandemic including data on 65 countries<sup>3</sup> has found that the cumulative number  
11 of infected patients in each country was directly associated with the case fatality rate, whilst  
12 testing intensity was inversely associated with case fatality rate. This study found no  
13 association between health expenditure and case fatality rate. However, other important  
14 country-level determinants were not evaluated and thus their relationship with pandemic  
15 severity remains unknown.

16 Several risk factors for COVID-related mortality have been proposed, including older  
17 population,<sup>4</sup> higher population co-morbid burden,<sup>5</sup> smoking,<sup>6</sup> obesity,<sup>7</sup> pollution levels<sup>8</sup> and  
18 healthcare system performance.<sup>9</sup> Furthermore, countries outside China most severely hit by  
19 the pandemic were those with a high income, high GDP per capita and well-established  
20 healthcare systems, such as Italy, Spain, France, the United Kingdom and the United States.<sup>10</sup>  
21 In contrast, lower- and middle-income countries reported much lower COVID-19 incidence  
22 and mortality rates.<sup>10</sup> Whilst these differences may be attributable to case under-reporting and  
23 infrequent testing in these countries, other factors may also be involved.



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1            In this study, we aimed to assess the country-level determinants of the severity of the  
2 first wave of the COVID-19 pandemic based on currently available evidence using publicly  
3 available data and an ecological study design.

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## 1   **METHODS**

### 2   ***Patient and Public Involvement***

3           There was no patient or public involvement in designing the study given the urgent  
4 nature of the COVID-19 pandemic and the usage of publicly available data.

### 5   ***Study Design***

6           An ecological study design was used. The outcome was the steepness of the  
7 ascending curve of country specific daily reports of COVID-19 related deaths between  
8 31/12/2019-08/06/2020. The following determinants were assessed: demographic predictors  
9 (population and population density, percentage population living in urban areas, proportion of  
10 population aged 65 and over, average body mass index (BMI), smoking prevalence),  
11 economic predictors (gross Domestic Product (GDP) per capita), environmental predictors  
12 (pollution levels, mean temperature (January-May) [2010-2016] ), prevalent co-morbidities  
13 (diabetes, hypertension and cancer), health systems predictors (WHO Health Index and  
14 hospital beds per 10,000 population), international arrivals (as a proxy measure of the  
15 globalisation status of each country), the stringency index (as measure of country level  
16 response to the pandemic)<sup>11</sup>, exposure to UV radiation (as a proxy for sunlight exposure),  
17 BCG vaccination coverage and testing capacity.

### 18   ***Ethics Committee Approval***

19           Given the study design and the use of publicly available data, no ethical approval was  
20 considered necessary.

### 21   ***Selection criteria***

22           Countries reporting at least 25 daily deaths up to the 8<sup>th</sup> of June 2020 with available  
23 data for all chosen determinants were included. A total of 37 countries from 4 continents  
24 were included in the analysis: Africa (Algeria, Egypt, South Africa), America (Argentina,  
25 Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Mexico, Peru and the

1 United States of America), Asia (India, Indonesia, Japan, the Philippines, Saudi Arabia,  
2 Turkey) and Europe (Austria, Belgium, Finland, France, Germany, Hungary, Ireland, Italy,  
3 the Netherlands, Poland, Portugal, Romania, the Russian Federation, Spain, Sweden,  
4 Switzerland, Ukraine, the United Kingdom). China was not included in the analysis due to  
5 potential inaccuracies in the number of daily reported deaths which may have occurred  
6 subsequent to 1290 deaths which were retrospectively reported on the 17<sup>th</sup> of April.<sup>12</sup>

### 8 **Data Sources**

9 Country-level parameters were obtained from freely accessible data sources. The  
10 daily reported number of COVID-19 cases and deaths between 31/12/2019-08/06/2020 as  
11 well as the 2018 population data were extracted from the European Centre for Disease  
12 Control.<sup>13</sup>

13 The data regarding the median population age and population density were extracted  
14 from the United Nations World Population Prospects<sup>14</sup> and United Nations Statistics  
15 Division, respectively.<sup>15</sup> The data regarding the percentage of the population living in urban  
16 areas were extracted from the World Urbanisation Prospects, issued by the United Nations  
17 Population Division.<sup>16</sup> Temperature data were extracted from the Climate Change Knowledge  
18 Portal from the World Bank Group.<sup>17</sup> Prevalent diabetes, gross domestic product,  
19 international arrivals in 2018, and current health expenditure data were extracted from the  
20 World Development Indicators (WDI) database, provided by the World Bank Group.<sup>18</sup> Data  
21 regarding prevalent cancers, proportion of population aged 65 and over and the total number  
22 of COVID-19 tests performed were extracted from the Our World in Data and the  
23 Sustainable Development Goals (SDG) tracker,<sup>19, 20</sup> an open-access publication tracking  
24 global progress to the United Nations Sustainable Development Goals for global  
25 development, adopted in September 2015. Prevalent hypertension, body mass index (BMI),

1 cigarette smoking, ambient air pollution, ultraviolet (UV) radiation and Bacillus Calmette–  
2 Guérin (BCG) vaccination data were obtained from the Global Health Observatory (GHO)  
3 data repository of the World Health Organization.<sup>21</sup> The world health organisation health  
4 index was extracted from the WHO Global Partnership for Education (GPE) paper series  
5 published in 2000.<sup>22</sup> Country-level total hospital beds per 10,000 population data were  
6 extracted from the World Bank Dataset “World Bank Indicators of Interest to the COVID-19  
7 Outbreak”.<sup>23</sup> Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020  
8 were extracted from the Oxford COVID-19 Government Response Tacker (OxCGRT).<sup>11</sup>

### 9 ***Definition of outcome and predictors***

#### 10 *Outcome*

11 Whilst previous ecological studies of other epidemics have utilised case or death  
12 counts as outcome,<sup>24</sup> this may be prone to bias due to variations in country-level testing  
13 strategies,<sup>25</sup> variations in population movement controls and differences in secondary attack  
14 rates within community cohorts<sup>26</sup>. The mean mortality rate was thus chosen as outcome  
15 instead, since it is independent of these parameters and may thus represent a more reliable  
16 indicator of the country-level severity of the COVID-19 pandemic

17 Mean mortality rate was defined as the mean slope of the mortality curve (Figure 1),  
18 measured from the first day when more than 2 COVID-19 deaths were reported until either  
19 the mortality curve reached a peak value or the 8<sup>th</sup> of June 2020, whichever occurred first.  
20 The peak of each mortality curve was defined as the first point at which the first derivate of  
21 the COVID-19 mortality as a function of the pandemic timeline became zero. Before slope  
22 calculation, the mortality curve in each country was smoothed using a locally weighted  
23 (Lowess) regression using a bandwidth of 0.4. In order to ensure a good fit of the Lowess  
24 regression line, only countries having reported at least 25 daily deaths until the 8<sup>th</sup> of June

1  
2  
3 1 2020 were included. The mean mortality rate thus represents an estimate of the country-level  
4  
5 2 daily increase in reported deaths during the ascending phase of the epidemic curve.  
6

### 7 3 *Determinants*

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10 4 Data on population density were extracted as the country-level population per square  
11  
12 5 kilometre in 2019.<sup>27</sup> Data on ambient air pollution were extracted as the country-level mean  
13  
14 6 concentration of fine particulate matter (PM<sub>2.5</sub>) measured in 2016.<sup>28</sup> Temperature data were  
15  
16 7 extracted as the mean temperature recorded in each country between January and May using  
17  
18 8 temperature data recorded between 2010 and 2016.<sup>17</sup> Data on International Arrivals were  
19  
20 9 extracted as the total number of country-level international arrivals in 2018.<sup>29</sup>  
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24 10 Data on prevalent diabetes were extracted as the percentage of the population aged 20  
25  
26 11 to 79 years in 2019.<sup>18</sup> Data on prevalent cancers were extracted as the age-standardized  
27  
28 12 cancer prevalence among both sexes in 2017, expressed as percentages.<sup>30</sup> Data on prevalent  
29  
30 13 hypertension were extracted as the age-standardised percentage of the population over 18  
31  
32 14 years of age with systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg  
33  
34 15 in 2015.<sup>31</sup> Data on BMI were extracted as the age-standardised mean body mass index trend  
35  
36 16 estimates for both sexes amongst adults ( $\geq 18$  years) in 2016.<sup>32</sup> Data on daily cigarette  
37  
38 17 smoking were extracted as the age-standardised smoking rate across both sexes amongst  
39  
40 18 adults ( $\geq 18$  years) in 2013.<sup>33</sup> Whilst the definition of “daily cigarette smoking” varies across  
41  
42 19 surveys, it habitually refers to current smoking of cigarettes at least once a day.<sup>33</sup>  
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47 20 Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in  
48  
49 21 current international dollars in 2018.<sup>34</sup> The percentage of population living in urban areas was  
50  
51 22 defined as the percentage of de facto population living in areas classified as urban according  
52  
53 23 to the criteria used by each area or country.<sup>16</sup> The World Health Organisation (WHO) health  
54  
55 24 index is a composite index that aims to evaluate a given countries healthcare system  
56  
57 25 performance relative to the maximum it could achieve given its level of resources and non-  
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1 healthcare system determinants. It was calculated in the year 2000. The index uses five  
2 weighted parameters: overall or average disability-adjusted life expectancy (25%),  
3 distribution or equality of disability-adjusted life expectancy (25%), overall or average  
4 healthcare system responsiveness (including speed of provision and quality of amenities;  
5 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare  
6 expenditure (25%). Data on hospital beds per 10,000 population were defined by the World  
7 Bank as including 'inpatient beds available in public, private, general, and specialized  
8 hospitals and rehabilitation centres'. The published data for countries included was from  
9 2000 to 2017. In most cases beds for both acute and chronic care are included.<sup>23</sup> The  
10 Stringency Index is an overall indicator of public health measures adopted by each country in  
11 response to the COVID-19 pandemic and includes containment and closure indicators (school  
12 closures, workplace closures, cancelling public events, restrictions on gatherings, public  
13 transport closures, stay-at-home requirements, restrictions on internal movements,  
14 international travel controls), economic response indicators (income support, debt/contract  
15 relief, fiscal measures, international support) as well as health systems indicators (public  
16 information campaigns, testing policy, contact tracing, emergency investment in healthcare,  
17 investment in vaccines).<sup>11</sup> The mean daily Stringency Index was calculated for each country  
18 between 31/12/2019 and until either the mortality curve reached a peak value or the 8<sup>th</sup> of  
19 June 2020, whichever occurred first.

20 Country-level exposure to UV radiation was quantified as the population-weighted  
21 average daily ambient ultraviolet radiation level measured in J/m<sup>2</sup> for the years 1997-2003.<sup>35</sup>  
22 BCG vaccination coverage was quantified as the average percentage of 1 year-old children  
23 having received the BCG vaccine between 1980 and 2019 in each country. Testing capacity  
24 was quantified as the total number of COVID-19 tests per 1000 population performed until  
25 the 8<sup>th</sup> of June 2020.

## 1 **Statistical analysis**

2 All analyses were performed in Stata 15.1SE, Stata Statistical Software. A 5%  
3 threshold of statistical significance was utilised for all analyses ( $P < 0.05$ ). Linear regressions  
4 were performed to assess the univariable relationship between each country-level predictor  
5 and the calculated mean mortality rate for each country. The following predictors were  
6 included in the univariable analyses: the natural logarithm of the population in 2018 (10  
7 million increase), percentage of population aged 65 and over, pollution levels, mean  
8 temperature (January-May), international arrivals, population density, prevalent diabetes,  
9 prevalent neoplasms, median BMI, prevalent hypertension, smoking prevalence, hospital  
10 beds (per 10,000 population), WHO health index, percentage population living in urban  
11 areas, GDP per capita (PPP), UV radiation exposure, mean BCG coverage and the stringency  
12 index. Predictors reaching a  $P$ -value  $< 0.3$  at univariable level were then included in a  
13 multivariable logistic regression model with the natural logarithm of the mean mortality rate  
14 as outcome: the logarithm of the total population in 2018, percentage of population aged 65  
15 and over, pollution, mean temperature (January-May), international arrivals, population  
16 density, prevalent neoplasms, prevalent hypertension, the WHO health index, population  
17 living in urban areas, GDP per capita, UV radiation exposure, mean BCG coverage and the  
18 stringency index.

19 Given that testing capacity data for 8 (Algeria, Brazil, Egypt, France, Germany, the  
20 Netherlands, Spain and Sweden) of the 37 included countries were not available, a secondary  
21 analysis also including testing capacity as a predictor was performed considering only the  
22 remaining 29 countries. Linear regressions were performed to assess the univariable  
23 relationship between each country-level predictor and the calculated mean mortality rate for  
24 each country. Predictors reaching a  $P$ -value  $< 0.3$  at univariable level were then included in a  
25 multivariable logistic regression model with the natural logarithm of the mean mortality rate

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2  
3 1 as outcome: the logarithm of the total population in 2018, percentage of population aged 65  
4  
5 2 and over, international arrivals, population density, prevalent neoplasms, prevalent  
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7 3 hypertension, GDP per capita, UV radiation exposure, mean BCG coverage, the stringency  
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9 4 index and testing capacity.  
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## 1 RESULTS

2 Table 1 and Supplementary File 1 detail the analysed data for the 37 included  
3 countries, including the calculated mean mortality rates. The mean mortality rates ranged  
4 between 0.22 (Chile) and 43.74 (the United States) new daily deaths. Only five included  
5 countries had a high mean mortality rate (>10): the United States (43.74), Spain (29.23), the  
6 United Kingdom (24.05), France (22.13), Italy (18.79) and Brazil (13.09).

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**Table 1.** Observed mean mortality rate and number of international arrivals in 2018 (millions) for each country included in the analyses. Countries were categorised in 3 groups: high mean mortality rate group (>20 additional daily deaths), medium mean mortality rate group (2-20 additional daily deaths) and low mean mortality rate group (<2 additional daily deaths).

Country Name	Mean Mortality Rate (daily increase in deaths) [up to 01/05/20]	International Arrivals (millions) [2018]
<b>High Mean Mortality Rate</b>		
United States of America	43.74	79.75
Spain	29.23	82.77
United Kingdom	24.05	36.32
France	22.13	89.32
Italy	18.79	61.57
Brazil	13.09	6.62
<b>Medium Mean Mortality Rate</b>		
Belgium	7.86	9.12
Mexico	7.15	41.31
Germany	6.58	38.88
Netherlands	5.40	18.78
Turkey	3.48	45.77
India	3.48	17.42
Canada	3.27	21.13
Sweden	2.59	7.44
Russian Federation	2.52	24.55
Peru	2.05	4.42
<b>Low Mean Mortality Rate</b>		
Switzerland	1.60	10.36
Ireland	1.58	10.93
Portugal	1.03	16.19
Algeria	0.88	2.66
South Africa	0.84	10.47
Ecuador	0.81	2.54
Poland	0.79	19.62
Indonesia	0.72	15.81
Austria	0.70	30.82
Romania	0.60	11.72
Egypt	0.50	11.20
Japan	0.48	31.19
Saudi Arabia	0.48	15.33
Philippines	0.46	7.17
Colombia	0.42	3.90

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Hungary	0.38	17.55
Ukraine	0.31	14.10
Dominican Republic	0.28	6.57
Finland	0.26	3.22
Argentina	0.25	6.94
Chile	0.22	5.72

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4 1 Table 2 details the results of the linear regression analyses. The following country-  
5  
6 2 level predictors showed a statistically significant relationship with log mean mortality rate at  
7  
8 3 univariable level: natural logarithm of population, international arrivals, prevalent neoplasms,  
9  
10 4 prevalent hypertension, GDP per capita and BCG vaccination coverage. Upon multivariable  
11  
12 5 adjustment, International arrivals in 2018, as a marker of global connection, was the main  
13  
14 6 statistically significant predictor of log mean mortality rate (0.040 (0.017, 0.063) for 1  
15  
16 7 million increase in international arrivals,  $P=0.002$ ) along with mean BCG vaccination  
17  
18 8 coverage (-0.018 (-0.034, -0.002) for 1% increase in BCG vaccination coverage,  $P=0.031$ ) .  
19  
20 9 Figures 2 and 3 detail the relationship between the country-level log mean mortality rate  
21  
22 10 (predicted and observed) and each country-level predictor included in the multivariable  
23  
24 11 regression model.  
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**Table 2.** Results of the linear regression assessing the country-level predictors of the daily increase in deaths. The predictors achieving a 30% statistical significance level at univariable levels ( $P < 0.3$ ) were included in the multivariable model.

Predictor	Univariable		Multivariable	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Natural logarithm of population (10 million increase) [2018]	<b>0.432 (0.050, 0.814)</b>	<b>0.033</b>	0.393 (-0.087, 0.873)	0.103
% population aged 65 and older	0.065 (-0.010, 0.139)	0.097	-0.020 (-0.143, 0.103)	0.741
Pollution levels	-0.017 (-0.044, 0.011)	0.247	-0.005 (-0.031, 0.020)	0.659
Mean Temperature (January-May) [2010-2016]	-0.031 (-0.078, 0.017)	0.218	0.052 (-0.025, 0.128)	0.175
International Arrivals (1 million increase) [2018]	<b>0.049 (0.033, 0.064)</b>	<b>&lt;0.001</b>	<b>0.033 (0.012, 0.054)</b>	<b>0.003</b>
Population Density	-0.002 (-0.006, 0.002)	0.268	-0.001 (-0.004, 0.002)	0.560
Diabetes prevalence (% of population ages 20 to 79) [2019]	-0.0031 (-0.189, 0.126)	0.700	-	-
Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017]	<b>0.614 (0.209, 1.019)</b>	<b>0.005</b>	-0.404 (-1.079, 0.271)	0.227
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	<b>-0.150 (-0.254, -0.045)</b>	<b>0.008</b>	-0.107 (-0.249, 0.035)	0.132
Smoking prevalence, 2016 total (ages 15+)	0.002 (-0.058, 0.062)	0.952	-	-
Hospital beds (per 10, 000 population)	-0.004 (-0.022, 0.014)	0.632	-	-
WHO health index, [2000]	2.259 (-0.920, 5.439)	0.173	-2.616 (-6.157, 0.925)	0.140
Population living in urban areas (%)	0.023 (-0.011, 0.580)	0.193	0.010 (-0.019, 0.039)	0.468
GDP per capita, PPP (\$1000 increase), [2018]	<b>0.280 (0.037, 0.524)</b>	<b>0.030</b>	0.154 (-0.174, 0.482)	0.340
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	-0.000 (-0.001, 0.000)	0.133	-0.001 (-0.001, 0.000)	0.109
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	<b>-0.027 (-0.037, -0.016)</b>	<b>&lt;0.001</b>	<b>-0.018 (-0.034, -0.002)</b>	<b>0.031</b>
Mean Daily Stringency Index	-0.036 (-0.072, 0.001)	0.057	0.004 (-0.028, 0.037)	0.790

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3  $R^2$  for multivariable linear regression = 0.8031  
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5 BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-  
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3 1 Table 3 details the results of the secondary linear regression analyses, including only  
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5 2 countries having reported COVID-19 testing data up to the 8<sup>th</sup> of June 2020. The following  
6  
7 3 country-level predictors showed a statistically significant relationship with log mean mortality  
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9 4 rate at univariable level: natural logarithm of population, international arrivals, prevalent  
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11 5 neoplasms, prevalent hypertension, BCG vaccination coverage and total COVID-19 tests per  
12  
13 6 1000 population performed until the 8<sup>th</sup> of June 2020. Upon multivariable adjustment, the  
14  
15 7 statistically significant predictors of log mean mortality rate were: international arrivals in 2018  
16  
17 8 (0.036 (0.008, 0.063) for 1 million increase in international arrivals,  $P = 0.013$ ), prevalent  
18  
19 9 hypertension (-0.129 (-0.246,-0.012) for 1% increase in country-level hypertension prevalence,  
20  
21 10  $P = 0.032$ ) and testing capacity (0.018 (0.001, 0.034) for 1 per 1000 population increase in the  
22  
23 11 number of total COVID-19 tests performed until the 8<sup>th</sup> of June 2020,  $P = 0.039$ ).  
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**Table 3.** Results of the secondary linear regression assessing the country-level predictors of the daily increase in deaths, including only countries reporting total COVID-19 tests performed up to the 8<sup>th</sup> of June 2020. The predictors achieving a 30% statistical significance level at univariable levels ( $P < 0.3$ ) were included in the multivariable model.

Predictor	Univariable		Multivariable	
	Coefficient (95% CI)	<i>P</i> value	Coefficient (95% CI)	<i>P</i> value
Natural logarithm of population (10 million increase) [2018]	<b>0.419 (0.038, 0.800)</b>	<b>0.040</b>	0.385 (-0.044, 0.813)	0.075
% population aged 65 and older	0.035 (-0.047, 0.118)	0.407	-	-
Pollution levels	-0.003 (-0.037, 0.030)	0.848	-	-
Mean Temperature (January-May) [2010-2016]	-0.032 (-0.081, 0.017)	0.207	0.026 (-0.052, 0.104)	0.484
International Arrivals (1 million increase) [2018]	<b>0.059 (0.039, 0.079)</b>	<b>&lt;0.001</b>	<b>0.036 (0.008, 0.063)</b>	<b>0.013</b>
Population Density	0.002 (-0.002, 0.007)	0.270	0.000 (-0.004, 0.003)	0.822
Diabetes prevalence (% of population ages 20 to 79) [2019]	0.012 (-0.173, 0.196)	0.903	-	-
Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017]	<b>0.582 (0.177, 0.987)</b>	<b>0.009</b>	-0.391 (-1.014, 0.233)	0.203
Median BMI	0.107 (-0.205, 0.419)	0.507	-	-
Prevalent Hypertension (%), [2015]	<b>-0.140 (-0.240, -0.039)</b>	<b>0.011</b>	<b>-0.129 (-0.246, -0.012)</b>	<b>0.032</b>
Smoking prevalence, 2016 total (ages 15+)	-0.016 (-0.077, 0.045)	0.610	-	-
Hospital beds (per 10, 000 population)	-0.009 (-0.027, 0.009)	0.323	-	-
WHO health index, [2000]	1.247 (-2.180, 4.675)	0.482	-	-
Population living in urban areas (%)	0.007 (-0.030, 0.044)	0.710	-	-
GDP per capita, PPP (\$1000 increase), [2018]	0.242 (-0.016, 0.499)	0.077	-0.045 (-0.325, 0.235)	0.739
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	-0.000 (-0.001, 0.000)	0.283	0.000 (-0.001, 0.000)	0.310
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	<b>-0.028 (-0.039, -0.017)</b>	<b>&lt;0.001</b>	-0.011 (-0.029, 0.007)	0.221
Mean Daily Stringency Index	-0.033 (-0.074, 0.008)	0.128	0.013 (-0.021, 0.048)	0.425
Total COVID-19 tests per 1000 population	<b>0.024 (0.008, 0.039)</b>	<b>0.007</b>	<b>0.018 (0.001, 0.034)</b>	<b>0.039</b>



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3 (up to the 8<sup>th</sup> of June 2020)  
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7  $R^2$  for multivariable linear regression = 0.8373

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9 BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-  
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## 1 DISCUSSION

### 2 Principal findings

3 In this ecological study including data from 37 countries which were most severely  
4 affected by COVID-19 in the first wave of current Global pandemic, we assessed 19 country-  
5 level socioeconomic, environmental, health and healthcare system, and globalisation  
6 parameters as potential predictors of variation in death rates from COVID 19 infection. In the  
7 multivariable linear regression model, the main predictor that reached statistical significance  
8 was international arrivals, a proxy of global connection: increases in international arrivals  
9 were associated with higher mean mortality rate. Furthermore, country-level BCG  
10 vaccination coverage was associated with decreases in the COVID-19 mean mortality rate  
11 during the first wave of the pandemic. Finally, in our secondary analyses including only  
12 country with available testing capacity data, the total number of COVID-19 tests performed  
13 per 1000 population until the 8<sup>th</sup> of June 2020 was associated with increases in the COVID-  
14 19 mean mortality rate.

### 16 Comparison with previous literature

17 A previous ecological study analysed the country-level predictors of the COVID-19  
18 case fatality rate including 65 countries.<sup>3</sup> This study found that upon adjustment for epidemic  
19 age, health expenditure and world region, the case fatality rate was significantly associated  
20 with increasing cumulative number of COVID-19 cases and decreasing testing intensity.<sup>3</sup>  
21 Nevertheless, no other country-level predictors were included in this study.

22 Further comparisons can be made with data from previous pandemics. A negative  
23 association has been reported between health expenditure and death rates from the 2009  
24 influenza pandemic in 30 European countries.<sup>24</sup> Associations have also been reported  
25 between airline travel and spread of the H1N1 influenza virus infection.<sup>36</sup>

1 Comorbidities may account for mortality rate differences between countries. A study  
2 among laboratory-confirmed cases of COVID-19 in China showed that patients with any  
3 comorbidity, including diabetes, malignancy and hypertension, had poorer clinical outcomes  
4 than those without.<sup>5</sup> We thus accounted for country-level data on a selection of key  
5 comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI  
6  $\geq 40$  kg/m<sup>2</sup> has been identified as an independent risk factor for severe COVID-19 illness.<sup>7</sup>  
7 Finally, a recent systematic review on 5 studies from China showed that smoking is likely  
8 associated with negative outcomes and progression of COVID-19.<sup>6</sup>

### 10 **Interpretation of findings.**

11 In our multivariate model, the main significant determinant of mortality was  
12 international arrivals. Travel restrictions and their effectiveness in containing respiratory  
13 virus pandemics remains a contentious subject. In 2007 the WHO published a protocol on  
14 ‘rapid operations to contain the initial emergence of pandemic influenza’, which included  
15 recommendations on travel restrictions.<sup>37</sup> However, subsequent guidance advises such  
16 restrictions are not recommended once a virus has spread significantly.<sup>38</sup> A recent systematic  
17 review of 23 studies that demonstrated limited impact of travel restrictions in the containment  
18 of influenza: internal travel restrictions delayed pandemic peak by approximately 1.5 weeks,  
19 while 90% air travel restriction delayed the spread of pandemics by approximately 3–4 weeks  
20 but only reduced attack rates by less than 0.02%.<sup>39</sup> However, another systematic review of  
21 combination strategies for pandemic influenza response showed that combination strategies  
22 including travel restrictions increased the effectiveness of individual policies.<sup>40</sup>

23 The WHO recommendations for pandemic preparedness and resilience suggest that  
24 points of entry into the country should be monitored by focussing on surveillance and risk  
25 communication to travellers but falls short of closing down international travel.<sup>41</sup>

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3 1 Interestingly, during the COVID-19 pandemic, some countries such as Thailand have adopted  
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5 2 aggressive international travel screening and isolation policies, which may have led to lower  
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7 3 infection rates.<sup>42</sup> Our study suggests that travel restrictions have the potential to influence the  
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9 4 impact of the COVID-19 pandemic and should be considered as part of a structured and  
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11 5 rapidly instigated pandemic preparedness plan. Furthermore, the mean stringency index,  
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13 6 which also accounts for international travel restrictions amongst other measures, was not  
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15 7 associated with the mean mortality rate in the multivariable model. This suggest that  
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17 8 international travel restrictions and other containment measures may have been imposed too  
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19 9 late to influence the steepness of the mortality curve and that the level of global connectivity  
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21 10 of each country may influence the course of the epidemic mortality curve before the number  
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23 11 of COVID-19 related cases and deaths reaches worrying levels.

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28 12 Our multivariable model also suggests an inverse relationship between BCG  
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30 13 vaccination coverage the mean mortality rate, in which increasing BCG vaccination coverage  
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32 14 was associated with decreased mean mortality rate. The relationship between BCG  
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34 15 vaccination and the evolution of the COVID-19 transmission and disease severity remains  
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36 16 controversial.<sup>43, 44</sup> While the BCG vaccine has been postulated to exhibit non-specific  
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38 17 immunomodulatory properties, which may reduce SARS-CoV-2 viraemia after exposure,<sup>43</sup>  
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40 18 current epidemiological evidence is derived from ecological studies<sup>45</sup> and needs to be  
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42 19 interpreted in the light of the inherent limitations of this study design. Further ongoing studies  
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44 20 (NCT04327206<sup>46</sup>, NCT04328441<sup>47</sup>) may provide more robust evidence regarding the  
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46 21 association between BCG vaccination and COVID-19.

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51 22 Our analyses also revealed a few surprising findings: the intensity of COVID-19  
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53 23 testing was apparently associated with mean mortality rate increases while the country-level  
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55 24 prevalence of hypertension was apparently associated with mean mortality rate decreases.  
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57 25 These findings appear to be contradictory to previous evidence suggesting that testing  
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1 intensity may be associated with decreased COVID-19 mortality,<sup>48</sup> while hypertension was  
2 clearly associated with increased mortality.<sup>49</sup> These surprising findings need to be interpreted  
3 in the light of our ecological study design in which residual confounders may influence these  
4 associations.

## 6 **Strengths and Limitations.**

7 The main strength of this study lies in its use of comparable and relevant outcome data  
8 derived from contemporary death reporting from countries affected by COVID-19. As testing  
9 rates for the virus vary across countries, the incidence or prevalence of the disease cannot be  
10 compared between countries. While death from the disease is a hard outcome, the  
11 denominator information to calculate death rates make between-country comparisons  
12 difficult. In addition, the deaths in the community, particularly in the elderly living in care  
13 homes, often go untested and thus firm diagnosis remains impossible. Therefore, in this  
14 study we have adopted an outcome that is comparable in terms of the increase in the rate of  
15 death, rather than death rates *per se*. Therefore, this may better represent the spread and  
16 seriousness of pandemic in individual countries when comparing countries at different stages  
17 of the pandemic. The country-level parameters assessed as potential predictors have all been  
18 implicated at some point to be associated with severity and consequently mortality. We  
19 however found that the main predictor of the total number of international arrivals in the  
20 country (2018 figures), signifying transmission of the infection through travel. Although the  
21 data was from 2018, there is no reason to believe that international travel figures between  
22 countries would be different in early 2020. Furthermore, our multivariable model also  
23 accounts for country-level international travel restrictions adopted in response to the spread  
24 of COVID-19.

1           The main limitation of the study stems from the ecological study design. Despite the  
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1           The main limitation of the study stems from the ecological study design. Despite the  
2 fact that we did not find any association between comorbidities such as diabetes and cancer  
3 and the mean death rates at country level, it is possible for an individual with any or all of  
4 these comorbid conditions to be more susceptible to the infection and consequently at  
5 increased risk of dying. Only including countries that had reported at least 25 deaths reduced  
6 our sample and consequently the power. Furthermore, the reasonably large number of  
7 country level predictors relative to the number of countries means that we cannot rule out the  
8 potential for overfitting in the multivariable model. This may lead to spurious associations  
9 between predictors and the outcome. Other explanatory variables associated with COVID-19  
10 related mortality may have been missed and some of the covariate data used in our model  
11 predate the COVID outbreak and may not be relevant at this time point. Furthermore, as new  
12 countries are affected by the epidemic, the virulence of the virus and resistance of the human  
13 body may have changed over time which was not accounted for in our model. It is also  
14 possible that the quality of data, especially underreporting of deaths related to between-  
15 country differences in defining COVID-19 deaths, may have been associated with some of  
16 the predictors in our model as well as our chosen outcome and thus biased our results.  
17 Furthermore, the delay between COVID-19 symptom onset and hospitalisation may be an  
18 important factor in the overall clinical prognosis of patients with severe COVID-19 disease.  
19 Nevertheless, given that our analyses rely on country-level determinants and in the absence  
20 of individual patient data, it is impossible to ascertain the country-level trends of delay to  
21 hospital admission. Notwithstanding, some other country-level parameters pertaining to the  
22 accessibility of healthcare included in our analyses such as the number of hospital beds per  
23 10,000 population, proportion of population living in urban areas as well as the WHO health  
24 index may account for such differences.

## 1 CONCLUSION

2 Out of all the country-level parameters assessed, international travel was the main  
3 predictor of the severity of the first global wave of the COVID-19 pandemic. Given that  
4 many of world middle and lower-income countries are showing signs of continued rise in  
5 infection rates, international travel restrictions applied very early in the pandemic course  
6 should be considered to avoid rapidly increasing infection and death rates globally. The  
7 associations between other predictors, such as BCG vaccination coverage, prevalent  
8 hypertension and COVID-19 testing capacity, and the outcome were weaker and need to be  
9 interpreted in the light of our ecological study design. Further studies are required to  
10 determine the relationship between previous BCG vaccination and COVID-19 disease  
11 progression.

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3 **1 CONTRIBUTORSHIP**  
4

5 2 PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP and KDE collected data and  
6  
7 performed literature search. TAP, PKM, DJM and SB developed analysis plan. TAP analysed  
8 3  
9 the data under supervision of DJM. TAP and SB drafted the paper. All authors contributed to  
10 4  
11 the interpretation of results and in making an important intellectual contribution to the  
12 5  
13 manuscript. All authors read and approved the final manuscript.  
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19 **8 ACKNOWLEDGEMENTS**  
20

21 9 We would like to thank Dr Kathryn Martin who provided valuable advice in study design.  
22  
23

24 **10 CONFLICTS OF INTEREST**  
25

26 11 None.  
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28 **12 FUNDING**  
29

30 13 None.  
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33 **14 DATA SHARING STATEMENT**  
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35 15 All data relevant to the study have been submitted to the journal as supplementary materials.  
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## FIGURE LEGENDS

**Figure 1.** Graphical representation of the smoothed\* number of daily deaths of each country (before reaching mortality peak, if applicable) as a function of the number of days passed since the first day when an excess of 3 deaths were reported. Countries with higher mortality rates are depicted in blue, while those with lower mortality rates are depicted in red.

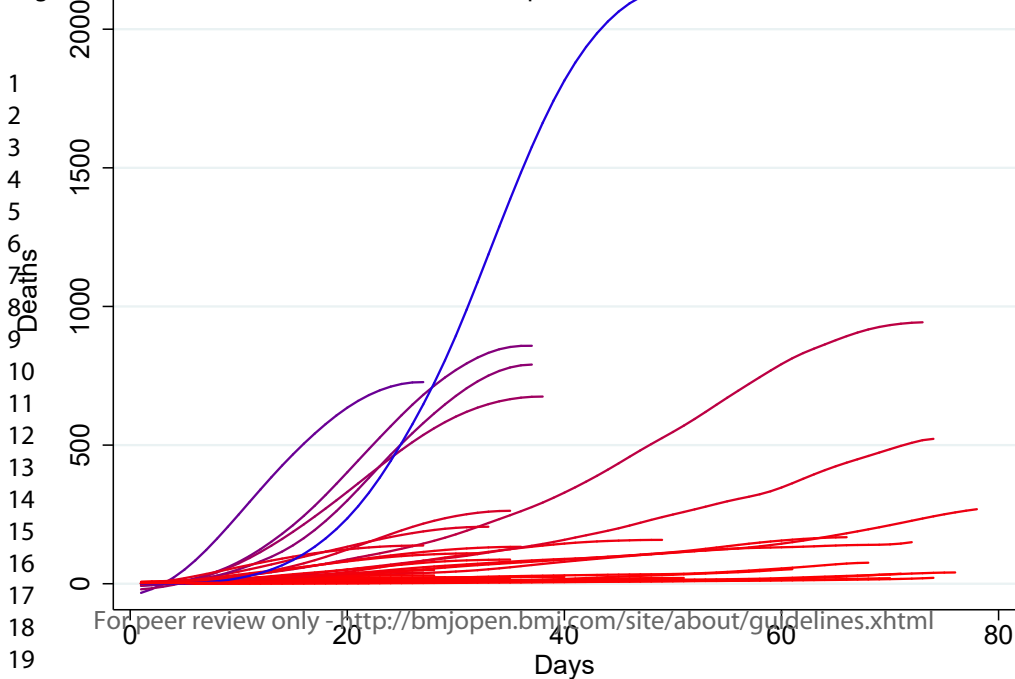
\*smoothed using a local regression (lowess) function with a bandwidth of 0.4

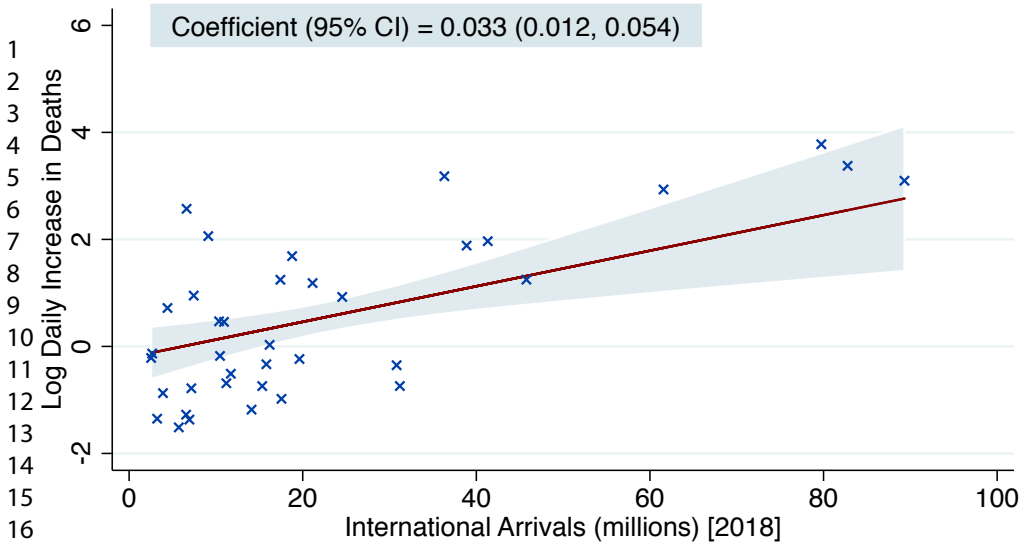
**Figure 2.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions). The solid red line represents the point estimate of the predicted log daily increase in deaths, while the blue-grey area represents the corresponding 95% confidence interval. The crosses represent the observed values of the log daily increase in deaths.

**Figure 3.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of each country-level predictor included in the multivariable model. The solid red lines represent the point estimates of the predicted log daily increase in deaths, while the blue-grey areas represent the corresponding 95% confidence intervals. The crosses represent the observed values of the log daily increase in deaths.



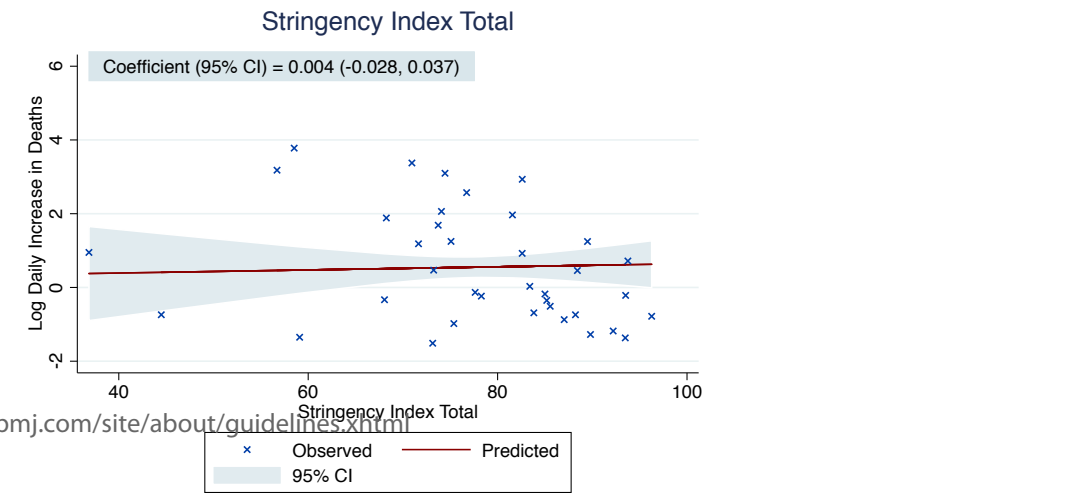
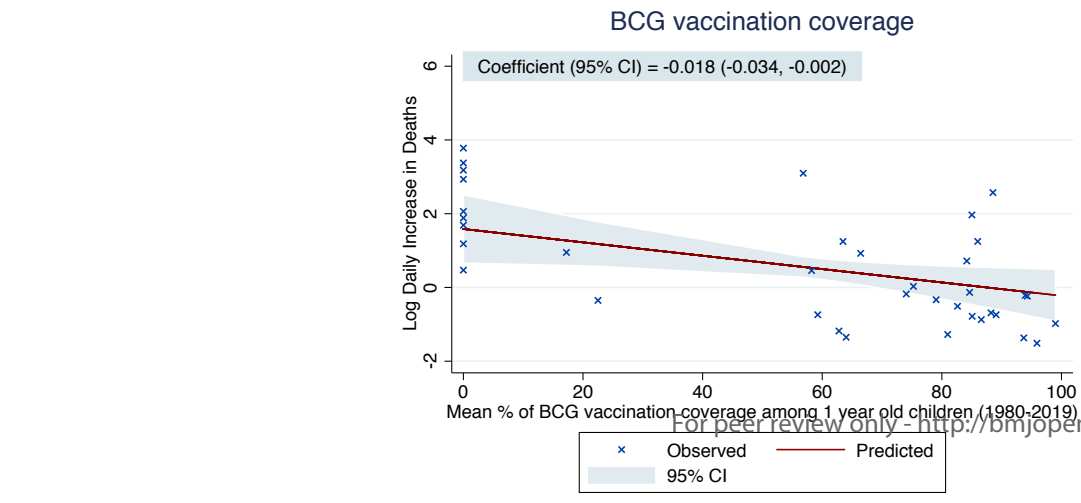
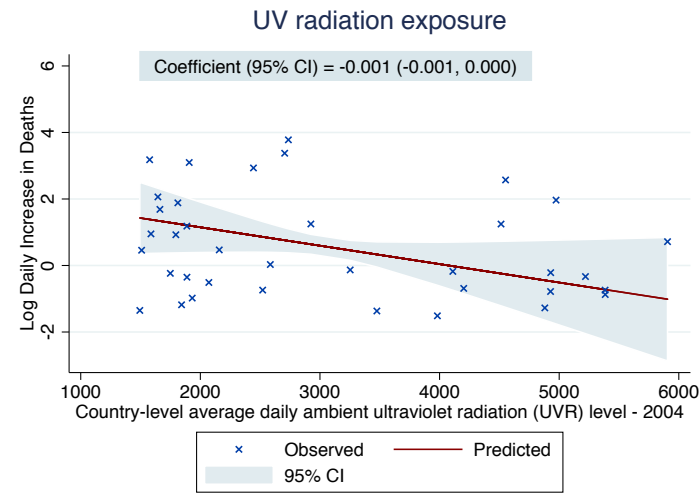
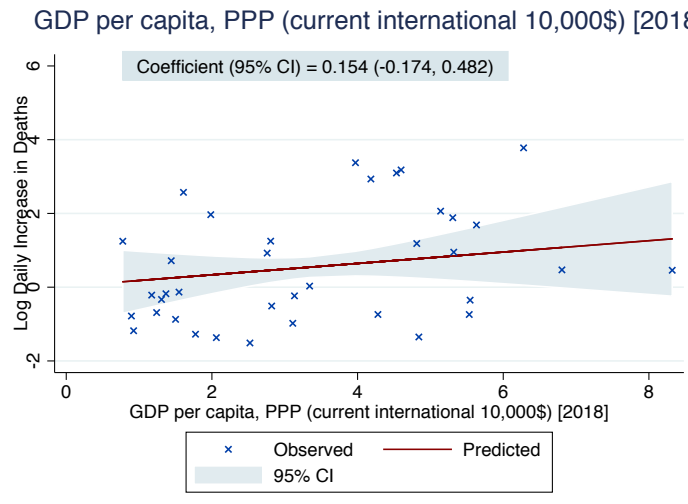
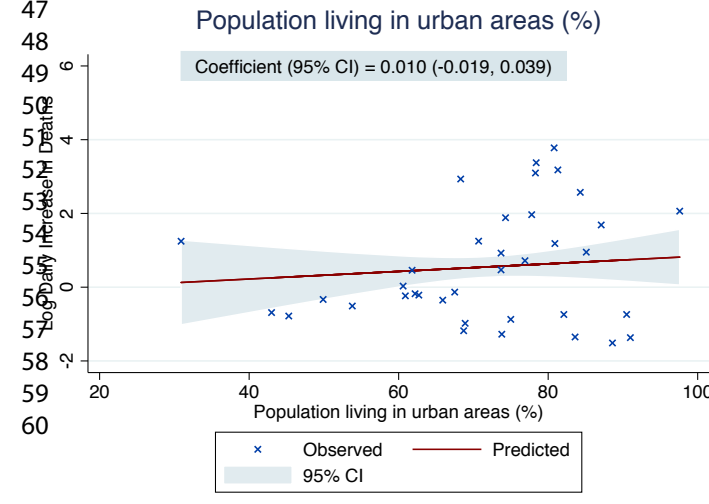
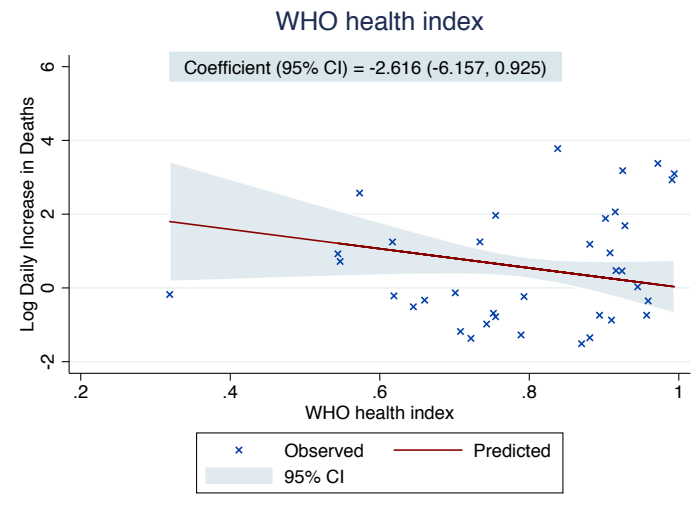
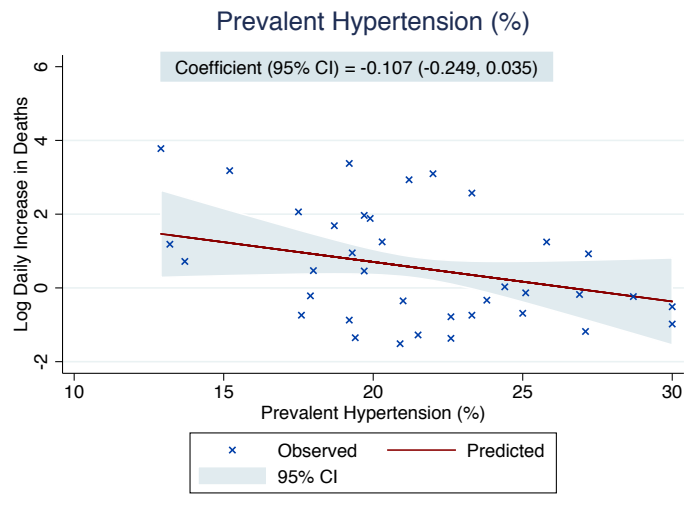
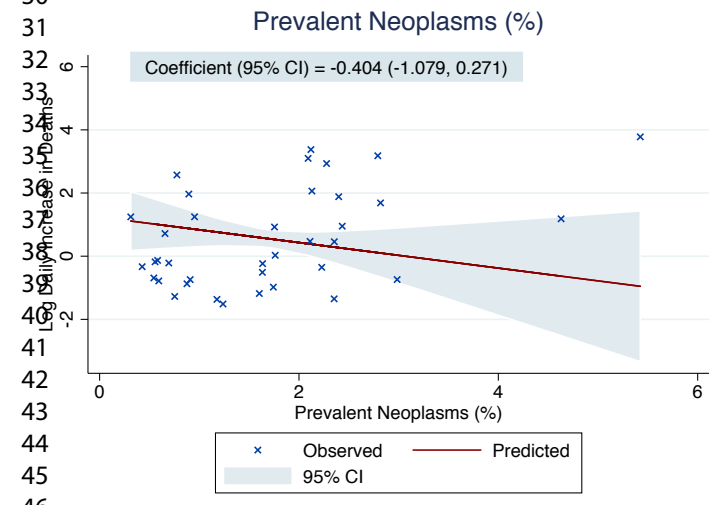
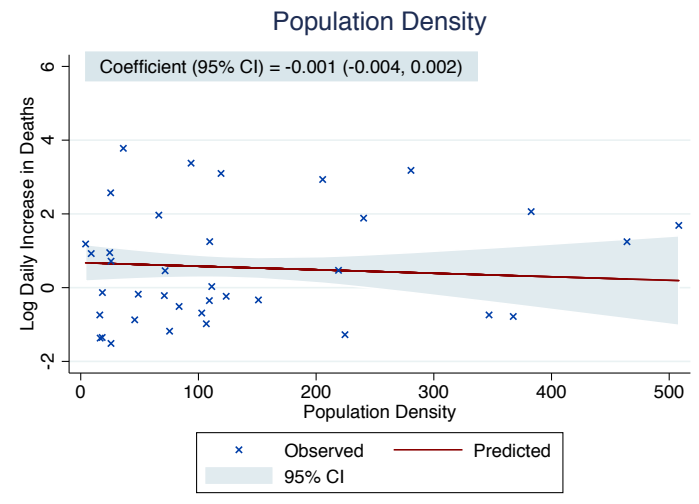
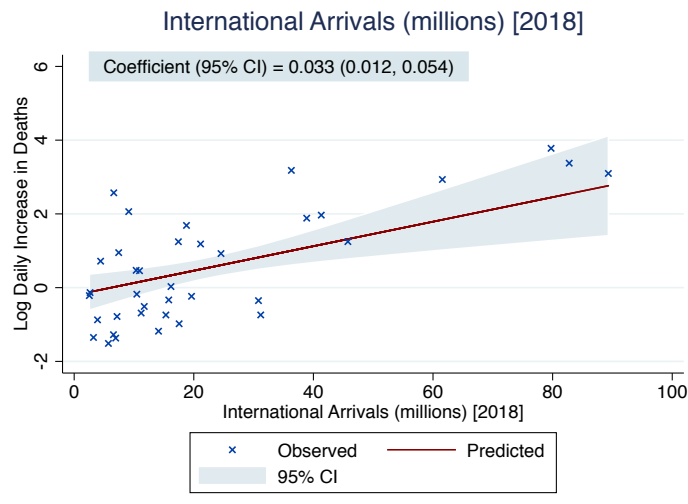
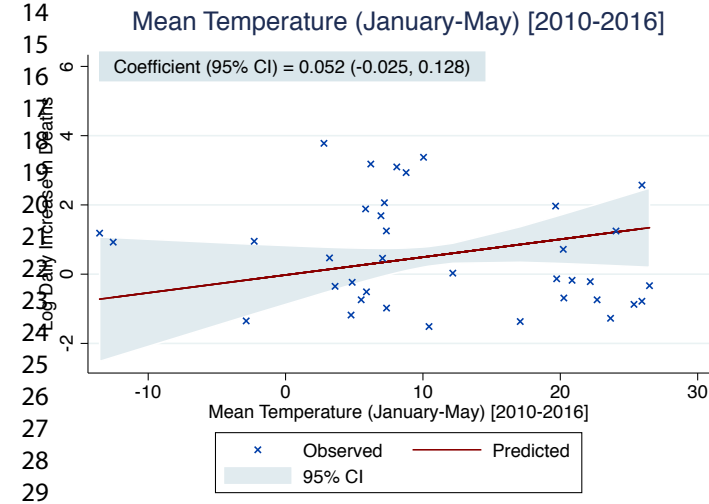
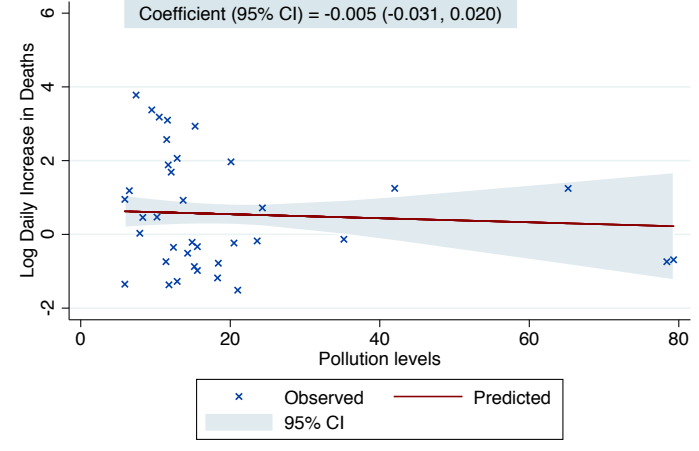
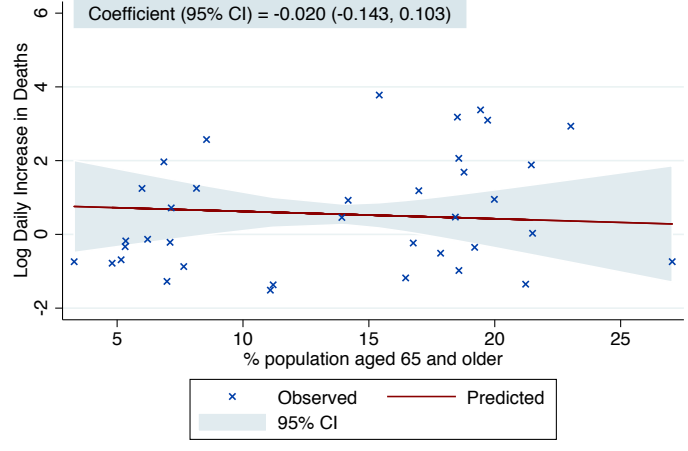
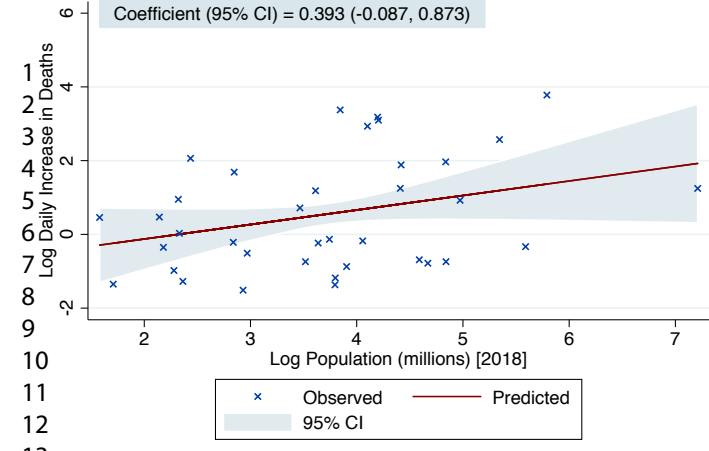
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x Observed     — Predicted  
95% CI



Country Name	Country ISO3	Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	Log Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	Population (millions) [2018]
Argentina	ARG	0.254453868	-1.368635774	44.494502
Austria	AUT	0.70305109	-0.352325708	8.847037
Belgium	BEL	7.861977577	2.062038183	11.422068
Brazil	BRA	13.08982944	2.571835518	209.469333
Canada	CAN	3.267152071	1.183918715	37.058856
Switzerland	CHE	1.598400593	0.469003499	8.516543
Chile	CHL	0.220118642	-1.513588548	18.72916
Colombia	COL	0.417602718	-0.873224735	49.648685
Germany	DEU	6.579157352	1.883906722	82.927922
Dominican Republic	DOM	0.279192001	-1.275855541	10.627165
Algeria	DZA	0.874736667	-0.133832395	42.228429
Ecuador	ECU	0.805740535	-0.215993509	17.084357
Egypt	EGY	0.501979768	-0.689195454	98.423595
Spain	ESP	29.23356628	3.375317574	46.723749
Finland	FIN	0.258884579	-1.351372957	5.51805
France	FRA	22.12519836	3.096717119	66.987244
United Kingdom of	GBR	24.04783058	3.180044889	66.488991
Hungary	HUN	0.375261575	-0.980131984	9.768785
Indonesia	IDN	0.716477156	-0.333408922	267.663435
India	IND	3.476038218	1.24589324	1352.617328
Ireland	IRL	1.581101656	0.458121866	4.853506
Italy	ITA	18.78667641	2.933147907	60.431283
Japan	JPN	0.476880431	-0.740489483	126.5291
Mexico	MEX	7.145730972	1.966515064	126.190788
Netherlands (the)	NLD	5.404974937	1.687319756	17.231017
Peru	PER	2.04847312	0.717094719	31.989256
Philippines (the)	PHL	0.457063943	-0.782931983	106.651922
Poland	POL	0.789834261	-0.235932156	37.978548
Portugal	PRT	1.029355645	0.028933018	10.281762
Romania	ROU	0.599669456	-0.511376679	19.473936
Russian Federation	RUS	2.520816803	0.924582958	144.47805
Saudi Arabia	SAU	0.476594448	-0.741089344	33.699947
Sweden	SWE	2.585143805	0.94978112	10.183175
Turkey	TUR	3.484348059	1.248281002	82.319724
Ukraine	UKR	0.30672127	-1.181815863	44.622516
United States of An	USA	43.73626709	3.778177738	327.167434
South Africa	ZAF	0.836880863	-0.178073555	57.779622

Log Population (millions) [2018]	Median age	% population aged 65 and older	Pollution levels
3.795365572	31.532	11.198	11.8
2.18008256	43.483	19.202	12.4
2.435547352	41.928	18.571	12.9
5.344577312	33.481	8.552	11.5
3.612507343	41.124	16.984	6.5
2.14201045	43.053	18.436	10.2
2.930081606	35.339	11.087	21
3.904971838	31.307	7.646	15.2
4.417971611	45.744	21.453	11.7
2.363413572	28.002	6.981	12.9
3.743093729	28.521	6.211	35.2
2.838163137	27.93	7.104	14.9
4.589280605	24.606	5.159	79.3
3.844252586	44.858	19.436	9.5
1.708024502	43.128	21.228	5.9
4.204502106	42.338	19.718	11.6
4.197036266	40.467	18.517	10.5
2.279192209	43.336	18.577	15.6
5.589730263	29.744	5.319	15.6
7.209796906	28.426	5.989	65.2
1.579701304	38.246	13.928	8.3
4.10150671	47.288	23.021	15.3
4.840472221	48.358	27.049	11.4
4.837794781	29.171	6.857	20.1
2.846711159	43.314	18.779	12.1
3.465399981	30.984	7.151	24.3
4.669570446	25.687	4.803	18.4
3.637021542	41.678	16.763	20.5
2.330371618	46.158	21.502	7.9
2.969076872	43.171	17.85	14.3
4.973127365	39.586	14.178	13.7
3.517496347	31.797	3.295	78.4
2.320736885	41.078	19.985	5.9
4.410610676	31.549	8.153	42
3.798238516	41.178	16.462	18.3
5.790472031	38.308	15.413	7.4
4.056636333	27.621	5.344	23.6

Mean Temperature (January-May) [2010-2016]	International Arrivals (millions) [2018]	Population Density	Diabetes prevalence (% of population ages 20 to 79) [2019]
17.08312035	6.942	16.51475944	5.9
3.60226965	30.816	109.289034	6.6
7.198050499	9.119	382.7482166	4.6
25.94433403	6.621	25.43142481	10.4
-13.5369606	21.134	4.150449826	7.6
3.199521542	10.362	219.015538	5.7
10.44359493	5.723	25.71000172	8.6
25.36407089	3.904	45.86109419	7.4
5.824878693	38.881	240.3716577	10.4
23.65955734	6.569	224.5013245	8.6
19.73687172	2.657	18.41134759	6.7
22.18272591	2.535	71.03825093	5.5
20.25822067	11.196	102.8021528	17.2
10.04498005	82.773	93.73452887	6.9
-2.867335558	3.224	18.23264339	5.6
8.096049309	89.322	119.2086157	4.8
6.205169678	36.316	280.6018435	3.9
7.352726936	17.552	106.7088258	6.9
26.49332619	15.81	150.987056	6.3
24.05548096	17.423	464.1494102	10.4
7.058465958	10.926	71.6765278	3.2
8.776521683	61.5672	205.5545931	5
5.503757954	31.192	346.9338179	5.6
19.65898323	41.313	66.32513851	13.5
6.944470882	18.78	508.1516311	5.4
20.21702194	4.419	25.75925469	6.6
25.9392662	7.168	367.5121072	7.1
4.848646641	19.622	123.5888221	6.1
12.17464447	16.186	111.3299159	9.8
5.888294697	11.72	83.58031889	6.9
-12.54715347	24.551	8.911010468	6.1
22.67894936	15.334	16.19483135	15.8
-2.283463001	7.44	24.61195594	4.8
7.340251446	45.768	109.583913	11.1
4.765891075	14.104	75.49154008	6.1
2.793249846	79.74592	36.18535576	10.8
20.85716248	10.472	48.89059344	12.7

<b>Prevalence - Neoplasms - Sex: Both - Age: Age- standardized (Percent) (%) [2017]</b>	<b>Median BMI</b>	<b>Prevalent Hypertension (%)</b>	<b>Smoking prevalence, 2016 total (ages 15+)</b>
1.176868831	27.7	22.6	21.8
2.228314728	25.6	21	29.6
2.129967521	26.1	17.5	28.2
0.775327051	26.6	23.3	13.9
4.629727772	26.9	13.2	14.3
2.110949955	25.2	18	25.7
1.237788506	28	20.9	37.8
0.875953763	26.2	19.2	9
2.398478606	26.6	19.9	30.6
0.753248307	26.5	21.5	13.7
0.581716794	25.5	25.1	15.6
0.693830173	27.3	17.9	7.1
0.543731123	29.6	25	25.2
2.119853473	25.9	19.2	29.3
2.353037036	25.9	19.4	20.4
2.091774092	25	22	32.7
2.791155517	27.1	15.2	22.3
1.7429261	27.3	30	30.6
0.426835825	23.1	23.8	39.4
0.312306273	21.8	25.8	11.5
2.354530107	27.5	19.7	24.3
2.277105536	25.6	21.2	23.7
2.985185404	22.7	17.6	22.1
0.894715491	28	19.7	14
2.818549509	25.6	18.7	25.8
0.655925982	26.7	13.7	4.8
0.593539368	23.2	22.6	24.3
1.635208395	26.7	28.7	28
1.761483237	25.6	24.4	22.7
1.633056952	26.9	30	29.7
1.754436206	26.2	27.2	39.3
0.908721275	28.5	23.3	15.6
2.433869445	26	19.3	18.8
0.95246871	27.9	20.3	27.2
1.602203378	26.6	27.1	28.9
5.42440701	28.9	12.9	21.8
0.556269555	27.3	26.9	20.3

Hospital beds (per 10, 000 pop)	WHO health index	Population living in urban areas (%)	GDP per capita, PPP (current international 10,000\$) [2018]
50	0.722	91	2.061056855
76	0.959	65.9	5.545468929
62	0.915	97.6	5.140799834
22	0.573	84.3	1.609640096
27	0.881	80.9	4.813025597
47	0.916	73.7	6.806094105
22	0.87	88.6	2.522252778
15	0.91	75	1.501293027
83	0.902	74.3	5.307454012
16	0.789	73.8	1.774818532
19	0.701	67.5	1.548178762
15	0.619	62.7	1.173438739
16	0.752	43	1.24123094
30	0.972	78.4	3.971543906
44	0.881	83.6	4.841693603
65	0.994	78.3	4.534239574
28	0.925	81.3	4.59735735
70	0.743	68.9	3.110250275
12	0.66	49.9	1.30796193
7	0.617	30.9	0.776288177
28	0.924	61.8	8.320339468
34	0.991	68.3	4.183042633
134	0.957	90.5	4.279745852
15	0.755	77.8	1.984464567
47	0.928	87.1	5.632894114
16	0.547	76.9	1.441807067
5	0.755	45.3	0.895108565
65	0.793	60.9	3.13366035
34	0.945	60.6	3.34154379
63	0.645	53.8	2.820635705
82	0.544	73.7	2.758812544
27	0.894	82.1	5.533567959
26	0.908	85.1	5.320888436
27	0.734	70.7	2.806885941
88	0.708	68.7	0.924946213
29	0.838	80.8	6.279458565
28	0.319	62.2	1.368688236



Total COVID-19 tests per 1000 population (23/01/2020-08/06/2020)	Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	Stringency Index Total
4.453	93.69999695	3476	93.48109436
54.934	22.5	1888	85.19000244
85.212	0	1645	74.07343292
	88.55000305	4552	76.73246765
51.14	0	1887	71.65020752
49.728	0	2158	73.24888611
37.706	95.90000153	3982	73.15000153
8.184	86.59999847	5385	87.03500366
	0	1812	68.25333405
9.043	80.97499847	4880	89.80999756
	84.65000153	3253	77.63316345
4.579	93.94999695	4929	93.51999664
	88.22499847	4202	83.8278656
	0	2705	70.95444489
38.309	64	1494	59.09785461
	56.82500076	1907	74.44837952
59.799	0	1576	56.70891953
21.792	99	1932	75.38137817
1.003	79.05000305	5220	68.05999756
3.46	63.47499847	4514	89.49436188
74.011	58.22499847	1509	88.42713928
70.518	0	2444	82.60578918
2.376	59.25	2521	44.48974991
2.888	85.02500153	4974	81.5681839
	0	1662	73.73036957
6.087	84.17500305	5906	93.75784302
3.805	85.07499695	4928	96.26882172
25.724	94.30000305	1749	78.28689575
94.2	75.25	2585	83.40107727
26.309	82.625	2071	85.55750275
90.826	66.42500305	1795	82.5987854
29.844	89.07499695	5384	88.22161865
	17.22500038	1587	36.85228729
28.195	86	2924	75.08468628
9.857	62.79999924	1843	92.20458221
70.074	0	2736	58.52120209
15.901	74.05000305	4111	85

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A

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60**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	12-13
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

**Discussion**

Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-20

**Other information**

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21
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\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Country-level Determinants of the Severity of the First Global Wave of the COVID-19 Pandemic: An Ecological Study

Journal:	<i>BMJ Open</i>
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Date Submitted by the Author:	16-Jan-2021
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<b>Primary Subject Heading</b>:	Public health
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3 1 **Country-level Determinants of the Severity of the First Global Wave of the COVID-19**  
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6 **Pandemic: An Ecological Study**  
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## 1 ABSTRACT

2 **Objective:** We aimed to identify the country-level determinants of the severity of the  
3 first wave of the COVID-19 pandemic.

4 **Design:** Ecological study of publicly available data. Countries reporting >25 COVID-  
5 related deaths until 08/06/2020 were included. The outcome was log mean mortality  
6 rate from COVID-19, an estimate of the country-level daily increase in reported deaths  
7 during the ascending phase of the epidemic curve. Potential determinants assessed  
8 were most recently published demographic parameters (population and population  
9 density, percentage population living in urban areas, median age, average body mass  
10 index, smoking prevalence), Economic parameters (Gross Domestic Product per  
11 capita); environmental parameters: pollution levels, mean temperature (January-May)),  
12 co- morbidities (prevalence of diabetes, hypertension and cancer), health system  
13 parameters (WHO Health Index and hospital beds per 10,000 population); international  
14 arrivals, the stringency index, as a measure of country-level response to COVID-19, BCG  
15 vaccination coverage, UV radiation exposure and testing capacity. Multivariable linear  
16 regression was used to analyse the data.

17 **Primary Outcome:** Country-level mean mortality rate: the mean slope of the COVID-19  
18 mortality curve during its ascending phase.

19 **Participants:** Thirty-seven countries were included: Algeria, Argentina, Austria, Belgium,  
20 Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Egypt, Finland, France,  
21 Germany, Hungary, India, Indonesia, Ireland, Italy, Japan, Mexico, the Netherlands, Peru, the  
22 Philippines, Poland, Portugal, Romania, the Russian Federation, Saudi Arabia, South Africa,  
23 Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom and the United States.

24 **Results:** Of all country-level determinants included in the multivariable model, total  
25 number of international arrivals (beta 0.033 (95% Confidence Interval 0.012,0.054))

1 and BCG vaccination coverage (-0.018 (-0.034,-0.002)), were significantly associated  
2 with the natural logarithm of the mean death rate.

3 **Conclusions:** International travel was directly associated with the mortality slope and  
4 thus potentially the spread of COVID-19. Very early restrictions on international travel  
5 should be considered to control COVID-19 outbreak and prevent related deaths.  
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# 1 ARTICLE SUMMARY

## 2 Strengths and limitations

- 3 • A relevant outcome variable quantifying country-level increases in the COVID-19  
4 death rate was derived which is largely independent of different testing policies  
5 adopted by each country.
- 6 • Our multivariable regression models accounted for public health and economic  
7 measures which were adopted by each country in response to the COVID-19  
8 pandemic by adjusting for the Stringency Index.
- 9 • The main limitation of the study stems from the ecological study design which does  
10 not allow for conclusions to be drawn for individual COVID-19 patients.
- 11 • Only countries that had reported at least 25 daily deaths over the analysed period were  
12 included, which reduced our sample and consequently the power.

## 1 INTRODUCTION

2 The atypical pneumonia caused by SARS-CoV 2 has spread rapidly. As of the 8<sup>th</sup> of  
3 June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.<sup>1</sup>  
4 The estimated overall case fatality rate is ~7%, with country-level estimates ranging between  
5 0.5-14%.<sup>2</sup> Nevertheless, there is wide variation in the reported country-specific death rates  
6 which may be attributed to variation in testing rates, underreporting or real differences in  
7 environmental, sociodemographic and health system parameters.

8 Country-level determinants of the pandemic severity are largely unknown. The only  
9 previous ecological study to date assessing country-level determinants of the severity of the  
10 COVID-19 pandemic including data on 65 countries<sup>3</sup> has found that the cumulative number  
11 of infected patients in each country was directly associated with the case fatality rate, whilst  
12 testing intensity was inversely associated with case fatality rate. This study found no  
13 association between health expenditure and case fatality rate. However, other important  
14 country-level determinants were not evaluated and thus their relationship with pandemic  
15 severity remains unknown.

16 Several risk factors for COVID-related mortality have been proposed, including older  
17 population,<sup>4</sup> higher population co-morbid burden,<sup>5</sup> smoking,<sup>6</sup> obesity,<sup>7</sup> pollution levels<sup>8</sup> and  
18 healthcare system performance.<sup>9</sup> Furthermore, countries outside China most severely hit by  
19 the first wave of the pandemic were those with a high income, high GDP per capita and well-  
20 established healthcare systems, such as Italy, Spain, France, the United Kingdom and the  
21 United States.<sup>10</sup> In contrast, lower- and middle-income countries reported much lower  
22 COVID-19 incidence and mortality rates.<sup>10</sup> Whilst these differences may be attributable to  
23 case under-reporting and infrequent testing in these countries, other factors may also be  
24 involved.

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1            In this study, we aimed to assess the country-level determinants of the severity of the  
2 first wave of the COVID-19 pandemic based on currently available evidence using publicly  
3 available data and an ecological study design.

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## 1 **METHODS**

### 2 ***Patient and Public Involvement***

3           There was no patient or public involvement in designing the study given the urgent  
4 nature of the COVID-19 pandemic and the usage of publicly available data.

### 5 ***Study Design***

6           An ecological study design was used. The outcome was the steepness of the  
7 ascending curve of country specific daily reports of COVID-19 related deaths between  
8 31/12/2019-08/06/2020. The following determinants were assessed: demographic  
9 determinants (population and population density, percentage population living in urban areas,  
10 proportion of population aged 65 and over, average body mass index (BMI), smoking  
11 prevalence), economic determinants (gross Domestic Product (GDP) per capita),  
12 environmental determinants (pollution levels, mean temperature (January-May) [2010-  
13 2016]), prevalent co-morbidities (diabetes, hypertension and cancer), health systems  
14 determinants (WHO Health Index and hospital beds per 10,000 population), international  
15 arrivals (as a proxy measure of the globalisation status of each country), the stringency index  
16 (as measure of country level response to the pandemic)<sup>11</sup>, exposure to UV radiation (as a  
17 proxy for sunlight exposure), BCG vaccination coverage and testing capacity.

### 18 ***Ethics Committee Approval***

19           Given the study design and the use of publicly available data, no ethical approval was  
20 considered necessary.

### 21 ***Selection criteria***

22           Countries reporting at least 25 daily deaths up to the 8<sup>th</sup> of June 2020 with available  
23 data for all chosen determinants were included. A total of 37 countries from 4 continents  
24 were included in the analysis: Africa (Algeria, Egypt, South Africa), America (Argentina,  
25 Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Mexico, Peru and the

1 United States of America), Asia (India, Indonesia, Japan, the Philippines, Saudi Arabia,  
2 Turkey) and Europe (Austria, Belgium, Finland, France, Germany, Hungary, Ireland, Italy,  
3 the Netherlands, Poland, Portugal, Romania, the Russian Federation, Spain, Sweden,  
4 Switzerland, Ukraine, the United Kingdom). China was not included in the analysis due to  
5 potential inaccuracies in the number of daily reported deaths which may have occurred  
6 subsequent to 1290 deaths which were retrospectively reported on the 17<sup>th</sup> of April.<sup>12</sup>

### 8 ***Data Sources***

9 Country-level parameters were obtained from freely accessible data sources. The  
10 daily reported number of COVID-19 cases and deaths between 31/12/2019-08/06/2020 as  
11 well as the 2018 population data were extracted from the European Centre for Disease  
12 Control.<sup>13</sup>

13 The data regarding the median population age and population density were extracted  
14 from the United Nations World Population Prospects<sup>14</sup> and United Nations Statistics  
15 Division, respectively.<sup>15</sup> The data regarding the percentage of the population living in urban  
16 areas were extracted from the World Urbanisation Prospects, issued by the United Nations  
17 Population Division.<sup>16</sup> Temperature data were extracted from the Climate Change Knowledge  
18 Portal from the World Bank Group.<sup>17</sup> Prevalent diabetes, gross domestic product,  
19 international arrivals in 2018, and current health expenditure data were extracted from the  
20 World Development Indicators (WDI) database, provided by the World Bank Group.<sup>18</sup> Data  
21 regarding prevalent cancers, proportion of population aged 65 and over and the total number  
22 of COVID-19 tests performed were extracted from the Our World in Data and the  
23 Sustainable Development Goals (SDG) tracker,<sup>19, 20</sup> an open-access publication tracking  
24 global progress to the United Nations Sustainable Development Goals for global  
25 development, adopted in September 2015. Prevalent hypertension, body mass index (BMI),

1 cigarette smoking, ambient air pollution, ultraviolet (UV) radiation and Bacillus Calmette–  
2 Guérin (BCG) vaccination data were obtained from the Global Health Observatory (GHO)  
3 data repository of the World Health Organization.<sup>21</sup> The world health organisation health  
4 index was extracted from the WHO Global Partnership for Education (GPE) paper series  
5 published in 2000.<sup>22</sup> Country-level total hospital beds per 10,000 population data were  
6 extracted from the World Bank Dataset “World Bank Indicators of Interest to the COVID-19  
7 Outbreak”.<sup>23</sup> Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020  
8 were extracted from the Oxford COVID-19 Government Response Tacker (OxCGRT).<sup>11</sup>

### 9 ***Definition of outcome and determinants***

#### 10 *Outcome*

11 Whilst previous ecological studies of other epidemics have utilised case or death  
12 counts as outcome,<sup>24</sup> this may be prone to bias due to variations in country-level testing  
13 strategies,<sup>25</sup> variations in population movement controls and differences in secondary attack  
14 rates within community cohorts<sup>26</sup>. The mean mortality rate was thus chosen as outcome  
15 instead, since it is independent of these parameters and may thus represent a more reliable  
16 indicator of the country-level severity of the COVID-19 pandemic

17 Mean mortality rate was defined as the mean slope of the mortality curve (Figure 1),  
18 measured from the first day when more than 2 COVID-19 deaths were reported until either  
19 the mortality curve reached a peak value or the 8<sup>th</sup> of June 2020, whichever occurred first.  
20 The peak of each mortality curve was defined as the first point at which the first derivate of  
21 the COVID-19 mortality as a function of the pandemic timeline became zero. Before slope  
22 calculation, the mortality curve in each country was smoothed using a locally weighted  
23 (Lowess) regression using a bandwidth of 0.4. In order to ensure a good fit of the Lowess  
24 regression line, only countries having reported at least 25 daily deaths until the 8<sup>th</sup> of June

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3 1 2020 were included. The mean mortality rate thus represents an estimate of the country-level  
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5 2 daily increase in reported deaths during the ascending phase of the epidemic curve.  
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### 7 3 *Determinants*

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10 4 Data on population density were extracted as the country-level population per square  
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12 5 kilometre in 2019.<sup>27</sup> Data on ambient air pollution were extracted as the country-level mean  
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14 6 concentration of fine particulate matter (PM<sub>2.5</sub>) measured in 2016.<sup>28</sup> Temperature data were  
15  
16 7 extracted as the mean temperature recorded in each country between January and May using  
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18 8 temperature data recorded between 2010 and 2016.<sup>17</sup> Data on International Arrivals were  
19  
20 9 extracted as the total number of country-level international arrivals in 2018.<sup>29</sup>  
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24 10 Data on prevalent diabetes were extracted as the percentage of the population aged 20  
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26 11 to 79 years in 2019.<sup>18</sup> Data on prevalent cancers were extracted as the age-standardized  
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28 12 cancer prevalence among both sexes in 2017, expressed as percentages.<sup>30</sup> Data on prevalent  
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30 13 hypertension were extracted as the age-standardised percentage of the population over 18  
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32 14 years of age with systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg  
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34 15 in 2015.<sup>31</sup> Data on BMI were extracted as the age-standardised mean body mass index trend  
35  
36 16 estimates for both sexes amongst adults ( $\geq 18$  years) in 2016.<sup>32</sup> Data on daily cigarette  
37  
38 17 smoking were extracted as the age-standardised smoking rate across both sexes amongst  
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40 18 adults ( $\geq 18$  years) in 2013.<sup>33</sup> Whilst the definition of “daily cigarette smoking” varies across  
41  
42 19 surveys, it habitually refers to current smoking of cigarettes at least once a day.<sup>33</sup>  
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47 20 Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in  
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49 21 current international dollars in 2018.<sup>34</sup> The percentage of population living in urban areas was  
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51 22 defined as the percentage of de facto population living in areas classified as urban according  
52  
53 23 to the criteria used by each area or country.<sup>16</sup> The World Health Organisation (WHO) health  
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55 24 index is a composite index that aims to evaluate a given countries healthcare system  
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57 25 performance relative to the maximum it could achieve given its level of resources and non-  
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1 healthcare system determinants. It was calculated in the year 2000. The index uses five  
2 weighted parameters: overall or average disability-adjusted life expectancy (25%),  
3 distribution or equality of disability-adjusted life expectancy (25%), overall or average  
4 healthcare system responsiveness (including speed of provision and quality of amenities;  
5 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare  
6 expenditure (25%). Data on hospital beds per 10,000 population were defined by the World  
7 Bank as including 'inpatient beds available in public, private, general, and specialized  
8 hospitals and rehabilitation centres'. The published data for the included countries was  
9 between 2000 and 2017. In most cases beds for both acute and chronic care were included.<sup>23</sup>  
10 The Stringency Index is an overall indicator of public health measures adopted by each  
11 country in response to the COVID-19 pandemic and includes containment and closure  
12 indicators (school closures, workplace closures, cancelling public events, restrictions on  
13 gatherings, public transport closures, stay-at-home requirements, restrictions on internal  
14 movements, international travel controls), economic response indicators (income support,  
15 debt/contract relief, fiscal measures, international support) as well as health system indicators  
16 (public information campaigns, testing policy, contact tracing, emergency investment in  
17 healthcare, investment in vaccines).<sup>11</sup> The mean daily Stringency Index was calculated for  
18 each country between 31/12/2019 and until either the mortality curve reached a peak value or  
19 the 8<sup>th</sup> of June 2020, whichever occurred first.

20 Country-level exposure to UV radiation was quantified as the population-weighted  
21 average daily ambient ultraviolet radiation level measured in J/m<sup>2</sup> for the years 1997-2003.<sup>35</sup>  
22 BCG vaccination coverage was quantified as the average percentage of 1 year-old children  
23 having received the BCG vaccine between 1980 and 2019 in each country. Testing capacity  
24 was quantified as the total number of COVID-19 tests per 1000 population performed until  
25 the 8<sup>th</sup> of June 2020.



1 Country-level intensive care unit (ICU) capacity was not included in the analyses,  
2 given the absence of a database centralising this information and the resulting poor reporting.  
3 Furthermore, ICU capacity data were unavailable for several important countries included in  
4 our analyses, such as Algeria, Argentina, Chile, the Dominican Republic, Ecuador, Egypt,  
5 India, Indonesia, Peru, the Philippines, Saudi Arabia and Ukraine.

### 6 ***Statistical analysis***

7 All analyses were performed in Stata 15.1SE, Stata Statistical Software. A 5%  
8 threshold of statistical significance was utilised for all analyses ( $P < 0.05$ ). Linear regressions  
9 were performed to assess the univariable relationship between each country-level determinant  
10 and the calculated mean mortality rate for each country. The following factors were included  
11 in the univariable analyses: the natural logarithm of the population in 2018 (10 million  
12 increase) , percentage of population aged 65 and over, pollution levels, mean temperature  
13 (January-May), international arrivals in 2018, population density, prevalent diabetes,  
14 prevalent neoplasms, median BMI, prevalent hypertension, smoking prevalence, hospital  
15 beds (per 10,000 population), WHO health index, percentage population living in urban  
16 areas, GDP per capita (PPP), UV radiation exposure, mean BCG coverage and the stringency  
17 index. The following determinants reaching a  $P$ -value  $< 0.3$  at univariable level were then  
18 included in a multivariable logistic regression model with the natural logarithm of the mean  
19 mortality rate as outcome: the logarithm of the total population in 2018, percentage of  
20 population aged 65 and over, pollution, mean temperature (January-May), international  
21 arrivals, population density, prevalent neoplasms, prevalent hypertension, the WHO health  
22 index, population living in urban areas, GDP per capita, UV radiation exposure, mean BCG  
23 coverage and the stringency index. Such a determinant selection process was chosen in order  
24 to lessen the likelihood of excluding factors which may be important but would not reach  
25 statistical significance due to the relatively small sample size of the study.

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3 1 Given that testing capacity data for 8 (Algeria, Brazil, Egypt, France, Germany, the  
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5 2 Netherlands, Spain and Sweden) of the 37 included countries were not available, a secondary  
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7 3 analysis also including testing capacity as a determinant was performed considering only the  
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9 4 remaining 29 countries. Linear regressions were performed to assess the univariable  
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11 5 relationship between each country-level determinant and the calculated mean mortality rate  
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13 6 for each country. The following determinants reaching a *P*-value <0.3 at univariable level  
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15 7 were then included in a multivariable logistic regression model with the natural logarithm of  
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17 8 the mean mortality rate as outcome: the logarithm of the total population in 2018, percentage  
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19 9 of population aged 65 and over, international arrivals, population density, prevalent  
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21 10 neoplasms, prevalent hypertension, GDP per capita, UV radiation exposure, mean BCG  
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23 11 coverage, the stringency index and testing capacity.  
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## 1 RESULTS

2 Table 1 and Supplementary File 1 detail the analysed data for the 37 included  
3 countries, including the calculated mean mortality rates. The mean mortality rates ranged  
4 between 0.22 (Chile) and 43.74 (the United States) new daily deaths. Only five included  
5 countries had a high mean mortality rate (>10): the United States (43.74), Spain (29.23), the  
6 United Kingdom (24.05), France (22.13), Italy (18.79) and Brazil (13.09).

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**Table 1.** Observed mean mortality rate during the ascending phase of the first wave of the COVID-19 pandemic and number of international arrivals in 2018 (millions) for each country included in the analyses. Countries were categorised in 3 groups: high mean mortality rate group (>20 additional daily deaths), medium mean mortality rate group (2-20 additional daily deaths) and low mean mortality rate group (<2 additional daily deaths).

Country Name	Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	International Arrivals (millions) [2018]
<b>High Mean Mortality Rate</b>		
United States of America	43.74	79.75
Spain	29.23	82.77
United Kingdom	24.05	36.32
France	22.13	89.32
Italy	18.79	61.57
Brazil	13.09	6.62
<b>Medium Mean Mortality Rate</b>		
Belgium	7.86	9.12
Mexico	7.15	41.31
Germany	6.58	38.88
Netherlands	5.40	18.78
Turkey	3.48	45.77
India	3.48	17.42
Canada	3.27	21.13
Sweden	2.59	7.44
Russian Federation	2.52	24.55
Peru	2.05	4.42
<b>Low Mean Mortality Rate</b>		
Switzerland	1.60	10.36
Ireland	1.58	10.93
Portugal	1.03	16.19
Algeria	0.88	2.66
South Africa	0.84	10.47
Ecuador	0.81	2.54
Poland	0.79	19.62
Indonesia	0.72	15.81
Austria	0.70	30.82
Romania	0.60	11.72
Egypt	0.50	11.20
Japan	0.48	31.19
Saudi Arabia	0.48	15.33
Philippines	0.46	7.17
Colombia	0.42	3.90

Hungary	0.38	17.55
Ukraine	0.31	14.10
Dominican Republic	0.28	6.57
Finland	0.26	3.22
Argentina	0.25	6.94
Chile	0.22	5.72

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2 COVID-19 – Coronarvirus disease 2019

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3 1 Table 2 details the results of the linear regression analyses. The following country-  
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5 2 level determinants showed a statistically significant relationship with log mean mortality rate  
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7 3 in univariable analyses: natural logarithm of population, international arrivals, prevalent  
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9 4 neoplasms, prevalent hypertension, GDP per capita and BCG vaccination coverage. Upon  
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11 5 multivariable adjustment, International arrivals in 2018, as a marker of global connection,  
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13 6 was significantly associated with an increase in the log mean mortality rate (0.033 (0.012,  
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15 7 0.054) per 1 million increase in international arrivals,  $P=0.003$ ). This translates to an  $\exp(B)$   
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17 8 of 1.034, equivalent to a 3.4% increase in the mean mortality rate for every 1 million increase  
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19 9 in the number of international arrivals in 2018. Furthermore, the mean BCG vaccination  
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21 10 coverage was associated with a decrease in log mean mortality rate (-0.018 (-0.034, -0.002)  
22  
23 11 per 1% increase in BCG vaccination coverage,  $P=0.031$ ). This translates to an  $\exp(B)$  of  
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25 12 0.982, equivalent to a 1.8% decrease in mean mortality rate for every 1% increase in BCG  
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27 13 vaccination coverage. Figures 2 and 3 detail the relationship between the country-level log  
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29 14 mean mortality rate (predicted and observed) and each country-level determinant included in  
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31 15 the multivariable regression model.  
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**Table 2.** Results of the linear regression assessing the association between country-level determinants and the daily increase in deaths. The determinants achieving a 30% statistical significance level in univariable analyses ( $P < 0.3$ ) were included in the multivariable model.

Country-level determinant	Univariable		Multivariable	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Natural logarithm of population (10 million increase) [2018]	<b>0.432 (0.050, 0.814)</b>	<b>0.033</b>	0.393 (-0.087, 0.873)	0.103
% population aged 65 and older	0.065 (-0.010, 0.139)	0.097	-0.020 (-0.143, 0.103)	0.741
Pollution levels	-0.017 (-0.044, 0.011)	0.247	-0.005 (-0.031, 0.020)	0.659
Mean Temperature (January-May) [2010-2016]	-0.031 (-0.078, 0.017)	0.218	0.052 (-0.025, 0.128)	0.175
International Arrivals (1 million increase) [2018]	<b>0.049 (0.033, 0.064)</b>	<b>&lt;0.001</b>	<b>0.033 (0.012, 0.054)</b>	<b>0.003</b>
Population Density	-0.002 (-0.006, 0.002)	0.268	-0.001 (-0.004, 0.002)	0.560
Diabetes prevalence (% of population ages 20 to 79) [2019]	-0.0031 (-0.189, 0.126)	0.700	-	-
Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017]	<b>0.614 (0.209, 1.019)</b>	<b>0.005</b>	-0.404 (-1.079, 0.271)	0.227
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	<b>-0.150 (-0.254, -0.045)</b>	<b>0.008</b>	-0.107 (-0.249, 0.035)	0.132
Smoking prevalence, 2016 total (ages 15+)	0.002 (-0.058, 0.062)	0.952	-	-
Hospital beds (per 10, 000 population)	-0.004 (-0.022, 0.014)	0.632	-	-
WHO health index, [2000]	2.259 (-0.920, 5.439)	0.173	-2.616 (-6.157, 0.925)	0.140
Population living in urban areas (%)	0.023 (-0.011, 0.580)	0.193	0.010 (-0.019, 0.039)	0.468
GDP per capita, PPP (\$1000 increase), [2018]	<b>0.280 (0.037, 0.524)</b>	<b>0.030</b>	0.154 (-0.174, 0.482)	0.340
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	-0.000 (-0.001, 0.000)	0.133	-0.001 (-0.001, 0.000)	0.109
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	<b>-0.027 (-0.037, -0.016)</b>	<b>&lt;0.001</b>	<b>-0.018 (-0.034, -0.002)</b>	<b>0.031</b>
Mean Daily Stringency Index	-0.036 (-0.072, 0.001)	0.057	0.004 (-0.028, 0.037)	0.790

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3  $R^2$  for multivariable linear regression = 0.8031  
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5 BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-  
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3 1 Table 3 details the results of the secondary linear regression analyses, including only  
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5 2 countries having reported COVID-19 testing data up to the 8<sup>th</sup> of June 2020. The following  
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7 3 country-level determinants showed a statistically significant relationship with log mean  
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9 4 mortality rate at univariable level: natural logarithm of population, international arrivals,  
10  
11 5 prevalent neoplasms, prevalent hypertension, BCG vaccination coverage and total COVID-19  
12  
13 6 tests per 1000 population performed until the 8<sup>th</sup> of June 2020. Upon multivariable adjustment,  
14  
15 7 the statistically significant determinants of log mean mortality rate were: international arrivals  
16  
17 8 in 2018 (0.036 (0.008, 0.063) per 1 million increase in international arrivals,  $P = 0.013$ ),  
18  
19 9 prevalent hypertension (-0.129 (-0.246,-0.012) per 1% increase in country-level hypertension  
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21 10 prevalence,  $P = 0.032$ ) and testing capacity (0.018 (0.001, 0.034) for 1 per 1000 population  
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23 11 increase in the number of total COVID-19 tests performed until the 8<sup>th</sup> of June 2020,  $P = 0.039$ ).  
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**Table 3.** Results of the secondary linear regression assessing the association between country-level determinants and the daily increase in deaths, including only countries reporting total COVID-19 tests performed up to the 8<sup>th</sup> of June 2020. The determinants achieving a 30% statistical significance level in univariable analyses ( $P < 0.3$ ) were included in the multivariable model.

Country-level determinant	Univariable		Multivariable	
	Coefficient (95% CI)	<i>P</i> value	Coefficient (95% CI)	<i>P</i> value
Natural logarithm of population (10 million increase) [2018]	<b>0.419 (0.038, 0.800)</b>	<b>0.040</b>	0.385 (-0.044, 0.813)	0.075
% population aged 65 and older	0.035 (-0.047, 0.118)	0.407	-	-
Pollution levels	-0.003 (-0.037, 0.030)	0.848	-	-
Mean Temperature (January-May) [2010-2016]	-0.032 (-0.081, 0.017)	0.207	0.026 (-0.052, 0.104)	0.484
International Arrivals (1 million increase) [2018]	<b>0.059 (0.039, 0.079)</b>	<b>&lt;0.001</b>	<b>0.036 (0.008, 0.063)</b>	<b>0.013</b>
Population Density	0.002 (-0.002, 0.007)	0.270	0.000 (-0.004, 0.003)	0.822
Diabetes prevalence (% of population ages 20 to 79) [2019]	0.012 (-0.173, 0.196)	0.903	-	-
Prevalence - Neoplasms - Sex: Both - Age: Age-standardized (Percent) (%) [2017]	<b>0.582 (0.177, 0.987)</b>	<b>0.009</b>	-0.391 (-1.014, 0.233)	0.203
Median BMI	0.107 (-0.205, 0.419)	0.507	-	-
Prevalent Hypertension (%), [2015]	<b>-0.140 (-0.240, -0.039)</b>	<b>0.011</b>	<b>-0.129 (-0.246, -0.012)</b>	<b>0.032</b>
Smoking prevalence, 2016 total (ages 15+)	-0.016 (-0.077, 0.045)	0.610	-	-
Hospital beds (per 10, 000 population)	-0.009 (-0.027, 0.009)	0.323	-	-
WHO health index, [2000]	1.247 (-2.180, 4.675)	0.482	-	-
Population living in urban areas (%)	0.007 (-0.030, 0.044)	0.710	-	-
GDP per capita, PPP (\$1000 increase), [2018]	0.242 (-0.016, 0.499)	0.077	-0.045 (-0.325, 0.235)	0.739
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	-0.000 (-0.001, 0.000)	0.283	0.000 (-0.001, 0.000)	0.310
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	<b>-0.028 (-0.039, -0.017)</b>	<b>&lt;0.001</b>	-0.011 (-0.029, 0.007)	0.221
Mean Daily Stringency Index	-0.033 (-0.074, 0.008)	0.128	0.013 (-0.021, 0.048)	0.425
Total COVID-19 tests per 1000 population	<b>0.024 (0.008, 0.039)</b>	<b>0.007</b>	<b>0.018 (0.001, 0.034)</b>	<b>0.039</b>

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3 (up to the 8<sup>th</sup> of June 2020)  
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7  $R^2$  for multivariable linear regression = 0.8373

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9 BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-  
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# 1 DISCUSSION

## 2 Principal findings

3 In this ecological study including data from 37 countries which were most severely  
4 affected by COVID-19 in the first wave of current global pandemic, we assessed 19 country-  
5 level socioeconomic, environmental, health and healthcare system, and globalisation  
6 parameters as potential determinants of the death rates associated with COVID-19. In the  
7 multivariable linear regression model, the main determinant that reached statistical  
8 significance was international arrivals, a proxy of global connection: a 1 million increase in  
9 the number of international arrivals in 2018 was associated with a 3.4% increase in the mean  
10 daily increase in COVID-19 deaths during the ascending phase of the first wave of the  
11 pandemic. Furthermore, country-level BCG vaccination coverage was associated with  
12 decreases in the COVID-19 mean mortality rate during the first wave of the pandemic.  
13 Finally, in our secondary analyses including only country with available testing capacity data,  
14 the total number of COVID-19 tests performed per 1000 population until the 8<sup>th</sup> of June 2020  
15 was also associated with increases in the COVID-19 mean mortality rate.

## 17 Comparison with previous literature

18 A previous ecological study analysed the country-level determinants of the COVID-  
19 19 case fatality rate including 65 countries.<sup>3</sup> This study found that upon adjustment for  
20 epidemic age, health expenditure and world region, the case fatality rate was significantly  
21 associated with increasing cumulative number of COVID-19 cases and decreasing testing  
22 intensity.<sup>3</sup> Nevertheless, no other country-level determinants were included in this study.

23 Further comparisons can be made with data from previous pandemics. A negative  
24 association has been reported between health expenditure and death rates from the 2009

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3 1 influenza pandemic in 30 European countries.<sup>24</sup> Associations have also been reported  
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5 2 between airline travel and spread of the H1N1 influenza virus infection.<sup>36</sup>  
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8 3 Comorbidities may account for mortality rate differences between countries. A study  
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10 4 among laboratory-confirmed cases of COVID-19 in China showed that patients with any  
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12 5 comorbidity, including diabetes, malignancy and hypertension, had poorer clinical outcomes  
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14 6 than those without.<sup>5</sup> We thus accounted for country-level data on a selection of key  
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16 7 comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI  
17  
18 8  $\geq 40$  kg/m<sup>2</sup> has been identified as an independent risk factor for severe COVID-19 illness.<sup>7</sup>  
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20 9 Finally, a recent systematic review on 5 studies from China showed that smoking is likely  
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22 10 associated with negative outcomes and progression of COVID-19.<sup>6</sup>  
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## 29 12 **Interpretation of findings.**

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31 13 In our multivariate model, the main significant determinant of mortality was  
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33 14 international arrivals. Travel restrictions and their effectiveness in containing respiratory  
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35 15 virus pandemics remains a contentious subject. In 2007 the WHO published a protocol on  
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37 16 ‘rapid operations to contain the initial emergence of pandemic influenza’, which included  
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39 17 recommendations on travel restrictions.<sup>37</sup> However, subsequent guidance advises such  
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41 18 restrictions are not recommended once a virus has spread significantly.<sup>38</sup> A recent systematic  
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43 19 review of 23 studies that demonstrated limited impact of travel restrictions in the containment  
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45 20 of influenza: internal travel restrictions delayed pandemic peak by approximately 1.5 weeks,  
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47 21 while 90% air travel restriction delayed the spread of pandemics by approximately 3–4 weeks  
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49 22 but only reduced attack rates by less than 0.02%.<sup>39</sup> However, another systematic review of  
50  
51 23 combination strategies for pandemic influenza response showed that combination strategies  
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53 24 including travel restrictions increased the effectiveness of individual policies.<sup>40</sup>  
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1 The WHO recommendations for pandemic preparedness and resilience suggest that  
2 points of entry into the country should be monitored by focussing on surveillance and risk  
3 communication to travellers but falls short of closing down international travel.<sup>41</sup>  
4 Interestingly, during the COVID-19 pandemic, some countries such as Thailand have adopted  
5 aggressive international travel screening and isolation policies, which may have led to lower  
6 infection rates.<sup>42</sup> Our study suggests that travel restrictions have the potential to influence the  
7 impact of the COVID-19 pandemic and should be considered as part of a structured and  
8 rapidly instigated pandemic preparedness plan.

9 Our multivariable model also suggests an inverse relationship between BCG  
10 vaccination coverage and the mean mortality rate, in which increasing BCG vaccination  
11 coverage was associated with decreased mean mortality rate. The relationship between BCG  
12 vaccination and the evolution of the COVID-19 transmission and disease severity remains  
13 controversial.<sup>43, 44</sup> While the BCG vaccine has been postulated to exhibit non-specific  
14 immunomodulatory properties, which may reduce SARS-CoV-2 viraemia after exposure,<sup>43</sup>  
15 current epidemiological evidence is derived from ecological studies<sup>45</sup> and needs to be  
16 interpreted in the light of the inherent limitations of this study design. Further ongoing studies  
17 (NCT04327206<sup>46</sup>, NCT04328441<sup>47</sup>) may provide more robust evidence regarding the  
18 association between BCG vaccination and COVID-19.

19 Our analyses also revealed a few surprising findings: the intensity of COVID-19  
20 testing was apparently associated with mean mortality rate increases while the country-level  
21 prevalence of hypertension was apparently associated with mean mortality rate decreases.  
22 These findings appear to be contradictory to previous evidence suggesting that testing  
23 intensity may be associated with decreased COVID-19 mortality,<sup>48</sup> while hypertension was  
24 clearly associated with increased mortality.<sup>49</sup> These surprising findings need to be interpreted

1 in the light of our ecological study design in which residual confounders may influence these  
2 associations.

#### 3 4 **Strengths and Limitations.**

5 The main strength of this study lies in its use of comparable and relevant outcome data  
6 derived from contemporary death reporting from countries affected by COVID-19. As testing  
7 rates for the virus vary across countries, the incidence or prevalence of the disease cannot be  
8 compared between countries. While death from the disease is a hard outcome, the  
9 denominator information to calculate death rates make between-country comparisons  
10 difficult. In addition, the deaths in the community, particularly in the elderly living in care  
11 homes, often go untested and thus firm diagnosis remains impossible. Therefore, in this  
12 study we have adopted an outcome that is comparable in terms of the increase in the rate of  
13 death, rather than death rates *per se*. This may better represent the spread and seriousness of  
14 pandemic in individual countries when comparing countries at different stages of the  
15 pandemic. The country-level parameters assessed as potential factors have all been  
16 implicated at some point to be associated with severity and consequently mortality. We  
17 however found that the main determinant was the total number of international arrivals in the  
18 country (2018 figures), signifying transmission of the infection through travel. Although the  
19 data was from 2018, there is no reason to believe that international travel figures between  
20 countries would be different in early 2020. Furthermore, our multivariable model also  
21 accounts for country-level international travel restrictions adopted in response to the spread  
22 of COVID-19.

23 The main limitation of the study stems from the ecological study design. Despite the  
24 fact that we did not find any association between comorbidities such as diabetes and cancer  
25 and the mean death rates at country level, it is possible for an individual with any or all of

1 these comorbid conditions to be more susceptible to the infection and consequently at  
2 increased risk of dying. Only including countries that had reported at least 25 deaths reduced  
3 our sample and consequently the power. Furthermore, the reasonably large number of  
4 country level determinants relative to the number of countries means that we cannot rule out  
5 the potential for overfitting in the multivariable model. This may lead to spurious  
6 associations between determinants and the outcome. Other explanatory variables associated  
7 with COVID-19 related mortality may have been missed and some of the covariate data used  
8 in our model predate the COVID-19 outbreak and may not be relevant at this time point.  
9 Furthermore, as new countries are affected by the epidemic, the virulence of the virus and  
10 resistance of the human body may have changed over time which was not accounted for in  
11 our model. It is also possible that the quality of data, especially underreporting of deaths  
12 related to between-country differences in defining COVID-19 deaths, may have been  
13 associated with some of the determinants in our model as well as our chosen outcome and  
14 thus biased our results. Furthermore, the delay between COVID-19 symptom onset and  
15 hospitalisation may be an important factor in the overall clinical prognosis of patients with  
16 severe COVID-19 disease. Nevertheless, given that our analyses rely on country-level  
17 determinants and in the absence of individual patient data, it is impossible to ascertain the  
18 country-level trends of delay to hospital admission. Notwithstanding, some other country-  
19 level parameters pertaining to the accessibility of healthcare included in our analyses such as  
20 the number of hospital beds per 10,000 population, proportion of population living in urban  
21 areas as well as the WHO health index may account for such differences. Finally, we did not  
22 include ICU capacity data in our analyses due to a lack of a reliable data source centralising  
23 this variable. Nevertheless, our analyses account for country-level hospital beds per 10,000  
24 population as an indicator of health systems' coping capacity with increased pressures related  
25 to the pandemic.



## 1 CONCLUSION

2 Out of all the country-level parameters assessed, international travel was the main  
3 determinant of the severity of the first global wave of the COVID-19 pandemic. Given that  
4 many of world middle and lower-income countries are showing signs of continued rise in  
5 infection rates, international travel restrictions applied very early in the pandemic course  
6 should be considered to avoid rapidly increasing infection and death rates globally. The  
7 associations between other determinants, such as BCG vaccination coverage, prevalent  
8 hypertension and COVID-19 testing capacity, and the outcome were weaker and need to be  
9 interpreted in the light of our ecological study design. Further studies are required to  
10 determine the relationship between previous BCG vaccination and COVID-19 disease  
11 progression.

## 1 **CONTRIBUTORSHIP**

2 PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP and KDE collected data and  
3 performed literature search. TAP, PKM, DJM and SB developed analysis plan. TAP analysed  
4 the data under supervision of DJM. TAP and SB drafted the paper. All authors contributed to  
5 the interpretation of results and in making an important intellectual contribution to the  
6 manuscript. All authors read and approved the final manuscript.

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9 We would like to thank Dr Kathryn Martin who provided valuable advice in study design.

## 10 **CONFLICTS OF INTEREST**

11 None.

## 12 **FUNDING**

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## 14 **DATA SHARING STATEMENT**

15 All data relevant to the study have been submitted to the journal as supplementary materials.

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## FIGURE LEGENDS

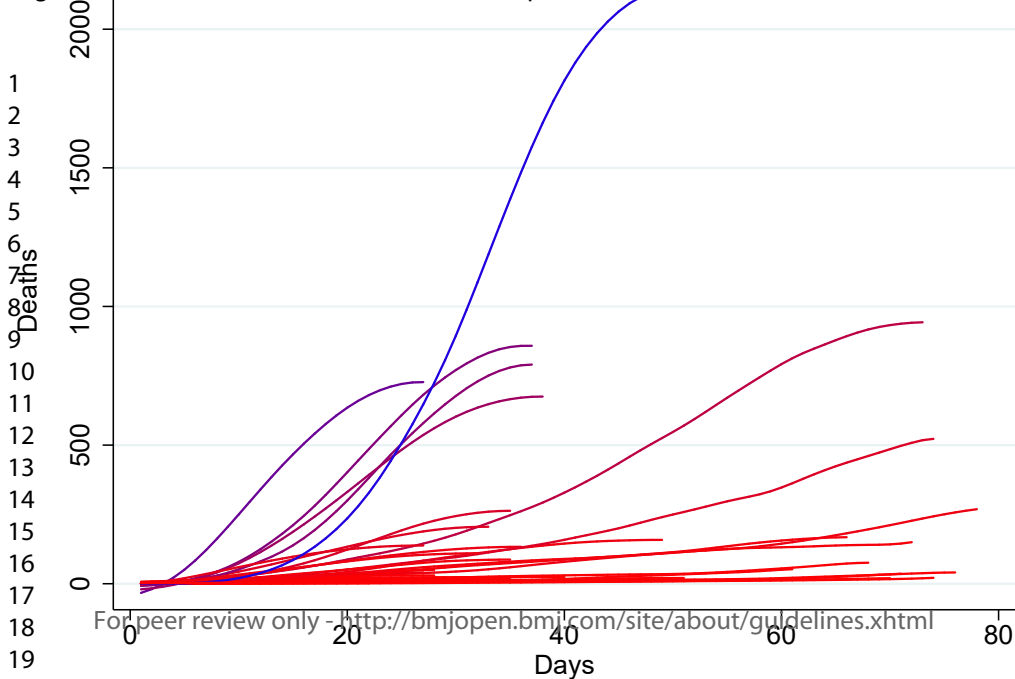
**Figure 1.** Graphical representation of the smoothed\* number of daily deaths of each country (before reaching mortality peak, if applicable) as a function of the number of days passed since the first day when an excess of 3 deaths were reported. Countries with higher mortality rates are depicted in blue, while those with lower mortality rates are depicted in red.

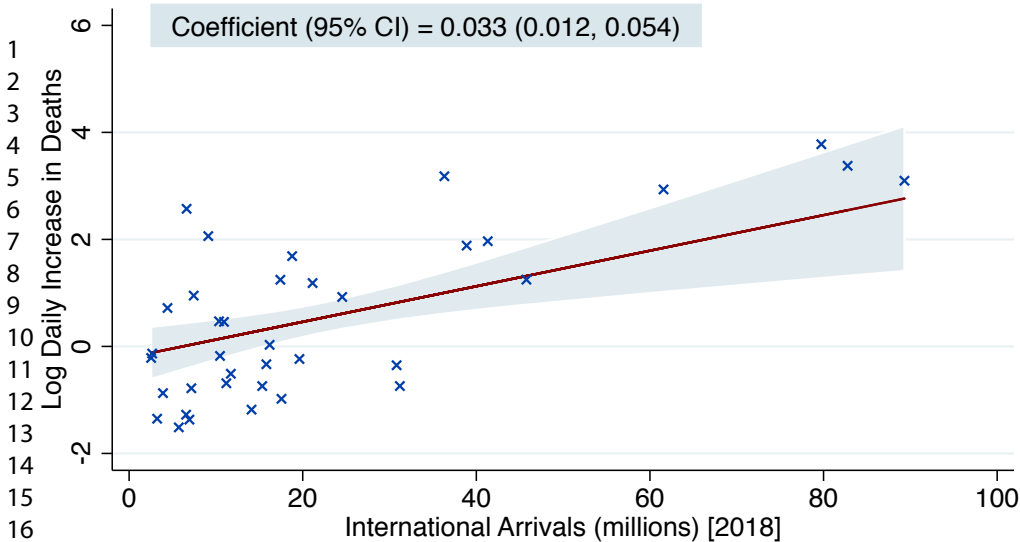
\*smoothed using a local regression (lowess) function with a bandwidth of 0.4

**Figure 2.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions). The solid red line represents the point estimate of the predicted log daily increase in deaths, while the blue-grey area represents the corresponding 95% confidence interval. The crosses represent the observed values of the log daily increase in deaths.

**Figure 3.** Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of each country-level determinant included in the multivariable model. The solid red lines represent the point estimates of the predicted log daily increase in deaths, while the blue-grey areas represent the corresponding 95% confidence intervals. The crosses represent the observed values of the log daily increase in deaths.

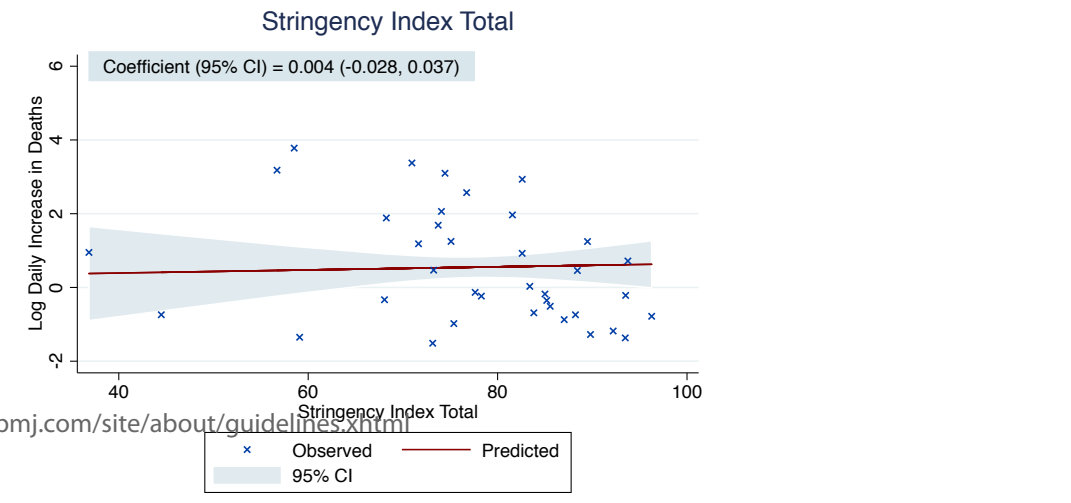
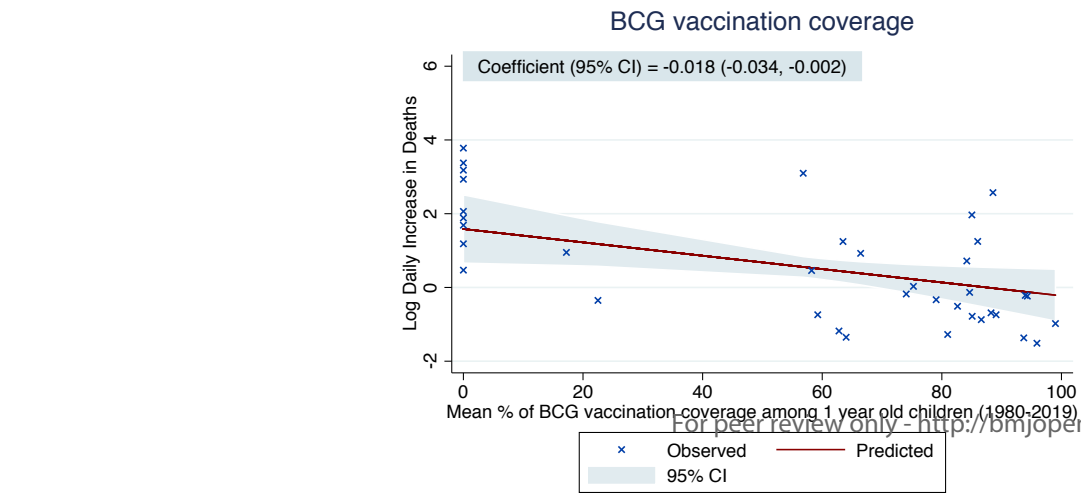
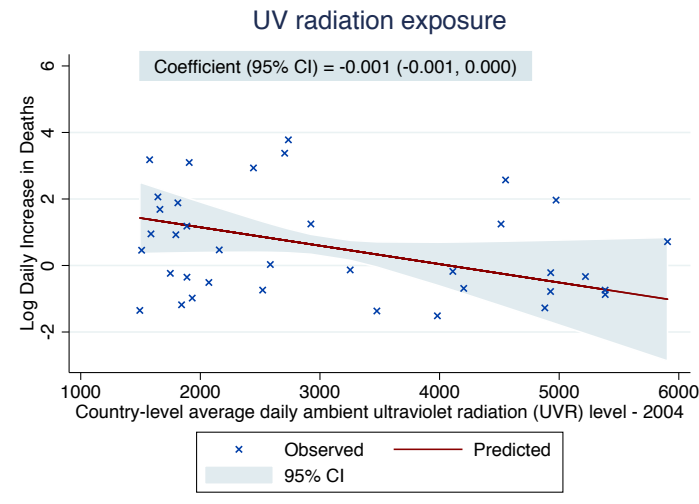
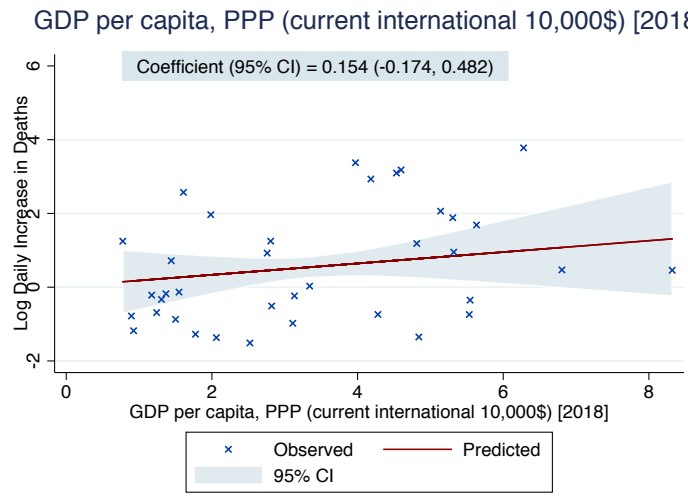
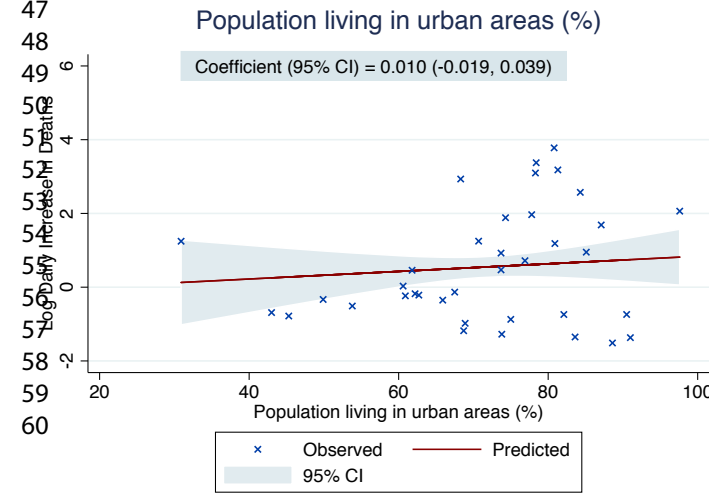
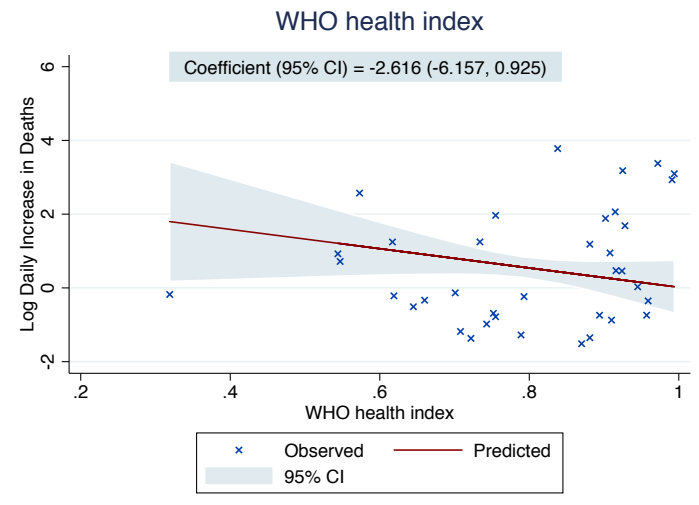
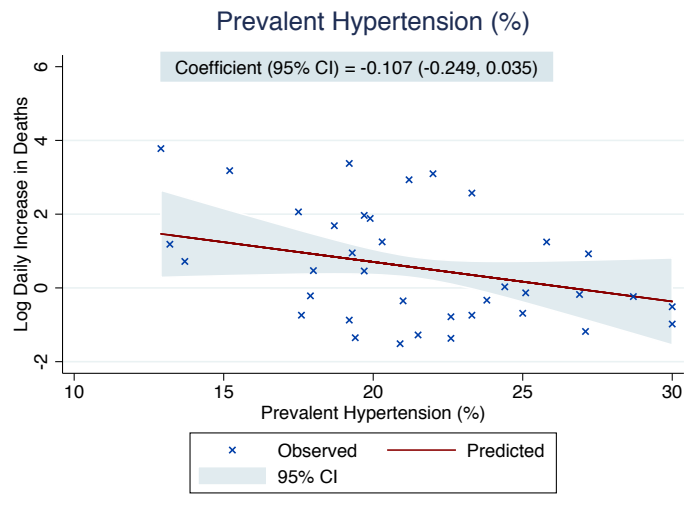
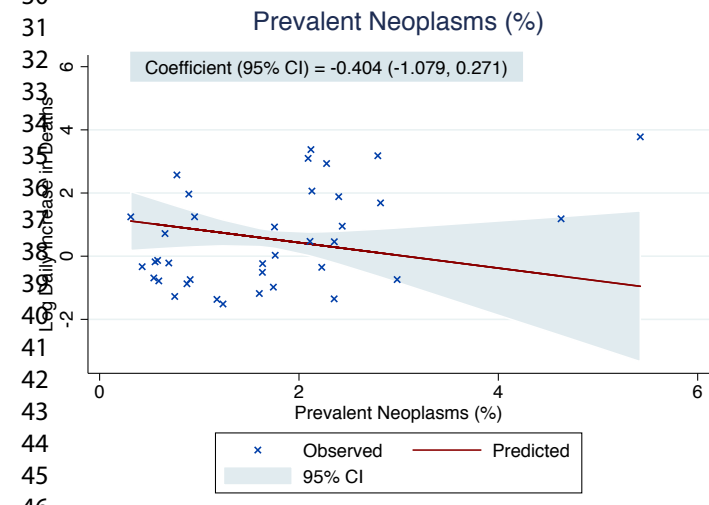
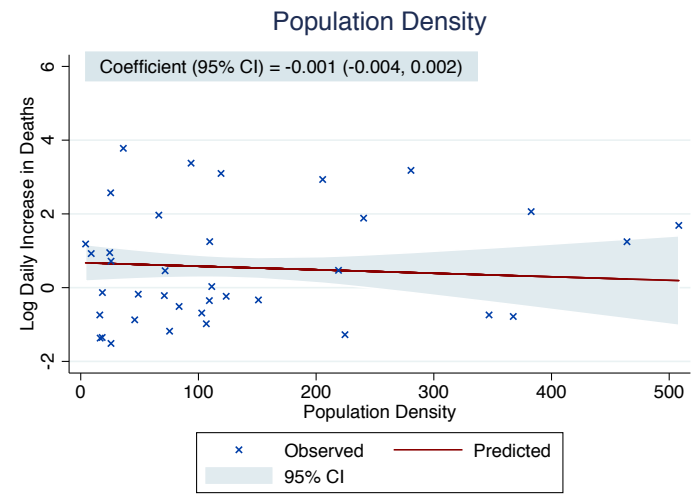
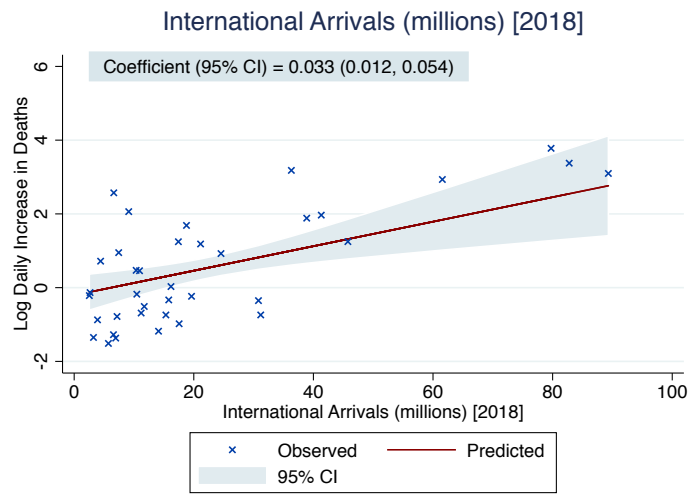
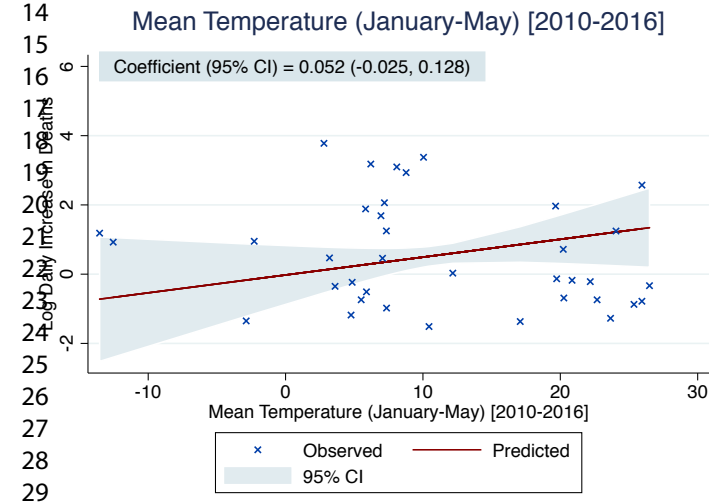
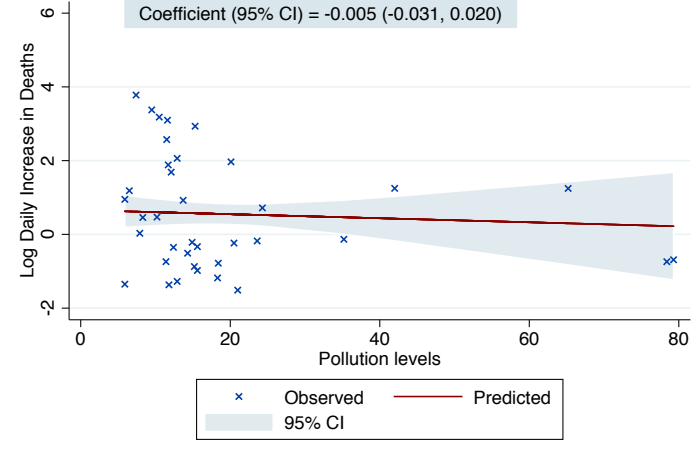
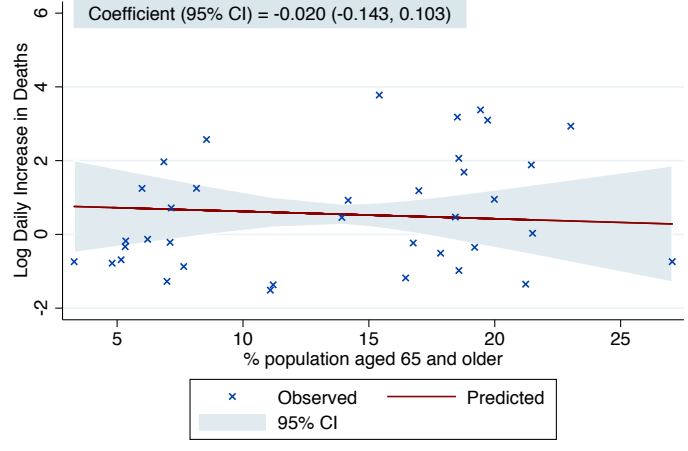
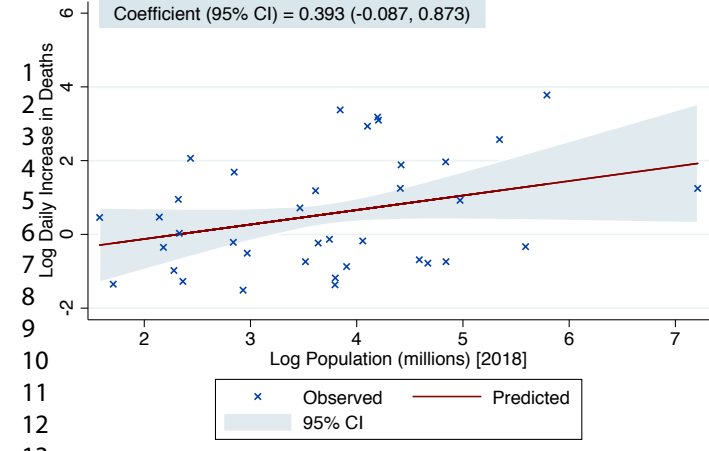
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Country Name	Country ISO3	Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	Log Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	Population (millions) [2018]
Argentina	ARG	0.254453868	-1.368635774	44.494502
Austria	AUT	0.70305109	-0.352325708	8.847037
Belgium	BEL	7.861977577	2.062038183	11.422068
Brazil	BRA	13.08982944	2.571835518	209.469333
Canada	CAN	3.267152071	1.183918715	37.058856
Switzerland	CHE	1.598400593	0.469003499	8.516543
Chile	CHL	0.220118642	-1.513588548	18.72916
Colombia	COL	0.417602718	-0.873224735	49.648685
Germany	DEU	6.579157352	1.883906722	82.927922
Dominican Republic	DOM	0.279192001	-1.275855541	10.627165
Algeria	DZA	0.874736667	-0.133832395	42.228429
Ecuador	ECU	0.805740535	-0.215993509	17.084357
Egypt	EGY	0.501979768	-0.689195454	98.423595
Spain	ESP	29.23356628	3.375317574	46.723749
Finland	FIN	0.258884579	-1.351372957	5.51805
France	FRA	22.12519836	3.096717119	66.987244
United Kingdom of	GBR	24.04783058	3.180044889	66.488991
Hungary	HUN	0.375261575	-0.980131984	9.768785
Indonesia	IDN	0.716477156	-0.333408922	267.663435
India	IND	3.476038218	1.24589324	1352.617328
Ireland	IRL	1.581101656	0.458121866	4.853506
Italy	ITA	18.78667641	2.933147907	60.431283
Japan	JPN	0.476880431	-0.740489483	126.5291
Mexico	MEX	7.145730972	1.966515064	126.190788
Netherlands (the)	NLD	5.404974937	1.687319756	17.231017
Peru	PER	2.04847312	0.717094719	31.989256
Philippines (the)	PHL	0.457063943	-0.782931983	106.651922
Poland	POL	0.789834261	-0.235932156	37.978548
Portugal	PRT	1.029355645	0.028933018	10.281762
Romania	ROU	0.599669456	-0.511376679	19.473936
Russian Federation	RUS	2.520816803	0.924582958	144.47805
Saudi Arabia	SAU	0.476594448	-0.741089344	33.699947
Sweden	SWE	2.585143805	0.94978112	10.183175
Turkey	TUR	3.484348059	1.248281002	82.319724
Ukraine	UKR	0.30672127	-1.181815863	44.622516
United States of An	USA	43.73626709	3.778177738	327.167434
South Africa	ZAF	0.836880863	-0.178073555	57.779622

<b>Log Population (millions) [2018]</b>	<b>Median age</b>	<b>% population aged 65 and older</b>	<b>Pollution levels</b>
3.795365572	31.532	11.198	11.8
2.18008256	43.483	19.202	12.4
2.435547352	41.928	18.571	12.9
5.344577312	33.481	8.552	11.5
3.612507343	41.124	16.984	6.5
2.14201045	43.053	18.436	10.2
2.930081606	35.339	11.087	21
3.904971838	31.307	7.646	15.2
4.417971611	45.744	21.453	11.7
2.363413572	28.002	6.981	12.9
3.743093729	28.521	6.211	35.2
2.838163137	27.93	7.104	14.9
4.589280605	24.606	5.159	79.3
3.844252586	44.858	19.436	9.5
1.708024502	43.128	21.228	5.9
4.204502106	42.338	19.718	11.6
4.197036266	40.467	18.517	10.5
2.279192209	43.336	18.577	15.6
5.589730263	29.744	5.319	15.6
7.209796906	28.426	5.989	65.2
1.579701304	38.246	13.928	8.3
4.10150671	47.288	23.021	15.3
4.840472221	48.358	27.049	11.4
4.837794781	29.171	6.857	20.1
2.846711159	43.314	18.779	12.1
3.465399981	30.984	7.151	24.3
4.669570446	25.687	4.803	18.4
3.637021542	41.678	16.763	20.5
2.330371618	46.158	21.502	7.9
2.969076872	43.171	17.85	14.3
4.973127365	39.586	14.178	13.7
3.517496347	31.797	3.295	78.4
2.320736885	41.078	19.985	5.9
4.410610676	31.549	8.153	42
3.798238516	41.178	16.462	18.3
5.790472031	38.308	15.413	7.4
4.056636333	27.621	5.344	23.6

Mean Temperature (January-May) [2010-2016]	International Arrivals (millions) [2018]	Population Density	Diabetes prevalence (% of population ages 20 to 79) [2019]
17.08312035	6.942	16.51475944	5.9
3.60226965	30.816	109.289034	6.6
7.198050499	9.119	382.7482166	4.6
25.94433403	6.621	25.43142481	10.4
-13.5369606	21.134	4.150449826	7.6
3.199521542	10.362	219.015538	5.7
10.44359493	5.723	25.71000172	8.6
25.36407089	3.904	45.86109419	7.4
5.824878693	38.881	240.3716577	10.4
23.65955734	6.569	224.5013245	8.6
19.73687172	2.657	18.41134759	6.7
22.18272591	2.535	71.03825093	5.5
20.25822067	11.196	102.8021528	17.2
10.04498005	82.773	93.73452887	6.9
-2.867335558	3.224	18.23264339	5.6
8.096049309	89.322	119.2086157	4.8
6.205169678	36.316	280.6018435	3.9
7.352726936	17.552	106.7088258	6.9
26.49332619	15.81	150.987056	6.3
24.05548096	17.423	464.1494102	10.4
7.058465958	10.926	71.6765278	3.2
8.776521683	61.5672	205.5545931	5
5.503757954	31.192	346.9338179	5.6
19.65898323	41.313	66.32513851	13.5
6.944470882	18.78	508.1516311	5.4
20.21702194	4.419	25.75925469	6.6
25.9392662	7.168	367.5121072	7.1
4.848646641	19.622	123.5888221	6.1
12.17464447	16.186	111.3299159	9.8
5.888294697	11.72	83.58031889	6.9
-12.54715347	24.551	8.911010468	6.1
22.67894936	15.334	16.19483135	15.8
-2.283463001	7.44	24.61195594	4.8
7.340251446	45.768	109.583913	11.1
4.765891075	14.104	75.49154008	6.1
2.793249846	79.74592	36.18535576	10.8
20.85716248	10.472	48.89059344	12.7



Prevalence - Neoplasms - Sex: Both - Age: Age- standardized (Percent) (%) [2017]	Median BMI	Prevalent Hypertension (%)	Smoking prevalence, 2016 total (ages 15+)
1.176868831	27.7	22.6	21.8
2.228314728	25.6	21	29.6
2.129967521	26.1	17.5	28.2
0.775327051	26.6	23.3	13.9
4.629727772	26.9	13.2	14.3
2.110949955	25.2	18	25.7
1.237788506	28	20.9	37.8
0.875953763	26.2	19.2	9
2.398478606	26.6	19.9	30.6
0.753248307	26.5	21.5	13.7
0.581716794	25.5	25.1	15.6
0.693830173	27.3	17.9	7.1
0.543731123	29.6	25	25.2
2.119853473	25.9	19.2	29.3
2.353037036	25.9	19.4	20.4
2.091774092	25	22	32.7
2.791155517	27.1	15.2	22.3
1.7429261	27.3	30	30.6
0.426835825	23.1	23.8	39.4
0.312306273	21.8	25.8	11.5
2.354530107	27.5	19.7	24.3
2.277105536	25.6	21.2	23.7
2.985185404	22.7	17.6	22.1
0.894715491	28	19.7	14
2.818549509	25.6	18.7	25.8
0.655925982	26.7	13.7	4.8
0.593539368	23.2	22.6	24.3
1.635208395	26.7	28.7	28
1.761483237	25.6	24.4	22.7
1.633056952	26.9	30	29.7
1.754436206	26.2	27.2	39.3
0.908721275	28.5	23.3	15.6
2.433869445	26	19.3	18.8
0.95246871	27.9	20.3	27.2
1.602203378	26.6	27.1	28.9
5.42440701	28.9	12.9	21.8
0.556269555	27.3	26.9	20.3

Hospital beds (per 10, 000 pop)	WHO health index	Population living in urban areas (%)	GDP per capita, PPP (current international 10,000\$) [2018]
50	0.722	91	2.061056855
76	0.959	65.9	5.545468929
62	0.915	97.6	5.140799834
22	0.573	84.3	1.609640096
27	0.881	80.9	4.813025597
47	0.916	73.7	6.806094105
22	0.87	88.6	2.522252778
15	0.91	75	1.501293027
83	0.902	74.3	5.307454012
16	0.789	73.8	1.774818532
19	0.701	67.5	1.548178762
15	0.619	62.7	1.173438739
16	0.752	43	1.24123094
30	0.972	78.4	3.971543906
44	0.881	83.6	4.841693603
65	0.994	78.3	4.534239574
28	0.925	81.3	4.59735735
70	0.743	68.9	3.110250275
12	0.66	49.9	1.30796193
7	0.617	30.9	0.776288177
28	0.924	61.8	8.320339468
34	0.991	68.3	4.183042633
134	0.957	90.5	4.279745852
15	0.755	77.8	1.984464567
47	0.928	87.1	5.632894114
16	0.547	76.9	1.441807067
5	0.755	45.3	0.895108565
65	0.793	60.9	3.13366035
34	0.945	60.6	3.34154379
63	0.645	53.8	2.820635705
82	0.544	73.7	2.758812544
27	0.894	82.1	5.533567959
26	0.908	85.1	5.320888436
27	0.734	70.7	2.806885941
88	0.708	68.7	0.924946213
29	0.838	80.8	6.279458565
28	0.319	62.2	1.368688236

Total COVID-19 tests per 1000 population (23/01/2020-08/06/2020)	Mean % of BCG vaccination coverage among 1 year old children (1980-2019)	Country-level average daily ambient ultraviolet radiation (UVR) level - 2004	Stringency Index Total
4.453	93.69999695	3476	93.48109436
54.934	22.5	1888	85.19000244
85.212	0	1645	74.07343292
	88.55000305	4552	76.73246765
51.14	0	1887	71.65020752
49.728	0	2158	73.24888611
37.706	95.90000153	3982	73.15000153
8.184	86.59999847	5385	87.03500366
	0	1812	68.25333405
9.043	80.97499847	4880	89.80999756
	84.65000153	3253	77.63316345
4.579	93.94999695	4929	93.51999664
	88.22499847	4202	83.8278656
	0	2705	70.95444489
38.309	64	1494	59.09785461
	56.82500076	1907	74.44837952
59.799	0	1576	56.70891953
21.792	99	1932	75.38137817
1.003	79.05000305	5220	68.05999756
3.46	63.47499847	4514	89.49436188
74.011	58.22499847	1509	88.42713928
70.518	0	2444	82.60578918
2.376	59.25	2521	44.48974991
2.888	85.02500153	4974	81.5681839
	0	1662	73.73036957
6.087	84.17500305	5906	93.75784302
3.805	85.07499695	4928	96.26882172
25.724	94.30000305	1749	78.28689575
94.2	75.25	2585	83.40107727
26.309	82.625	2071	85.55750275
90.826	66.42500305	1795	82.5987854
29.844	89.07499695	5384	88.22161865
	17.22500038	1587	36.85228729
28.195	86	2924	75.08468628
9.857	62.79999924	1843	92.20458221
70.074	0	2736	58.52120209
15.901	74.05000305	4111	85

## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A

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60**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	12-13
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

**Discussion**

Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-20

**Other information**

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21
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\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).