BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042034
Article Type:	Original research
Date Submitted by the Author:	24-Jun-2020

Complete List of Authors:	Pana, Tiberiu; University of Aberdeen, Bhattacharya, Sohinee; University of Aberdeen Gamble, David; University of Aberdeen Pasdar, Zahra; University of Aberdeen Szlachetka, Weronika; University of Aberdeen Perdomo-Lampignano, Jesus; University of Aberdeen Ewers, Kai; University of Aberdeen McLernon, David; University of Aberdeen Myint, Phyo; University of Aberdeen

Keywords:	INFECTIOUS DISEASES, PUBLIC HEALTH, EPIDEMIOLOGY

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

Tiberiu A Pana[1, †]; Sohinee Bhattacharya PhD[1, †]; David T Gamble, MBBS[1]; Zahra Pasdar[1]; Weronika A Szlachetka[1]; Jesus A Perdomo-Lampignano, MBChB[1]; Kai D Ewers[1]; David J McLernon, PhD[1]; Phyo K Myint, MD[1,*]

[†]Joint first authors. Authors Pana and Bhattacharya contributed equally

[1]Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, United Kingdom

Correspondence to:
Professor Phyo Kyaw Myint
Room 4:013, Polwarth Building
School of Medicine, Medical Sciences and Nutrition
Foresterhill, Aberdeen
AB25 2ZD,
Scotland, UK.
Tel: +44 (0) 1224 437841,
Mail to: phyo.myint@abdn.ac.uk

Tables 2, Figures 3
Word count: 2987
Abstract word count: 295

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

Arabia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom and the United States.

Results: Of all country-level predictors included in the multivariable model, only total number of international arrivals was significantly associated with the mean death rate: Beta 0.040 (95% Confidence Interval 0.017, 0.063), P <0.001.

Conclusions: International travel was directly associated with the mortality slope and thus potentially the spread of COVID-19. Very early restrictions on international travel may be a very effective strategy to control COVID outbreak and prevent related deaths.

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 8th of June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.[1] The estimated overall case fatality rate is ~7%, with country-level estimates ranging between 0.5-14%.[2] 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[3] 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,[4] higher population co-morbid burden,[5] smoking,[6] obesity,[7] pollution levels[8] and healthcare system performance.[9] 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.[10] In contrast, lower- and middle-income countries reported much lower COVID-19 incidence and mortality rates.[10] 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 association between potential country level determinants driven by hypothesis based on currently available evidence using country level publicly available data and an ecological study design.

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).[11]

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 8th 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, Turkey, Ukraine, the United Kingdom and the United States. China was not included in the analysis due to potential inaccuracies in the number of daily reported deaths which may have occurred subsequent to 1290 deaths which were retrospectively reported on the 17th of April.[12]

Data Sources

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

The data regarding the median population age and population density were extracted from the United Nations World Population Prospects[14] and United Nations Statistics Division, respectively.[15] The data regarding the percentage of the population living in urban areas were extracted from the World Urbanisation Prospects, issued by the United Nations Population Division.[16] Temperature data were extracted from the Climate Change Knowledge Portal from the World Bank Group.[17] Prevalent diabetes, gross domestic product, international arrivals in 2018, and current health expenditure data were extracted from the World Development Indicators (WDI) database, provided by the World Bank Group.[18] Prevalent cancers data were extracted from the Our World in Data and the Sustainable Development Goals (SDG) tracker,[19] an open-access publication tracking global progress to the United Nations Sustainable Development Goals for global development, adopted in September 2015. Prevalent hypertension, body mass index (BMI), cigarette smoking and ambient air pollution data were obtained from the Global Health Observatory (GHO) data repository of the World Health Organization.[20] The world health organisation health index was extracted from the WHO Global Partnership for Education (GPE) paper series published in 2000.[21] Country-level total hospital beds per 10,000 population data were extracted from the World Bank Dataset "World Bank Indicators of Interest to the COVID-19 Outbreak".[22] Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020 were extracted from the Oxford COVID-19 Government Response Tacker (OxCGRT).[11]

Definition of outcome and predictors

Outcome

Whilst previous ecological studies of other epidemics have utilised case or death counts as outcome,[23] this may be prone to bias due to variations in country-level testing strategies,[24] variations in population movement controls and differences in secondary attack rates within community cohorts[25]. The mean mortality rate was thus chosen as outcome instead, since it is independent of these parameters and may thus represent a more reliable indicator of the country-level severity of the COVID-19 pandemic

Mean mortality rate was defined as the mean slope of the mortality curve (Figure 1), measured from the first day when more than 2 COVID-19 deaths were reported until either the mortality curve reached a peak value or the 8th of June 2020, whichever occurred first. Before slope calculation, the mortality curve in each country was smoothed using a locally weighted (Lowess) regression using a bandwidth of 0.4. In order to ensure a good fit of the Lowess regression line, only countries having reported at least 25 daily deaths until the 8th of June 2020 were included. The mean mortality rate thus represents an estimate of the country-level daily increase in reported deaths during the ascending phase of the epidemic curve.

Determinants

Data on population density were extracted as the country-level population per square kilometre in 2019.[26] Data on ambient air pollution were extracted as the country-level mean concentration of fine particulate matter (PM2.5) measured in 2016.[27] Temperature data were extracted as the mean temperature recorded in each country between January and April between 2010 and 2016.[17] Data on International Arrivals were extracted as the total number of country-level international arrivals in 2018.[28]

Data on prevalent diabetes were extracted as the percentage of the population aged 20 to 79 years in 2019.[18] Data on prevalent cancers were extracted as the age-standardized cancer prevalence among both sexes in 2017, expressed as percentages.[29] Data on prevalent hypertension were extracted as the age-standardised percentage of the population over 18 years of age with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in 2015.[30] Data on BMI were extracted as the age-standardised mean body mass index trend estimates for both sexes amongst adults (≥18 years) in 2016.[31] Data on daily cigarette smoking were extracted as the age-standardised rate on both sexes amongst adults (≥18 years) in 2013.[32] Whilst the definition of "daily cigarette smoking" varies across surveys, it habitually refers to current smoking of cigarettes at least once a day.[32]

Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in current international dollars in 2018.[33] The percentage of population living in urban areas was defined as the percentage of de facto population living in areas classified as urban according to the criteria used by each area or country.[16] The World Health Organisation (WHO) heath index is a composite index that aims to evaluate a given countries healthcare system performance relative to the maximum it could achieve given its level of resources and non-healthcare system determinants. It was calculated in the year 2000. The index uses five weighted parameters: overall or average disability-adjusted life expectancy (25%), distribution or equality of disability-adjusted life expectancy (25%), overall or average healthcare system responsiveness (including speed of provision and quality of amenities; 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare expenditure (25%). Data on hospital beds per 10,000 population were defined by the World

Bank as including “inpatient beds available in public, private, general, and specialized hospitals and rehabilitation centres. The published data for countries included was from 2000 to 2017. In most cases beds for both acute and chronic care are included.[22] The SI is an overall indicator of public health measures adopted by each country in response to the COVID-19 pandemic and includes containment and closure indicators, economic response indicators as well as health systems indicators.[11] The mean SI was calculated for each country between 31/12/2019 and until either the mortality curve reached a peak value or the 8th of June 2020, whichever occurred first.

Statistical analysis

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

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).

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]
High Mean Mortality Rate		
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
Medium Mean Mortality Rate		
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
Low Mean Mortality Rate		
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

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

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]	**0.049 (0.033, 0.064)**	**<0.001**	**0.040 (0.017 ,0.063)**	**0.002**
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]	**0.614 (0.209, 1.019)**	**0.005**	-0.301 (-1.062 ,0.461)	0.423
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	**-0.150 (-0.254, -0.045)**	**0.008**	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^2 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.[3] 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.[3] 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.[23] Associations have also been reported between airline travel and spread of the H1N1 influenza virus infection.[34]

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.[5] We thus accounted for country-level data on a selection of key comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI $\geq$40kg/m2 has been identified as an independent risk factor for severe COVID-19 illness.[7]

Finally, a recent systematic review on 5 studies from China showed that smoking is likely associated with negative outcomes and progression of COVID-19.[6]

Interpretation of findings.

In our multivariate model, the only significant determinant of mortality was international arrivals. Travel restrictions and their effectiveness in containing respiratory virus pandemics remains a contentious subject. In 2007 the WHO published a protocol on 'rapid operations to contain the initial emergence of pandemic influenza', which included recommendations on travel restrictions.[35] However, subsequent guidance advises such restrictions are not recommended once a virus has spread significantly.[36] A recent systematic review of 23 studies that demonstrated limited impact of travel restrictions in the containment of influenza: internal travel restrictions delayed pandemic peak by approximately 1.5 weeks, while 90% air travel restriction delayed the spread of pandemics by approximately 3–4 weeks but only reduced attack rates by less than 0.02%.[37] However, another systematic review of combination strategies for pandemic influenza response showed that combination strategies including travel restrictions increased the effectiveness of individual policies.[38]

The WHO recommendations for pandemic preparedness and resilience recommends that points of entry into the country should be monitored by focussing on surveillance and risk communication to travellers but falls short of closing down international travel.[39] Interestingly, during the COVID-19 pandemic, some countries such as Thailand have adopted aggressive international travel screening and isolation policies, which may have led to lower infection rates.[40] Our study suggests that travel restrictions have the potential to influence the impact of the COVID-19 pandemic and should be part of a structured and rapidly instigated pandemic preparedness plan. Furthermore, the mean stringency index, which also accounts for international travel restrictions amongst other measures, was not associated with the mean mortality rate in the multivariable model. This suggest that international travel restrictions and other containment measures may have been imposed too late to influence the steepness of the mortality curve and that the level of global connectivity of each country may influence the course of the epidemic mortality curve before the number of COVID-19 related cases and deaths reaches worrying levels.

Strengths and Limitations.

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

The main limitation of the study stems from the ecological study design. Despite the fact that we did not find any association between comorbidities such as diabetes, cancer and hypertension and the mean death rates at country level, it is possible for an individual with any or all of these comorbid conditions to be more susceptible to the infection and consequently at increased risk of dying. Only including countries that had reported at least 25 deaths reduced our sample and consequently the power. This may also result in the regression model overfitting the data. Other explanatory variables associated with COVID-19 related mortality may have been missed and some of the covariate data used in our model predate the COVID outbreak and may not be relevant at this time point. Furthermore, as new countries are affected by the epidemic, the virulence of the virus and resistance of the human body may have changed over time which was not accounted for in our model. Lastly, it is possible that the quality of data, especially underreporting of deaths, may have been associated with some of the predictors in our model and thus biased our results.

CONCLUSION

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

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.

ACKNOWLEDGEMENTS

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

CONFLICTS OF INTEREST

None.

FUNDING

None.

DATA SHARING STATEMENT

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

REFERENCES

1. World Health Orgainzation. Coronavirus disease (COVID-19) Situation Report – 140. *WHO*. 2020;140:1.

2. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Mortality Risk of COVID-19. https://ourworldindata.org/mortality-risk-covid. Accessed 05/7, 2020.

3. Kenyon C. Flattening-the-curve associated with reduced COVID-19 case fatality rates- an ecological analysis of 65 countries. *J Infect*. 2020. doi: S0163-4453(20)30215-2 [pii].

4. Dowd JB, Andriano L, Brazel DM, et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. *Proc Natl Acad Sci U S A*. 2020;117(18):9696-9698. doi: 10.1073/pnas.2004911117 [doi].

5. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*. 2020. doi: 2000547 [pii].

6. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020;18:20. doi: 10.18332/tid/119324 [doi].

7. Flint SW, Tahrani AA. COVID-19 and obesity-lack of clarity, guidance, and implications for care. *The Lancet.Diabetes & Endocrinology*. 2020. doi: 10.1016/S2213-8587(20)30156-X.

8. Ogen Y. Assessing nitrogen dioxide (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ*. 2020;726:138605. doi: S0048-9697(20)32121-5 [pii].

9. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. *Lancet Glob Health*. 2020;8(4):e480-109X(20)30068-1. Epub 2020 Feb 25. doi: S2214-109X(20)30068-1 [pii].

10. World Health Organization. Coronavirus disease (COVID-19) Situation Report–108. 2020;108:5-6-14.

11. Hale T, Sam W, Petherick A, Phillips T, Kira B. Oxford COVID-19 Government Response Tracker, Blavatnik School of Government. https://www.bsg.ox.ac.uk/research/research-projects/coronavirus-government-response-tracker. Accessed 06/10, 2020.

12. European Centre for Disease Prevention and Control. Download today's data on the geographic distribution of COVID-19 cases worldwide. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 06/10, 2020.

13. European Centre for Disease Prevention and Control. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 05/01, .

14. United Nations. Department of Economic and Social Affairs Population Dynamics. https://population.un.org/wpp/DataQuery/. Accessed 05/07, .

15. United Nations Statistics Division. Population density and urbanization. https://unstats.un.org/unsd/demographic/sconcerns/densurb/. Accessed 05/07, 2020.

16. United Nations. World Urbanization Prospects 2018. https://population.un.org/wup/. Accessed 04/20, 2020.

17. World Bank Group Climate Change Knowledge Portal. Climate Data. https://climateknowledgeportal.worldbank.org/watershed/161/climate-data-historical. Accessed 04/30, 2020.

18. The World Bank Group. Data Bank, World Development Indicators. https://databank.worldbank.org/reports.aspx?source=2&series=SH.STA.DIAB.ZS&country=#dbMetadata. Accessed 04, 2020.

19. Roser M, Ortiz-Ospina. Measuring progress towards the Sustainable Development Goals. https://sdg-tracker.org/. Accessed 05/05, 2020.

20. World Health Organization. Global Health Observatory indicator views. https://apps.who.int/gho/data/node.imr. Accessed 04/20, 2020.

21. Tandon A, Murray CJL, Lauer JA, Evans D. Measuring overall health system performance for 191 countries. *World Health Organization*. 2000(30):18-19-21.

22. The Humanitarian Data Exchange. World Bank Indicators of Interest to the COVID-19 Outbreak. https://data.humdata.org/dataset/world-bank-indicators-of-interest-to-the-covid-19-outbreak#metadata-0. Accessed 04/20, 2020.

23. Nikolopoulos G, Bagos P, Lytras T, Bonovas S. An ecological study of the determinants of differences in 2009 pandemic influenza mortality rates between countries in Europe. *PLoS One*. 2011;6(5):e19432. doi: 10.1371/journal.pone.0019432 [doi].

24. Garcia-Basteiro AL, Chaccour C, Guinovart C, et al. Monitoring the COVID-19 epidemic in the context of widespread local transmission. *Lancet Respir Med*. 2020;8(5):440-442. doi: S2213-2600(20)30162-4 [pii].

25. Barmparis GD, Tsironis GP. Estimating the infection horizon of COVID-19 in eight countries with a data-driven approach. *Chaos Solitons Fractals*. 2020:109842. doi: 10.1016/j.chaos.2020.109842 [doi].

26. United Nations Department of Economics and Social Affairs. World Population Prospects 2019. https://population.un.org/wpp/Download/Standard/Population/. Accessed 04/20, 2020.

27. World Health Organization. Annual mean concentration of particulate matter of less than 2.5 microns of diameter (PM2.5) [ug/m3] in urban areas. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4674. Accessed 04/20, 2020.

28. The World Bank. International tourism, number of arrivals. https://data.worldbank.org/indicator/ST.INT.ARVL?view=map. Accessed 04/20, 2020.

29. Our World in Data. Cancer. https://ourworldindata.org/cancer. Accessed 04, 2020.

30. World Health Organization. Prevalence of raised blood pressure (SBP≥140 OR DBP≥90). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2386. Accessed 5, 2020.

31. World Health Organization. Mean BMI (kg/m²) (age-standardized estimate). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2388. Accessed 04/05/2020, 2020.

32. World Health Organization. Daily smoking of cigarettes (age-standardized rate). https://www.who.int/data/gho/data/indicators/indicator-details/GHO/daily-cigarette-smoking-age-standardised. Accessed 04/05/2020, 2020.

33. The World Bank. GDP Per Capita, PPP (current international $). https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?view=chart. Accessed 04/20, 2020.

34. Khan K, Arino J, Hu W, et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med*. 2009;361(2):212-214. doi: 10.1056/NEJMc0904559 [doi].

35. World Health Organization. WHO interim protocol: rapid operations to contain the initial emergence of pandemic influenza. *WHO*. 2007:1.

36. World Health Organization. Pandemic influenza preparedness and response, WHO guidance document. *WHO*. 2009:1.

37. Mateus AL, Otete HE, Beck CR, Dolan GP, Nguyen-Van-Tam JS. Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review. *Bull World Health Organ*. 2014;92(12):868-880D. doi: 10.2471/BLT.14.135590 [doi].

38. Lee VJ, Lye DC, Wilder-Smith A. Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies. *BMC Med*. 2009;7:76-7015-7-76. doi: 10.1186/1741-7015-7-76 [doi].

39. World Health Organization. COVID-19 Strategic Preparedness and Response Plan; Operational Planning Guidelines to Support Country Preparedness and Response. *WHO*. 2020:1.

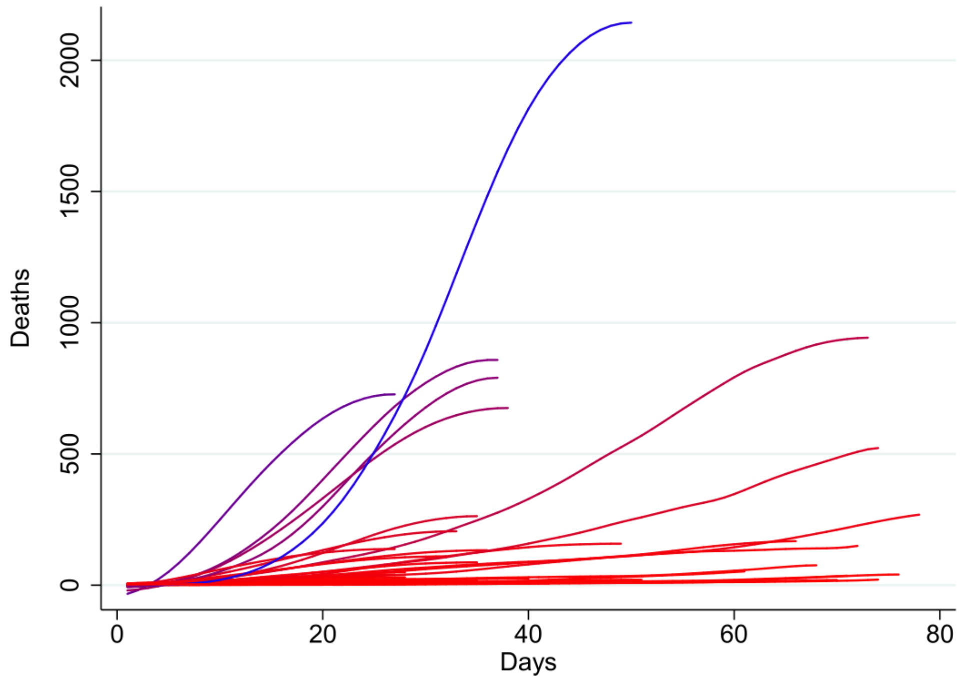
40. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report–1. 2020;1:4.

FIGURE LEGENDS

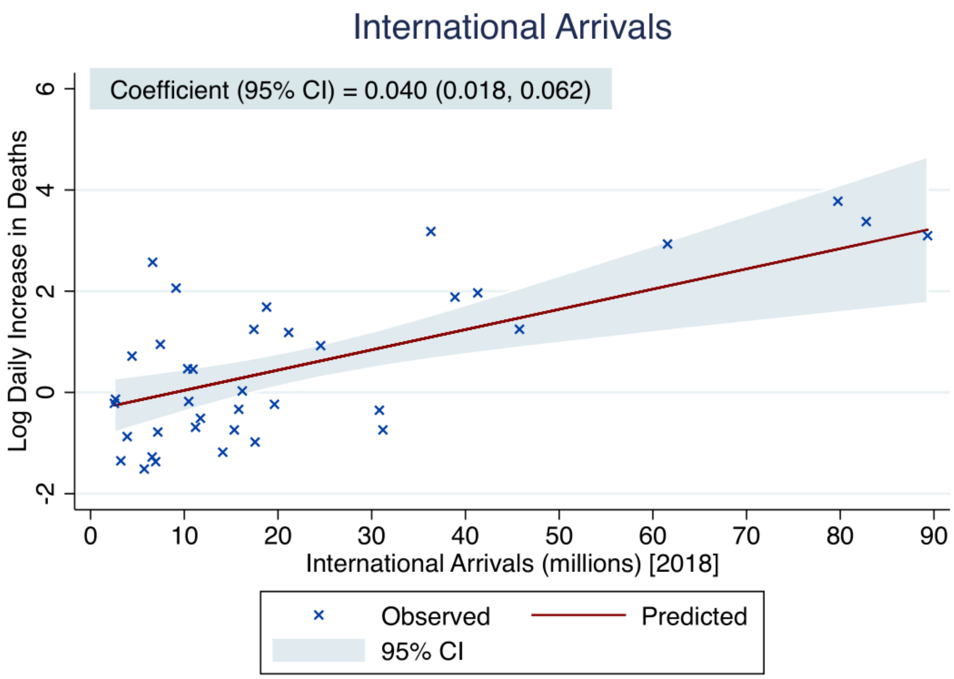
Figure 1. Graphical representation of the smoothed* number of daily deaths of each country (before reaching mortality peak, if applicable) as a function of the number of days passed since the first day when an excess of 3 deaths were reported. Countries with higher mortality rates are depicted in blue,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

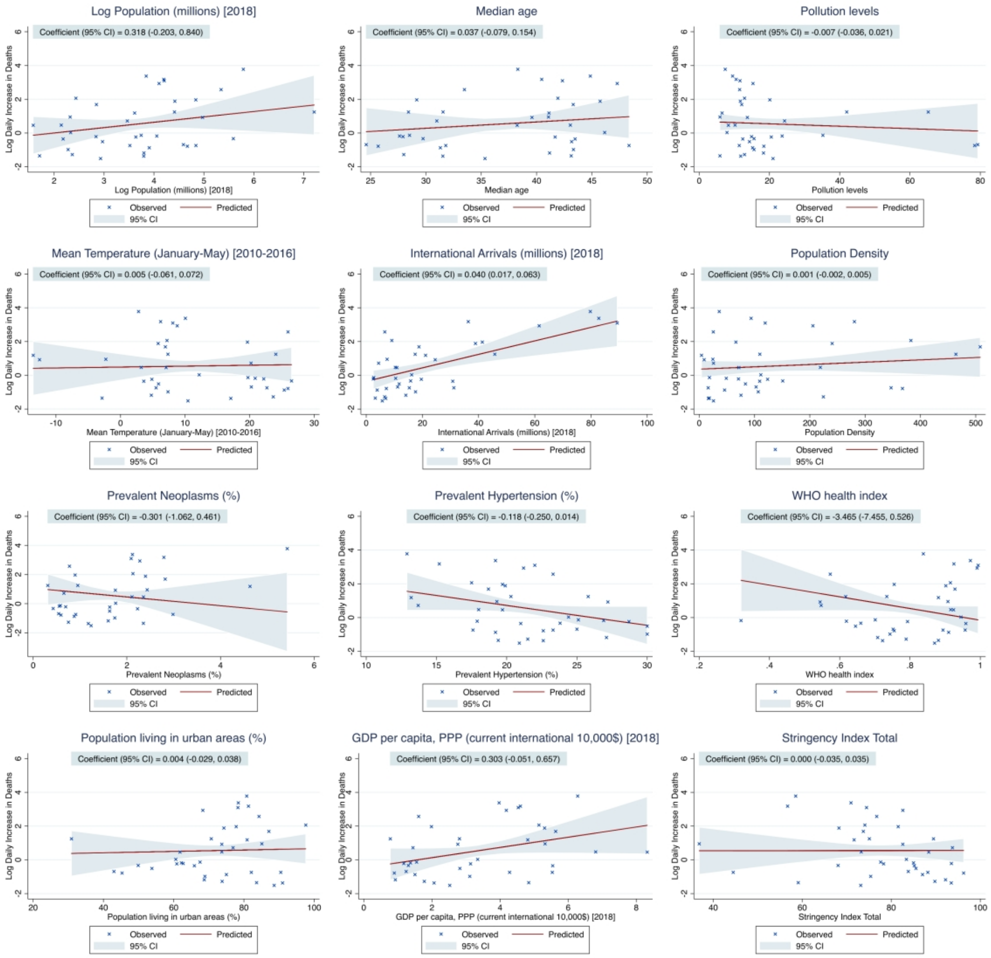
Figure 3. Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of each country-level predictor included in the multivariable model.



388x282mm (72 x 72 DPI)



388x282mm (72 x 72 DPI)



1165x1129mm (72 x 72 DPI)

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

Log Mean Mortality Rate (daily increase in deaths) [up to 08/06/20]	Population (millions) [2018]	Log Population (millions) [2018]	Median age	Pollution levels
-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: 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

Population living in urban areas (%)	GDP per capita, PPP (current international 10,000$) [2018]	Mean Stringency Index
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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

*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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042034.R1
Article Type:	Original research
Date Submitted by the Author:	28-Dec-2020
Complete List of Authors:	Pana, Tiberiu; University of Aberdeen, Bhattacharya, Sohinee; University of Aberdeen Gamble, David; University of Aberdeen Pasdar, Zahra; University of Aberdeen Szlachetka, Weronika; University of Aberdeen Perdomo-Lampignano, Jesus; University of Aberdeen Ewers, Kai; University of Aberdeen McLernon, David; University of Aberdeen Myint, Phyo; University of Aberdeen
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health
Keywords:	INFECTIOUS DISEASES, PUBLIC HEALTH, EPIDEMIOLOGY

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

Tiberiu A Pana, MRes[1,†]; Sohinee Bhattacharya, PhD[1, †]; David T Gamble, MBBS[1]; Zahra Pasdar[1]; Weronika A Szlachetka[1]; Jesus A Perdomo-Lampignano, MBChB[1]; Kai D Ewers[1]; David J McLernon, PhD[1]; Phyo K Myint, MD[1,*];

[†]Joint first authors. Authors Pana and Bhattacharya contributed equally

[1]Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, United Kingdom

Correspondence to:
Professor Phyo Kyaw Myint
Room 4:013, Polwarth Building
School of Medicine, Medical Sciences and Nutrition
Foresterhill, Aberdeen
AB25 2ZD,
Scotland, UK.
Tel: +44 (0) 1224 437841,
Mail to: phyo.myint@abdn.ac.uk

Tables 3, Figures 3
Word count: 3929
Abstract word count: 300

ABSTRACT

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

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-May)), co- morbidities (prevalence of diabetes, hypertension and cancer), health system parameters (WHO Health Index and hospital beds per 10,000 population); international arrivals, the stringency index, as a measure of country-level response to COVID-19, BCG vaccination coverage, UV radiation exposure and testing capacity. 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 Arabia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom and the United States.

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

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

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

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 8th of June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.[1] The estimated overall case fatality rate is ~7%, with country-level estimates ranging between 0.5-14%.[2] 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[3] 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,[4] higher population co-morbid burden,[5] smoking,[6] obesity,[7] pollution levels[8] and healthcare system performance.[9] 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.[10] In contrast, lower- and middle-income countries reported much lower COVID-19 incidence and mortality rates.[10] 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 assess the country-level determinants of the severity of the first wave of the COVID-19 pandemic based on currently available evidence using publicly available data and an ecological study design.

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, proportion of population aged 65 and over, average body mass index (BMI), smoking prevalence), economic predictors (gross Domestic Product (GDP) per capita), environmental predictors (pollution levels, mean temperature (January-May) [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), the stringency index (as measure of country level response to the pandemic)[11], exposure to UV radiation (as a proxy for sunlight exposure), BCG vaccination coverage and testing capacity.

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 8th of June 2020 with available data for all chosen determinants were included. A total of 37 countries from 4 continents were included in the analysis: Africa (Algeria, Egypt, South Africa), America (Argentina, Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Mexico, Peru and the

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

Data Sources

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

The data regarding the median population age and population density were extracted from the United Nations World Population Prospects[14] and United Nations Statistics Division, respectively.[15] The data regarding the percentage of the population living in urban areas were extracted from the World Urbanisation Prospects, issued by the United Nations Population Division.[16] Temperature data were extracted from the Climate Change Knowledge Portal from the World Bank Group.[17] Prevalent diabetes, gross domestic product, international arrivals in 2018, and current health expenditure data were extracted from the World Development Indicators (WDI) database, provided by the World Bank Group.[18] Data regarding prevalent cancers, proportion of population aged 65 and over and the total number of COVID-19 tests performed were extracted from the Our World in Data and the Sustainable Development Goals (SDG) tracker,[19, 20] an open-access publication tracking global progress to the United Nations Sustainable Development Goals for global development, adopted in September 2015. Prevalent hypertension, body mass index (BMI), cigarette smoking, ambient air pollution, ultraviolet (UV) radiation and Bacillus Calmette–Guérin (BCG) vaccination data were obtained from the Global Health Observatory (GHO) data repository of the World Health Organization.[21] The world health organisation health index was extracted from the WHO Global Partnership for Education (GPE) paper series published in 2000.[22] Country-level total hospital beds per 10,000 population data were extracted from the World Bank Dataset "World Bank Indicators of Interest to the COVID-19 Outbreak".[23] Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020 were extracted from the Oxford COVID-19 Government Response Tacker (OxCGRT).[11]

Definition of outcome and predictors

Outcome

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

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

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

Determinants

Data on population density were extracted as the country-level population per square kilometre in 2019.[27] Data on ambient air pollution were extracted as the country-level mean concentration of fine particulate matter (PM2.5) measured in 2016.[28] Temperature data were extracted as the mean temperature recorded in each country between January and May using temperature data recorded between 2010 and 2016.[17] Data on International Arrivals were extracted as the total number of country-level international arrivals in 2018.[29]

Data on prevalent diabetes were extracted as the percentage of the population aged 20 to 79 years in 2019.[18] Data on prevalent cancers were extracted as the age-standardized cancer prevalence among both sexes in 2017, expressed as percentages.[30] Data on prevalent hypertension were extracted as the age-standardised percentage of the population over 18 years of age with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in 2015.[31] Data on BMI were extracted as the age-standardised mean body mass index trend estimates for both sexes amongst adults (≥18 years) in 2016.[32] Data on daily cigarette smoking were extracted as the age-standardised smoking rate across both sexes amongst adults (≥18 years) in 2013.[33] Whilst the definition of "daily cigarette smoking" varies across surveys, it habitually refers to current smoking of cigarettes at least once a day.[33]

Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in current international dollars in 2018.[34] The percentage of population living in urban areas was defined as the percentage of de facto population living in areas classified as urban according to the criteria used by each area or country.[16] The World Health Organisation (WHO) health index is a composite index that aims to evaluate a given countries healthcare system performance relative to the maximum it could achieve given its level of resources and non-healthcare system determinants. It was calculated in the year 2000. The index uses five weighted parameters: overall or average disability-adjusted life expectancy (25%), distribution or equality of disability-adjusted life expectancy (25%), overall or average healthcare system responsiveness (including speed of provision and quality of amenities; 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare expenditure (25%). Data on hospital beds per 10,000 population were defined by the World Bank as including 'inpatient beds available in public, private, general, and specialized hospitals and rehabilitation centres'. The published data for countries included was from 2000 to 2017. In most cases beds for both acute and chronic care are included.[23] The Stringency Index is an overall indicator of public health measures adopted by each country in response to the COVID-19 pandemic and includes containment and closure indicators (school closures, workplace closures, cancelling public events, restrictions on gatherings, public transport closures, stay-at-home requirements, restrictions on internal movements, international travel controls), economic response indicators (income support, debt/contract relief, fiscal measures, international support) as well as health systems indicators (public information campaigns, testing policy, contact tracing, emergency investment in healthcare, investment in vaccines).[11] The mean daily Stringency Index was calculated for each country between 31/12/2019 and until either the mortality curve reached a peak value or the 8th of June 2020, whichever occurred first.

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

Statistical analysis

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

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

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).

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]
High Mean Mortality Rate		
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
Medium Mean Mortality Rate		
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
Low Mean Mortality Rate		
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

Table 2 details the results of the linear regression analyses. The following country-level predictors showed a statistically significant relationship with log mean mortality rate at univariable level: natural logarithm of population, international arrivals, prevalent neoplasms, prevalent hypertension, GDP per capita and BCG vaccination coverage. Upon multivariable adjustment, International arrivals in 2018, as a marker of global connection, was the main statistically significant predictor of log mean mortality rate (0.040 (0.017, 0.063) for 1 million increase in international arrivals, P =0.002) along with mean BCG vaccination coverage (-0.018 (-0.034, -0.002) for 1% increase in BCG vaccination coverage, P =0.031) . Figures 2 and 3 detail the relationship between the country-level log mean mortality rate (predicted and observed) and each country-level predictor included in the multivariable regression model.

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]	**0.432 (0.050, 0.814)**	**0.033**	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]	**0.049 (0.033, 0.064)**	**<0.001**	**0.033 (0.012, 0.054)**	**0.003**
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]	**0.614 (0.209, 1.019)**	**0.005**	-0.404 (-1.079, 0.271)	0.227
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	**-0.150 (-0.254, -0.045)**	**0.008**	-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]	**0.280 (0.037, 0.524)**	**0.030**	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)	**-0.027 (-0.037, -0.016)**	**<0.001**	**-0.018 (-0.034, -0.002)**	**0.031**
Mean Daily Stringency Index	-0.036 (-0.072, 0.001)	0.057	0.004 (-0.028, 0.037)	0.790

R^2 for multivariable linear regression = 0.8031

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-Calmette-Guerin

Table 3 details the results of the secondary linear regression analyses, including only countries having reported COVID-19 testing data up to the 8th of June 2020. The following country-level predictors showed a statistically significant relationship with log mean mortality rate at univariable level: natural logarithm of population, international arrivals, prevalent neoplasms, prevalent hypertension, BCG vaccination coverage and total COVID-19 tests per 1000 population performed until the 8th of June 2020. Upon multivariable adjustment, the statistically significant predictors of log mean mortality rate were: international arrivals in 2018 (0.036 (0.008, 0.063) for 1 million increase in international arrivals, *P* =0.013), prevalent hypertension (-0.129 (-0.246,-0.012) for 1% increase in country-level hypertension prevalence, *P* =0.032) and testing capacity (0.018 (0.001, 0.034) for 1 per 1000 population increase in the number of total COVID-19 tests performed until the 8th of June 2020, *P* =0.039).

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 8th 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)	*P* value	Coefficient (95% CI)	*P* value
Natural logarithm of population (10 million increase) [2018]	**0.419 (0.038, 0.800)**	**0.040**	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]	**0.059 (0.039, 0.079)**	**<0.001**	**0.036 (0.008, 0.063)**	**0.013**
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]	**0.582 (0.177, 0.987)**	**0.009**	-0.391 (-1.014, 0.233)	0.203
Median BMI	0.107 (-0.205, 0.419)	0.507	-	-
Prevalent Hypertension (%), [2015]	**-0.140 (-0.240, -0.039)**	**0.011**	**-0.129 (-0.246, -0.012)**	**0.032**
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)	**-0.028 (-0.039, -0.017)**	**<0.001**	-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	**0.024 (0.008, 0.039)**	**0.007**	**0.018 (0.001, 0.034)**	**0.039**

(up to the 8th of June 2020)				

R^2 for multivariable linear regression = 0.8373

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-Calmette-Guerin

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 19 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 main predictor that reached statistical significance was international arrivals, a proxy of global connection: increases in international arrivals were associated with higher mean mortality rate. Furthermore, country-level BCG vaccination coverage was associated with decreases in the COVID-19 mean mortality rate during the first wave of the pandemic. Finally, in our secondary analyses including only country with available testing capacity data, the total number of COVID-19 tests performed per 1000 population until the 8th of June 2020 was associated with increases in the COVID-19 mean mortality rate.

Comparison with previous literature

A previous ecological study analysed the country-level predictors of the COVID-19 case fatality rate including 65 countries.[3] 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.[3] 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.[24] Associations have also been reported between airline travel and spread of the H1N1 influenza virus infection.[36]

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.[5] We thus accounted for country-level data on a selection of key comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI ≥40kg/m2 has been identified as an independent risk factor for severe COVID-19 illness.[7] Finally, a recent systematic review on 5 studies from China showed that smoking is likely associated with negative outcomes and progression of COVID-19.[6]

Interpretation of findings.

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

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

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

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

Our analyses also revealed a few surprising findings: the intensity of COVID-19 testing was apparently associated with mean mortality rate increases while the country-level prevalence of hypertension was apparently associated with mean mortality rate decreases. These findings appear to be contradictory to previous evidence suggesting that testing intensity may be associated with decreased COVID-19 mortality,[48] while hypertension was clearly associated with increased mortality.[49] These surprising findings need to be interpreted in the light of our ecological study design in which residual confounders may influence these associations.

Strengths and Limitations.

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

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

CONCLUSION

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

CONTRIBUTORSHIP

PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP and KDE 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.

ACKNOWLEDGEMENTS

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

CONFLICTS OF INTEREST

None.

FUNDING

None.

DATA SHARING STATEMENT

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

REFERENCES

1. World Health Orgainzation. Coronavirus disease (COVID-19) Situation Report – 140. *WHO*. 2020;140:1.

2. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Mortality Risk of COVID-19. https://ourworldindata.org/mortality-risk-covid. Accessed 05/7, 2020.

3. Kenyon C. Flattening-the-curve associated with reduced COVID-19 case fatality rates- an ecological analysis of 65 countries. *J Infect*. 2020. doi: S0163-4453(20)30215-2 [pii].

4. Dowd JB, Andriano L, Brazel DM, et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. *Proc Natl Acad Sci U S A*. 2020;117(18):9696-9698. doi: 10.1073/pnas.2004911117 [doi].

5. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*. 2020. doi: 2000547 [pii].

6. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020;18:20. doi: 10.18332/tid/119324 [doi].

7. Flint SW, Tahrani AA. COVID-19 and obesity-lack of clarity, guidance, and implications for care. *The Lancet.Diabetes & Endocrinology*. 2020. doi: 10.1016/S2213-8587(20)30156-X.

8. Ogen Y. Assessing nitrogen dioxide (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ*. 2020;726:138605. doi: S0048-9697(20)32121-5 [pii].

9. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. *Lancet Glob Health*. 2020;8(4):e480-109X(20)30068-1. Epub 2020 Feb 25. doi: S2214-109X(20)30068-1 [pii].

10. World Health Organization. Coronavirus disease (COVID-19) Situation Report–108. 2020;108:5-6-14.

11. Hale T, Sam W, Petherick A, Phillips T, Kira B. Oxford COVID-19 Government Response Tracker, Blavatnik School of Government. https://www.bsg.ox.ac.uk/research/research-projects/coronavirus-government-response-tracker. Accessed 06/10, 2020.

12. European Centre for Disease Prevention and Control. Download today's data on the geographic distribution of COVID-19 cases worldwide. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 06/10, 2020.

13. European Centre for Disease Prevention and Control. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 05/01, .

14. United Nations. Department of Economic and Social Affairs Population Dynamics. https://population.un.org/wpp/DataQuery/. Accessed 05/07, .

15. United Nations Statistics Division. Population density and urbanization. https://unstats.un.org/unsd/demographic/sconcerns/densurb/. Accessed 05/07, 2020.

16. United Nations. World Urbanization Prospects 2018. https://population.un.org/wup/. Accessed 04/20, 2020.

17. World Bank Group Climate Change Knowledge Portal. Climate Data. https://climateknowledgeportal.worldbank.org/watershed/161/climate-data-historical. Accessed 04/30, 2020.

18. The World Bank Group. Data Bank, World Development Indicators. https://databank.worldbank.org/reports.aspx?source=2&series=SH.STA.DIAB.ZS&country=#dbMetadata. Accessed 04, 2020.

19. Roser M, Ortiz-Ospina. Measuring progress towards the Sustainable Development Goals. https://sdg-tracker.org/. Accessed 05/05, 2020.

20. Ritchie H. Coronavirus Source Data. https://ourworldindata.org/coronavirus-source-data. Accessed 12/21, 2020.

21. World Health Organization. Global Health Observatory indicator views. https://apps.who.int/gho/data/node.imr. Accessed 04/20, 2020.

22. Tandon A, Murray CJL, Lauer JA, Evans D. Measuring overall health system performance for 191 countries. *World Health Organization*. 2000(30):18-19-21.

23. The Humanitarian Data Exchange. World Bank Indicators of Interest to the COVID-19 Outbreak. https://data.humdata.org/dataset/world-bank-indicators-of-interest-to-the-covid-19-outbreak#metadata-0. Accessed 04/20, 2020.

24. Nikolopoulos G, Bagos P, Lytras T, Bonovas S. An ecological study of the determinants of differences in 2009 pandemic influenza mortality rates between countries in Europe. *PLoS One*. 2011;6(5):e19432. doi: 10.1371/journal.pone.0019432 [doi].

25. Garcia-Basteiro AL, Chaccour C, Guinovart C, et al. Monitoring the COVID-19 epidemic in the context of widespread local transmission. *Lancet Respir Med*. 2020;8(5):440-442. doi: S2213-2600(20)30162-4 [pii].

26. Barmparis GD, Tsironis GP. Estimating the infection horizon of COVID-19 in eight countries with a data-driven approach. *Chaos Solitons Fractals*. 2020:109842. doi: 10.1016/j.chaos.2020.109842 [doi].

27. United Nations Department of Economics and Social Affairs. World Population Prospects 2019. https://population.un.org/wpp/Download/Standard/Population/. Accessed 04/20, 2020.

28. World Health Organization. Annual mean concentration of particulate matter of less than 2.5 microns of diameter (PM2.5) [ug/m3] in urban areas. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4674. Accessed 04/20, 2020.

29. The World Bank. International tourism, number of arrivals. https://data.worldbank.org/indicator/ST.INT.ARVL?view=map. Accessed 04/20, 2020.

30. Our World in Data. Cancer. https://ourworldindata.org/cancer. Accessed 04, 2020.

31. World Health Organization. Prevalence of raised blood pressure (SBP≥140 OR DBP≥90). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2386. Accessed 5, 2020.

32. World Health Organization. Mean BMI (kg/m²) (age-standardized estimate). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2388. Accessed 04/05/2020, 2020.

33. World Health Organization. Daily smoking of cigarettes (age-standardized rate). https://www.who.int/data/gho/data/indicators/indicator-details/GHO/daily-cigarette-smoking-age-standardised. Accessed 04/05/2020, 2020.

34. The World Bank. GDP Per Capita, PPP (current international $). https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?view=chart. Accessed 04/20, 2020.

35. Bonjour S. Average daily ambient ultraviolet radiation (UVR) level. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2395. Accessed 12/21, 2020.

36. Khan K, Arino J, Hu W, et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med*. 2009;361(2):212-214. doi: 10.1056/NEJMc0904559 [doi].

37. World Health Organization. WHO interim protocol: rapid operations to contain the initial emergence of pandemic influenza. *WHO*. 2007:1.

38. World Health Organization. Pandemic influenza preparedness and response, WHO guidance document. *WHO*. 2009:1.

39. Mateus AL, Otete HE, Beck CR, Dolan GP, Nguyen-Van-Tam JS. Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review. *Bull World Health Organ*. 2014;92(12):868-880D. doi: 10.2471/BLT.14.135590 [doi].

40. Lee VJ, Lye DC, Wilder-Smith A. Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies. *BMC Med*. 2009;7:76-7015-7-76. doi: 10.1186/1741-7015-7-76 [doi].

41. World Health Organization. COVID-19 Strategic Preparedness and Response Plan; Operational Planning Guidelines to Support Country Preparedness and Response. *WHO*. 2020:1.

42. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report–1. 2020;1:4.

43. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. *Lancet*. 2020;395(10236):1545-1546. doi: S0140-6736(20)31025-4 [pii].

44. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci U S A*. 2020;117(30):17720-17726. doi: 10.1073/pnas.2008410117 [doi].

45. MacLean E. Universal BCG vaccination and protection against COVID-19: critique of an ecological study. https://naturemicrobiologycommunity.nature.com/posts/64892-universal-bcg-vaccination-and-protection-against-covid-19-critique-of-an-ecological-study. Accessed 12/21, 2020.

46. Curtis N. BCG Vaccination to Protect Healthcare Workers Against COVID-19 Status: Recruiting. https://clinicaltrials.gov/ct2/show/NCT04327206?term=BCG+Vaccination+to+Protect+Healthcare+Workers+Against+COVID-19+%28BRACE%29&id=NCT04327206&draw=2&rank=1. Accessed 12/21, 2020.

47. Bonten M. Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine Status: Active, not recruiting.

https://clinicaltrials.gov/ct2/show/NCT04328441?term=Reducing+Health+Care+Workers+Absenteeism+in+Covid-19+Pandemic+Through+BCG+Vaccine+AND+BCG-CORONA&draw=2&rank=1. Accessed 12/21, 2020.

48. Di Bari M, Balzi D, Carreras G, Onder G. Extensive Testing May Reduce COVID-19 Mortality: A Lesson From Northern Italy. *Front Med (Lausanne)*. 2020;7:402. doi: 10.3389/fmed.2020.00402 [doi].

49. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J*. 2020;41(22):2058-2066. doi: 10.1093/eurheartj/ehaa433 [doi].

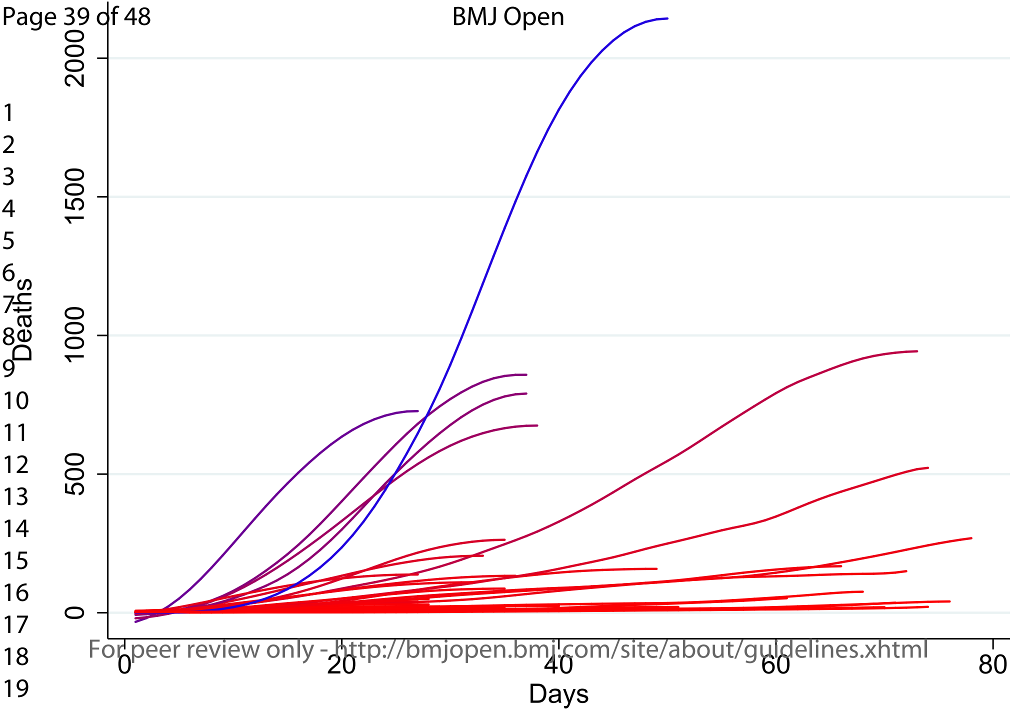
FIGURE LEGENDS

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.

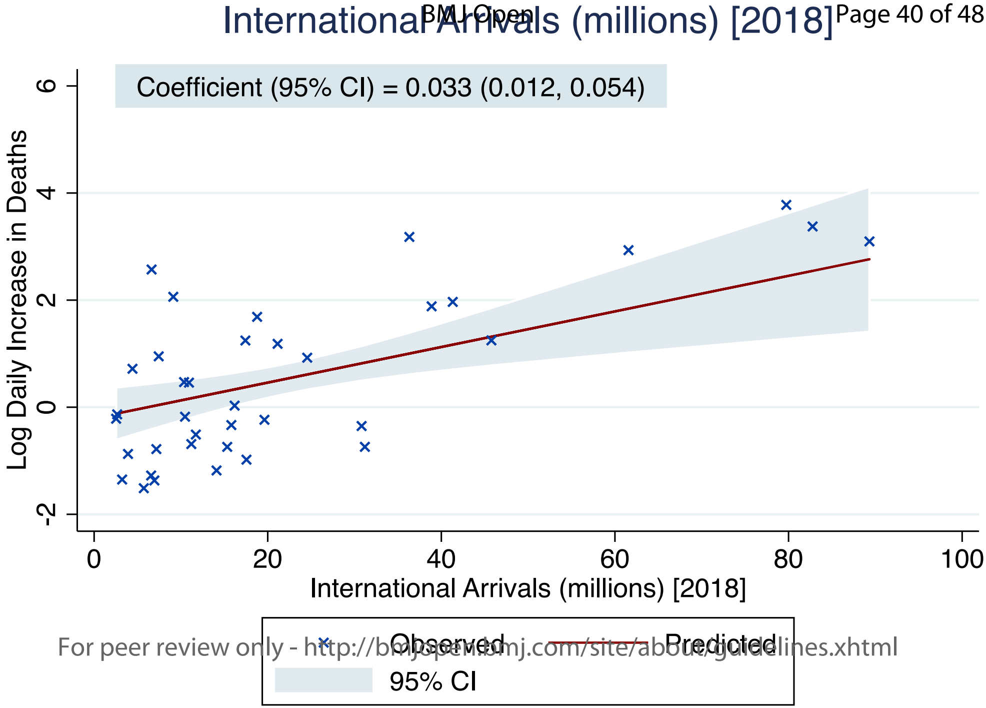
*smoothed using a local regression (lowess) function with a bandwidth of 0.4

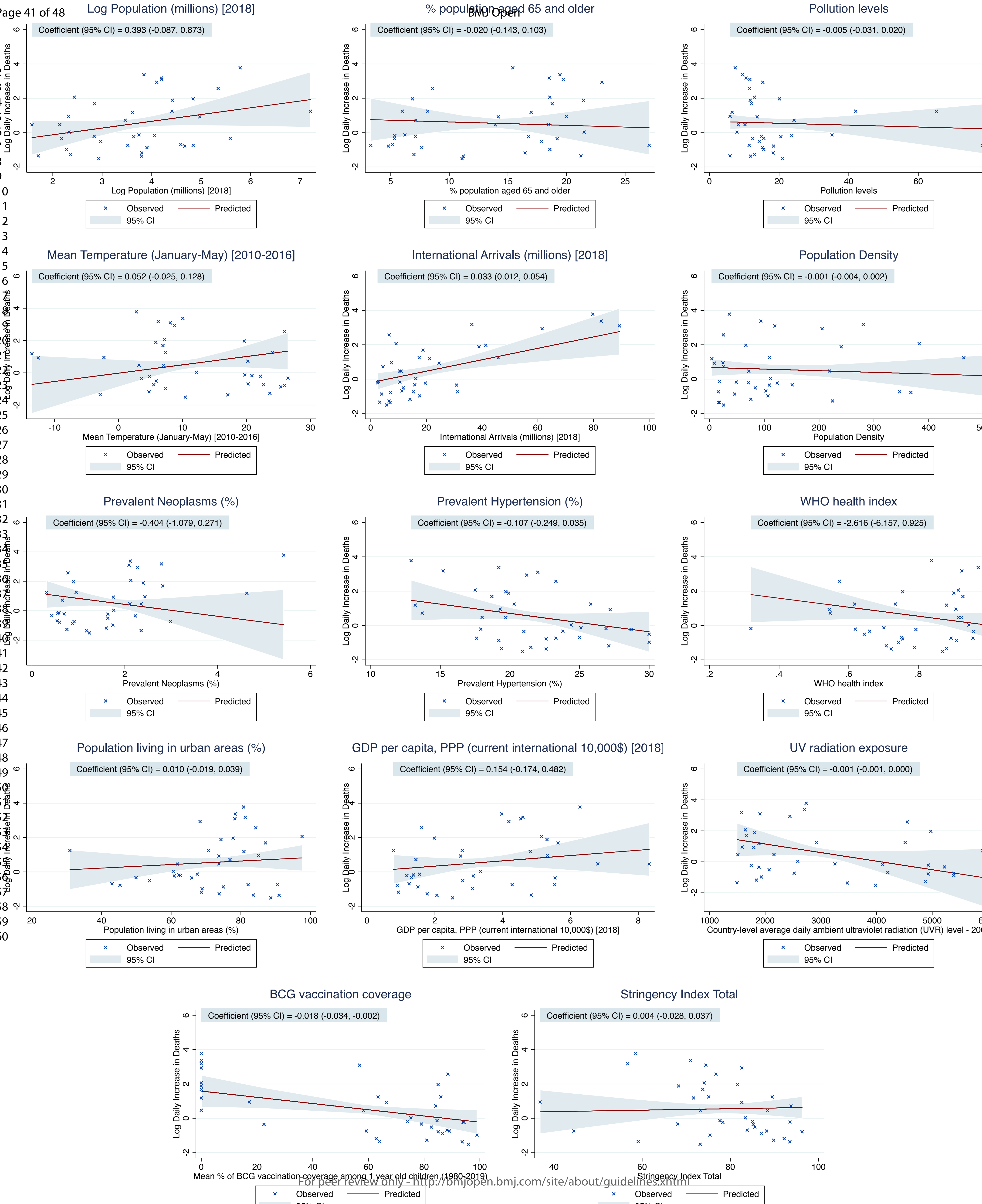
Figure 2. Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions). The solid red line represents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



Deaths
2000
1500
1000
500
0
0
20
40
60
80
Days


International Arrivals (millions) [2018]
Coefficient (95% CI) = 0.033 (0.012, 0.054)
Log Daily Increase in Deaths
-2
0
2
4
6
0
20
40
60
80
100
International Arrivals (millions) [2018]
Observed
Predicted
95% CI


Log Population (millions) [2018]
Coefficient (95% CI) = 0.393 (-0.087, 0.873)
% population aged 65 and older
Coefficient (95% CI) = -0.020 (-0.143, 0.103)
Pollution levels
Coefficient (95% CI) = -0.005 (-0.031, 0.020)
Mean Temperature (January-May) [2010-2016]
Coefficient (95% CI) = 0.052 (-0.025, 0.128)
International Arrivals (millions) [2018]
Coefficient (95% CI) = 0.033 (0.012, 0.054)
Population Density
Coefficient (95% CI) = -0.001 (-0.004, 0.002)
Prevalent Neoplasms (%)
Coefficient (95% CI) = -0.404 (-1.079, 0.271)
Prevalent Hypertension (%)
Coefficient (95% CI) = -0.107 (-0.249, 0.035)
WHO health index
Coefficient (95% CI) = -2.616 (-6.157, 0.925)
Population living in urban areas (%)
Coefficient (95% CI) = 0.010 (-0.019, 0.039)
GDP per capita, PPP (current international 10,000$) [2018]
Coefficient (95% CI) = 0.154 (-0.174, 0.482)
UV radiation exposure
Coefficient (95% CI) = -0.001 (-0.001, 0.000)
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004
BCG vaccination coverage
Coefficient (95% CI) = -0.018 (-0.034, -0.002)
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)
Stringency Index Total
Coefficient (95% CI) = 0.004 (-0.028, 0.037)
Log Daily Increase in Deaths
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 Republi	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

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

*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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042034.R2
Article Type:	Original research
Date Submitted by the Author:	16-Jan-2021
Complete List of Authors:	Pana, Tiberiu; University of Aberdeen, Bhattacharya, Sohinee; University of Aberdeen Gamble, David; University of Aberdeen Pasdar, Zahra; University of Aberdeen Szlachetka, Weronika; University of Aberdeen Perdomo-Lampignano, Jesus; University of Aberdeen Ewers, Kai; University of Aberdeen McLernon, David; University of Aberdeen Myint, Phyo; University of Aberdeen
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health
Keywords:	INFECTIOUS DISEASES, PUBLIC HEALTH, EPIDEMIOLOGY

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

Tiberiu A Pana, MRes[1,†]; Sohinee Bhattacharya, PhD[1, †]; David T Gamble, MBBS[1]; Zahra Pasdar[1]; Weronika A Szlachetka[1]; Jesus A Perdomo-Lampignano, MBChB[1]; Kai D Ewers[1]; David J McLernon, PhD[1]; Phyo K Myint, MD[1,*];

[†]Joint first authors. Authors Pana and Bhattacharya contributed equally

[1]Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, United Kingdom

Correspondence to:
Tiberiu Alexandru Pana
Room 1.130, Polwarth Building
School of Medicine, Medical Sciences and Nutrition
Foresterhill, Aberdeen
AB25 2ZD,
Scotland, UK.
Mail to: tiberiupana12@gmail.com

Tables 3, Figures 3
Word count: 4090
Abstract word count: 300

ABSTRACT

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

Design: Ecological study of publicly available data. 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-May)), co- morbidities (prevalence of diabetes, hypertension and cancer), health system parameters (WHO Health Index and hospital beds per 10,000 population); international arrivals, the stringency index, as a measure of country-level response to COVID-19, BCG vaccination coverage, UV radiation exposure and testing capacity. 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 Arabia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom and the United States.

Results: Of all country-level determinants included in the multivariable model, total number of international arrivals (beta 0.033 (95% Confidence Interval 0.012,0.054)) and BCG vaccination coverage (-0.018 (-0.034,-0.002)), were significantly associated with the natural logarithm of the mean death rate.

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

ARTICLE SUMMARY

Strengths and limitations

- A 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 8th of June 2020, there have been over 400,857 deaths related to COVID-19 infection worldwide.[1] The estimated overall case fatality rate is ~7%, with country-level estimates ranging between 0.5-14%.[2] 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 determinants of the severity of the COVID-19 pandemic including data on 65 countries[3] 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,[4] higher population co-morbid burden,[5] smoking,[6] obesity,[7] pollution levels[8] and healthcare system performance.[9] Furthermore, countries outside China most severely hit by the first wave of 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.[10] In contrast, lower- and middle-income countries reported much lower COVID-19 incidence and mortality rates.[10] 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 assess the country-level determinants of the severity of the first wave of the COVID-19 pandemic based on currently available evidence using publicly available data and an ecological study design.

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 determinants (population and population density, percentage population living in urban areas, proportion of population aged 65 and over, average body mass index (BMI), smoking prevalence), economic determinants (gross Domestic Product (GDP) per capita), environmental determinants (pollution levels, mean temperature (January-May) [2010-2016]), prevalent co-morbidities (diabetes, hypertension and cancer), health systems determinants (WHO Health Index and hospital beds per 10,000 population), international arrivals (as a proxy measure of the globalisation status of each country), the stringency index (as measure of country level response to the pandemic)[11], exposure to UV radiation (as a proxy for sunlight exposure), BCG vaccination coverage and testing capacity.

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 8th of June 2020 with available data for all chosen determinants were included. A total of 37 countries from 4 continents were included in the analysis: Africa (Algeria, Egypt, South Africa), America (Argentina, Brazil, Canada, Chile, Colombia, the Dominican Republic, Ecuador, Mexico, Peru and the

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

Data Sources

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

The data regarding the median population age and population density were extracted from the United Nations World Population Prospects[14] and United Nations Statistics Division, respectively.[15] The data regarding the percentage of the population living in urban areas were extracted from the World Urbanisation Prospects, issued by the United Nations Population Division.[16] Temperature data were extracted from the Climate Change Knowledge Portal from the World Bank Group.[17] Prevalent diabetes, gross domestic product, international arrivals in 2018, and current health expenditure data were extracted from the World Development Indicators (WDI) database, provided by the World Bank Group.[18] Data regarding prevalent cancers, proportion of population aged 65 and over and the total number of COVID-19 tests performed were extracted from the Our World in Data and the Sustainable Development Goals (SDG) tracker,[19, 20] an open-access publication tracking global progress to the United Nations Sustainable Development Goals for global development, adopted in September 2015. Prevalent hypertension, body mass index (BMI), cigarette smoking, ambient air pollution, ultraviolet (UV) radiation and Bacillus Calmette–Guérin (BCG) vaccination data were obtained from the Global Health Observatory (GHO) data repository of the World Health Organization.[21] The world health organisation health index was extracted from the WHO Global Partnership for Education (GPE) paper series published in 2000.[22] Country-level total hospital beds per 10,000 population data were extracted from the World Bank Dataset "World Bank Indicators of Interest to the COVID-19 Outbreak".[23] Daily Stringency Index (SI) measurements between 31/01/2019-08/06/2020 were extracted from the Oxford COVID-19 Government Response Tacker (OxCGRT).[11]

Definition of outcome and determinants

Outcome

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

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

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

Determinants

Data on population density were extracted as the country-level population per square kilometre in 2019.[27] Data on ambient air pollution were extracted as the country-level mean concentration of fine particulate matter (PM2.5) measured in 2016.[28] Temperature data were extracted as the mean temperature recorded in each country between January and May using temperature data recorded between 2010 and 2016.[17] Data on International Arrivals were extracted as the total number of country-level international arrivals in 2018.[29]

Data on prevalent diabetes were extracted as the percentage of the population aged 20 to 79 years in 2019.[18] Data on prevalent cancers were extracted as the age-standardized cancer prevalence among both sexes in 2017, expressed as percentages.[30] Data on prevalent hypertension were extracted as the age-standardised percentage of the population over 18 years of age with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in 2015.[31] Data on BMI were extracted as the age-standardised mean body mass index trend estimates for both sexes amongst adults (≥18 years) in 2016.[32] Data on daily cigarette smoking were extracted as the age-standardised smoking rate across both sexes amongst adults (≥18 years) in 2013.[33] Whilst the definition of "daily cigarette smoking" varies across surveys, it habitually refers to current smoking of cigarettes at least once a day.[33]

Data on GDP were extracted as GDP per capita by Purchasing Power Parity (PPP) in current international dollars in 2018.[34] The percentage of population living in urban areas was defined as the percentage of de facto population living in areas classified as urban according to the criteria used by each area or country.[16] The World Health Organisation (WHO) health index is a composite index that aims to evaluate a given countries healthcare system performance relative to the maximum it could achieve given its level of resources and non-healthcare system determinants. It was calculated in the year 2000. The index uses five weighted parameters: overall or average disability-adjusted life expectancy (25%), distribution or equality of disability-adjusted life expectancy (25%), overall or average healthcare system responsiveness (including speed of provision and quality of amenities; 12.5%), distribution or equality of healthcare system responsiveness (12.5%) and healthcare expenditure (25%). Data on hospital beds per 10,000 population were defined by the World Bank as including 'inpatient beds available in public, private, general, and specialized hospitals and rehabilitation centres'. The published data for the included countries was between 2000 and 2017. In most cases beds for both acute and chronic care were included.[23] The Stringency Index is an overall indicator of public health measures adopted by each country in response to the COVID-19 pandemic and includes containment and closure indicators (school closures, workplace closures, cancelling public events, restrictions on gatherings, public transport closures, stay-at-home requirements, restrictions on internal movements, international travel controls), economic response indicators (income support, debt/contract relief, fiscal measures, international support) as well as health system indicators (public information campaigns, testing policy, contact tracing, emergency investment in healthcare, investment in vaccines).[11] The mean daily Stringency Index was calculated for each country between 31/12/2019 and until either the mortality curve reached a peak value or the 8th of June 2020, whichever occurred first.

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

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

Statistical analysis

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

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

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).

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]**
High Mean Mortality Rate		
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
Medium Mean Mortality Rate		
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
Low Mean Mortality Rate		
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

COVID-19 – Coronarvirus disease 2019

Table 2 details the results of the linear regression analyses. The following country-level determinants showed a statistically significant relationship with log mean mortality rate in univariable analyses: natural logarithm of population, international arrivals, prevalent neoplasms, prevalent hypertension, GDP per capita and BCG vaccination coverage. Upon multivariable adjustment, International arrivals in 2018, as a marker of global connection, was significantly associated with an increase in the log mean mortality rate (0.033 (0.012, 0.054) per 1 million increase in international arrivals, *P* =0.003). This translates to an exp(B) of 1.034, equivalent to a 3.4% increase in the mean mortality rate for every 1 million increase in the number of international arrivals in 2018. Furthermore, the mean BCG vaccination coverage was associated with a decrease in log mean mortality rate (-0.018 (-0.034, -0.002) per 1% increase in BCG vaccination coverage, *P* =0.031). This translates to an exp(B) of 0.982, equivalent to a 1.8% decrease in mean mortality rate for every 1% increase in BCG vaccination coverage. Figures 2 and 3 detail the relationship between the country-level log mean mortality rate (predicted and observed) and each country-level determinant included in the multivariable regression model.

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]	**0.432 (0.050, 0.814)**	**0.033**	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]	**0.049 (0.033, 0.064)**	**<0.001**	**0.033 (0.012, 0.054)**	**0.003**
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]	**0.614 (0.209, 1.019)**	**0.005**	-0.404 (-1.079, 0.271)	0.227
Median BMI	0.010 (-0.297, 0.318)	0.947	-	-
Prevalent Hypertension (%), [2015]	**-0.150 (-0.254, -0.045)**	**0.008**	-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]	**0.280 (0.037, 0.524)**	**0.030**	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)	**-0.027 (-0.037, -0.016)**	**<0.001**	**-0.018 (-0.034, -0.002)**	**0.031**
Mean Daily Stringency Index	-0.036 (-0.072, 0.001)	0.057	0.004 (-0.028, 0.037)	0.790

R^2 for multivariable linear regression = 0.8031

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-Calmette-Guerin

Table 3 details the results of the secondary linear regression analyses, including only countries having reported COVID-19 testing data up to the 8th of June 2020. The following country-level determinants showed a statistically significant relationship with log mean mortality rate at univariable level: natural logarithm of population, international arrivals, prevalent neoplasms, prevalent hypertension, BCG vaccination coverage and total COVID-19 tests per 1000 population performed until the 8th of June 2020. Upon multivariable adjustment, the statistically significant determinants of log mean mortality rate were: international arrivals in 2018 (0.036 (0.008, 0.063) per 1 million increase in international arrivals, *P* =0.013), prevalent hypertension (-0.129 (-0.246,-0.012) per 1% increase in country-level hypertension prevalence, *P* =0.032) and testing capacity (0.018 (0.001, 0.034) for 1 per 1000 population increase in the number of total COVID-19 tests performed until the 8th of June 2020, *P* =0.039).

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 8th 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)	*P* value	Coefficient (95% CI)	*P* value
Natural logarithm of population (10 million increase) [2018]	**0.419 (0.038, 0.800)**	**0.040**	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]	**0.059 (0.039, 0.079)**	**<0.001**	**0.036 (0.008, 0.063)**	**0.013**
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]	**0.582 (0.177, 0.987)**	**0.009**	-0.391 (-1.014, 0.233)	0.203
Median BMI	0.107 (-0.205, 0.419)	0.507	-	-
Prevalent Hypertension (%), [2015]	**-0.140 (-0.240, -0.039)**	**0.011**	**-0.129 (-0.246, -0.012)**	**0.032**
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)	**-0.028 (-0.039, -0.017)**	**<0.001**	-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	**0.024 (0.008, 0.039)**	**0.007**	**0.018 (0.001, 0.034)**	**0.039**

(up to the 8th of June 2020)				

R^2 for multivariable linear regression = 0.8373

BMI – body mass index; WHO – world health organisation; GDP – gross domestic product; PPP – purchasing power parity; BCG – Bacille-Calmette-Guerin

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 19 country-level socioeconomic, environmental, health and healthcare system, and globalisation parameters as potential determinants of the death rates associated with COVID-19. In the multivariable linear regression model, the main determinant that reached statistical significance was international arrivals, a proxy of global connection: a 1 million increase in the number of international arrivals in 2018 was associated with a 3.4% increase in the mean daily increase in COVID-19 deaths during the ascending phase of the first wave of the pandemic. Furthermore, country-level BCG vaccination coverage was associated with decreases in the COVID-19 mean mortality rate during the first wave of the pandemic. Finally, in our secondary analyses including only country with available testing capacity data, the total number of COVID-19 tests performed per 1000 population until the 8th of June 2020 was also associated with increases in the COVID-19 mean mortality rate.

Comparison with previous literature

A previous ecological study analysed the country-level determinants of the COVID-19 case fatality rate including 65 countries.[3] 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.[3] Nevertheless, no other country-level determinants 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.[24] Associations have also been reported between airline travel and spread of the H1N1 influenza virus infection.[36]

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.[5] We thus accounted for country-level data on a selection of key comorbidities which included prevalent diabetes mellitus, neoplasms, and hypertension. BMI ≥40kg/m2 has been identified as an independent risk factor for severe COVID-19 illness.[7] Finally, a recent systematic review on 5 studies from China showed that smoking is likely associated with negative outcomes and progression of COVID-19.[6]

Interpretation of findings.

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

The WHO recommendations for pandemic preparedness and resilience suggest that points of entry into the country should be monitored by focussing on surveillance and risk communication to travellers but falls short of closing down international travel.[41] Interestingly, during the COVID-19 pandemic, some countries such as Thailand have adopted aggressive international travel screening and isolation policies, which may have led to lower infection rates.[42] Our study suggests that travel restrictions have the potential to influence the impact of the COVID-19 pandemic and should be considered as part of a structured and rapidly instigated pandemic preparedness plan.

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

Our analyses also revealed a few surprising findings: the intensity of COVID-19 testing was apparently associated with mean mortality rate increases while the country-level prevalence of hypertension was apparently associated with mean mortality rate decreases. These findings appear to be contradictory to previous evidence suggesting that testing intensity may be associated with decreased COVID-19 mortality,[48] while hypertension was clearly associated with increased mortality.[49] These surprising findings need to be interpreted in the light of our ecological study design in which residual confounders may influence these associations.

Strengths and Limitations.

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

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

CONCLUSION

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

CONTRIBUTORSHIP

PKM and SB conceived the idea. TAP, DTG, ZP, WAS, JAP and KDE 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.

ACKNOWLEDGEMENTS

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

CONFLICTS OF INTEREST

None.

FUNDING

This work was supported by the Aberdeen Clinical Academic Training Scheme.

DATA SHARING STATEMENT

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

REFERENCES

1. World Health Orgainzation. Coronavirus disease (COVID-19) Situation Report – 140. *WHO*. 2020;140:1.

2. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Mortality Risk of COVID-19. https://ourworldindata.org/mortality-risk-covid. Accessed 05/7, 2020.

3. Kenyon C. Flattening-the-curve associated with reduced COVID-19 case fatality rates- an ecological analysis of 65 countries. *J Infect*. 2020. doi: S0163-4453(20)30215-2 [pii].

4. Dowd JB, Andriano L, Brazel DM, et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. *Proc Natl Acad Sci U S A*. 2020;117(18):9696-9698. doi: 10.1073/pnas.2004911117 [doi].

5. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*. 2020. doi: 2000547 [pii].

6. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020;18:20. doi: 10.18332/tid/119324 [doi].

7. Flint SW, Tahrani AA. COVID-19 and obesity-lack of clarity, guidance, and implications for care. *The Lancet.Diabetes & Endocrinology*. 2020. doi: 10.1016/S2213-8587(20)30156-X.

8. Ogen Y. Assessing nitrogen dioxide (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ*. 2020;726:138605. doi: S0048-9697(20)32121-5 [pii].

9. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. *Lancet Glob Health*. 2020;8(4):e480-109X(20)30068-1. Epub 2020 Feb 25. doi: S2214-109X(20)30068-1 [pii].

10. World Health Organization. Coronavirus disease (COVID-19) Situation Report–108. 2020;108:5-6-14.

11. Hale T, Sam W, Petherick A, Phillips T, Kira B. Oxford COVID-19 Government Response Tracker, Blavatnik School of Government. https://www.bsg.ox.ac.uk/research/research-projects/coronavirus-government-response-tracker. Accessed 06/10, 2020.

12. European Centre for Disease Prevention and Control. Download today's data on the geographic distribution of COVID-19 cases worldwide. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 06/10, 2020.

13. European Centre for Disease Prevention and Control. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide. Accessed 05/01, .

14. United Nations. Department of Economic and Social Affairs Population Dynamics. https://population.un.org/wpp/DataQuery/. Accessed 05/07, .

15. United Nations Statistics Division. Population density and urbanization. https://unstats.un.org/unsd/demographic/sconcerns/densurb/. Accessed 05/07, 2020.

16. United Nations. World Urbanization Prospects 2018. https://population.un.org/wup/. Accessed 04/20, 2020.

17. World Bank Group Climate Change Knowledge Portal. Climate Data. https://climateknowledgeportal.worldbank.org/watershed/161/climate-data-historical. Accessed 04/30, 2020.

18. The World Bank Group. Data Bank, World Development Indicators. https://databank.worldbank.org/reports.aspx?source=2&series=SH.STA.DIAB.ZS&country=#dbMetadata. Accessed 04, 2020.

19. Roser M, Ortiz-Ospina. Measuring progress towards the Sustainable Development Goals. https://sdg-tracker.org/. Accessed 05/05, 2020.

20. Ritchie H. Coronavirus Source Data. https://ourworldindata.org/coronavirus-source-data. Accessed 12/21, 2020.

21. World Health Organization. Global Health Observatory indicator views. https://apps.who.int/gho/data/node.imr. Accessed 04/20, 2020.

22. Tandon A, Murray CJL, Lauer JA, Evans D. Measuring overall health system performance for 191 countries. *World Health Organization*. 2000(30):18-19-21.

23. The Humanitarian Data Exchange. World Bank Indicators of Interest to the COVID-19 Outbreak. https://data.humdata.org/dataset/world-bank-indicators-of-interest-to-the-covid-19-outbreak#metadata-0. Accessed 04/20, 2020.

24. Nikolopoulos G, Bagos P, Lytras T, Bonovas S. An ecological study of the determinants of differences in 2009 pandemic influenza mortality rates between countries in Europe. *PLoS One*. 2011;6(5):e19432. doi: 10.1371/journal.pone.0019432 [doi].

25. Garcia-Basteiro AL, Chaccour C, Guinovart C, et al. Monitoring the COVID-19 epidemic in the context of widespread local transmission. *Lancet Respir Med*. 2020;8(5):440-442. doi: S2213-2600(20)30162-4 [pii].

26. Barmparis GD, Tsironis GP. Estimating the infection horizon of COVID-19 in eight countries with a data-driven approach. *Chaos Solitons Fractals*. 2020:109842. doi: 10.1016/j.chaos.2020.109842 [doi].

27. United Nations Department of Economics and Social Affairs. World Population Prospects 2019. https://population.un.org/wpp/Download/Standard/Population/. Accessed 04/20, 2020.

28. World Health Organization. Annual mean concentration of particulate matter of less than 2.5 microns of diameter (PM2.5) [ug/m3] in urban areas. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4674. Accessed 04/20, 2020.

29. The World Bank. International tourism, number of arrivals. https://data.worldbank.org/indicator/ST.INT.ARVL?view=map. Accessed 04/20, 2020.

30. Our World in Data. Cancer. https://ourworldindata.org/cancer. Accessed 04, 2020.

31. World Health Organization. Prevalence of raised blood pressure (SBP≥140 OR DBP≥90). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2386. Accessed 5, 2020.

32. World Health Organization. Mean BMI (kg/m²) (age-standardized estimate). https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2388. Accessed 04/05/2020, 2020.

33. World Health Organization. Daily smoking of cigarettes (age-standardized rate). https://www.who.int/data/gho/data/indicators/indicator-details/GHO/daily-cigarette-smoking-age-standardised. Accessed 04/05/2020, 2020.

34. The World Bank. GDP Per Capita, PPP (current international $). https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?view=chart. Accessed 04/20, 2020.

35. Bonjour S. Average daily ambient ultraviolet radiation (UVR) level. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/2395. Accessed 12/21, 2020.

36. Khan K, Arino J, Hu W, et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med*. 2009;361(2):212-214. doi: 10.1056/NEJMc0904559 [doi].

37. World Health Organization. WHO interim protocol: rapid operations to contain the initial emergence of pandemic influenza. *WHO*. 2007:1.

38. World Health Organization. Pandemic influenza preparedness and response, WHO guidance document. *WHO*. 2009:1.

39. Mateus AL, Otete HE, Beck CR, Dolan GP, Nguyen-Van-Tam JS. Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review. *Bull World Health Organ*. 2014;92(12):868-880D. doi: 10.2471/BLT.14.135590 [doi].

40. Lee VJ, Lye DC, Wilder-Smith A. Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies. *BMC Med*. 2009;7:76-7015-7-76. doi: 10.1186/1741-7015-7-76 [doi].

41. World Health Organization. COVID-19 Strategic Preparedness and Response Plan; Operational Planning Guidelines to Support Country Preparedness and Response. *WHO*. 2020:1.

42. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report–1. 2020;1:4.

43. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. *Lancet*. 2020;395(10236):1545-1546. doi: S0140-6736(20)31025-4 [pii].

44. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci U S A*. 2020;117(30):17720-17726. doi: 10.1073/pnas.2008410117 [doi].

45. MacLean E. Universal BCG vaccination and protection against COVID-19: critique of an ecological study. https://naturemicrobiologycommunity.nature.com/posts/64892-universal-bcg-vaccination-and-protection-against-covid-19-critique-of-an-ecological-study. Accessed 12/21, 2020.

46. Curtis N. BCG Vaccination to Protect Healthcare Workers Against COVID-19 Status: Recruiting. https://clinicaltrials.gov/ct2/show/NCT04327206?term=BCG+Vaccination+to+Protect+Healthcare+Workers+Against+COVID-19+%28BRACE%29&id=NCT04327206&draw=2&rank=1. Accessed 12/21, 2020.

47. Bonten M. Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine Status: Active, not recruiting.

https://clinicaltrials.gov/ct2/show/NCT04328441?term=Reducing+Health+Care+Workers+Absenteeism+in+Covid-19+Pandemic+Through+BCG+Vaccine+AND+BCG-CORONA&draw=2&rank=1. Accessed 12/21, 2020.

48. Di Bari M, Balzi D, Carreras G, Onder G. Extensive Testing May Reduce COVID-19 Mortality: A Lesson From Northern Italy. *Front Med (Lausanne)*. 2020;7:402. doi: 10.3389/fmed.2020.00402 [doi].

49. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J*. 2020;41(22):2058-2066. doi: 10.1093/eurheartj/ehaa433 [doi].

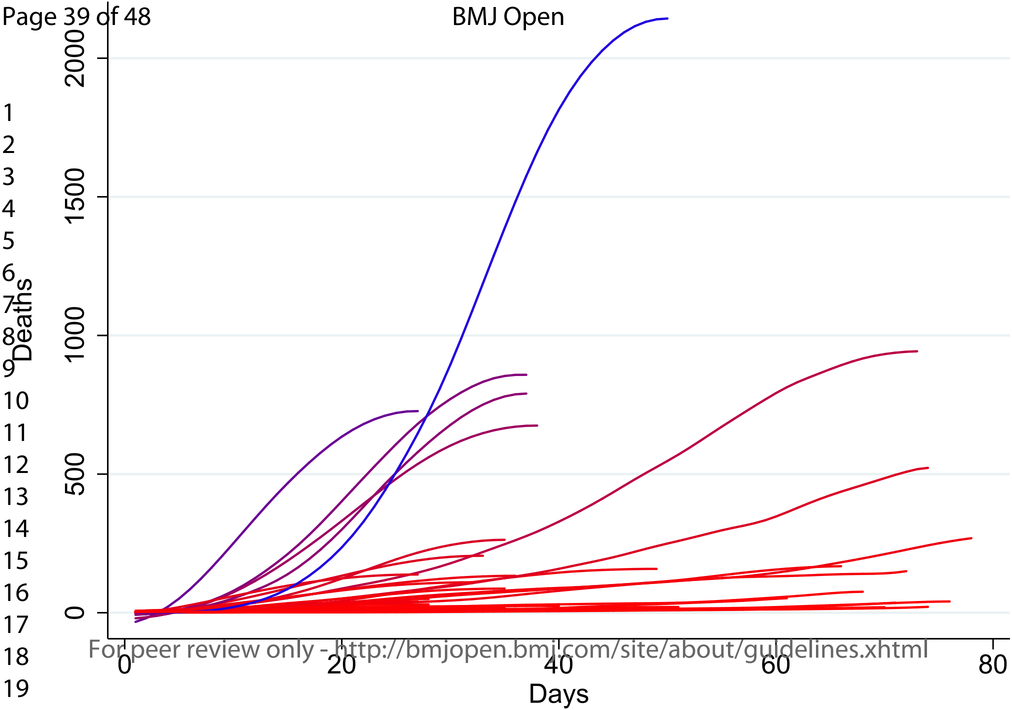
FIGURE LEGENDS

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.

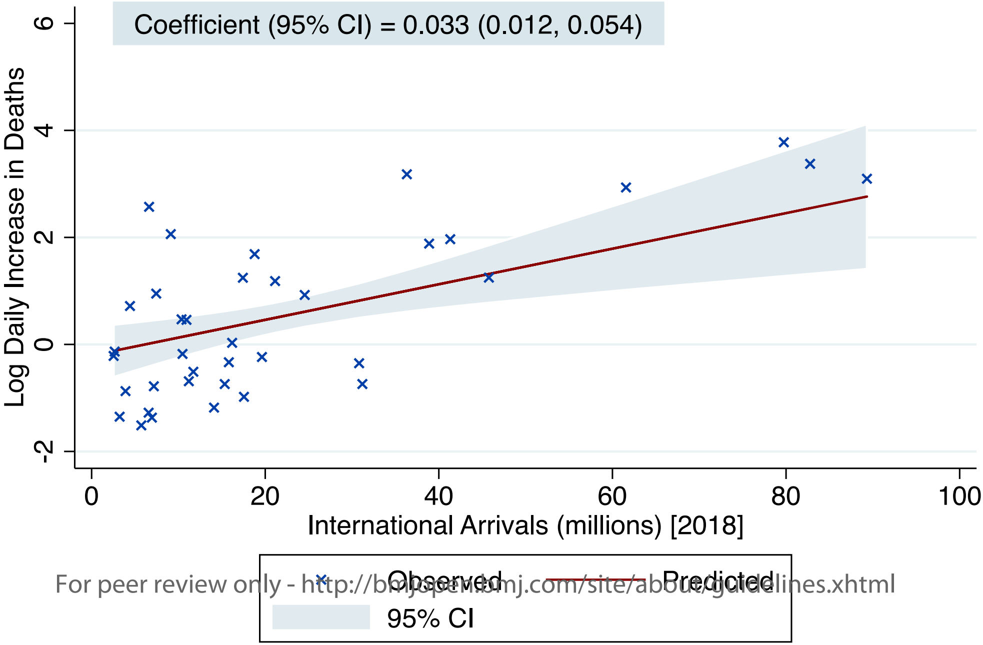
*smoothed using a local regression (lowess) function with a bandwidth of 0.4

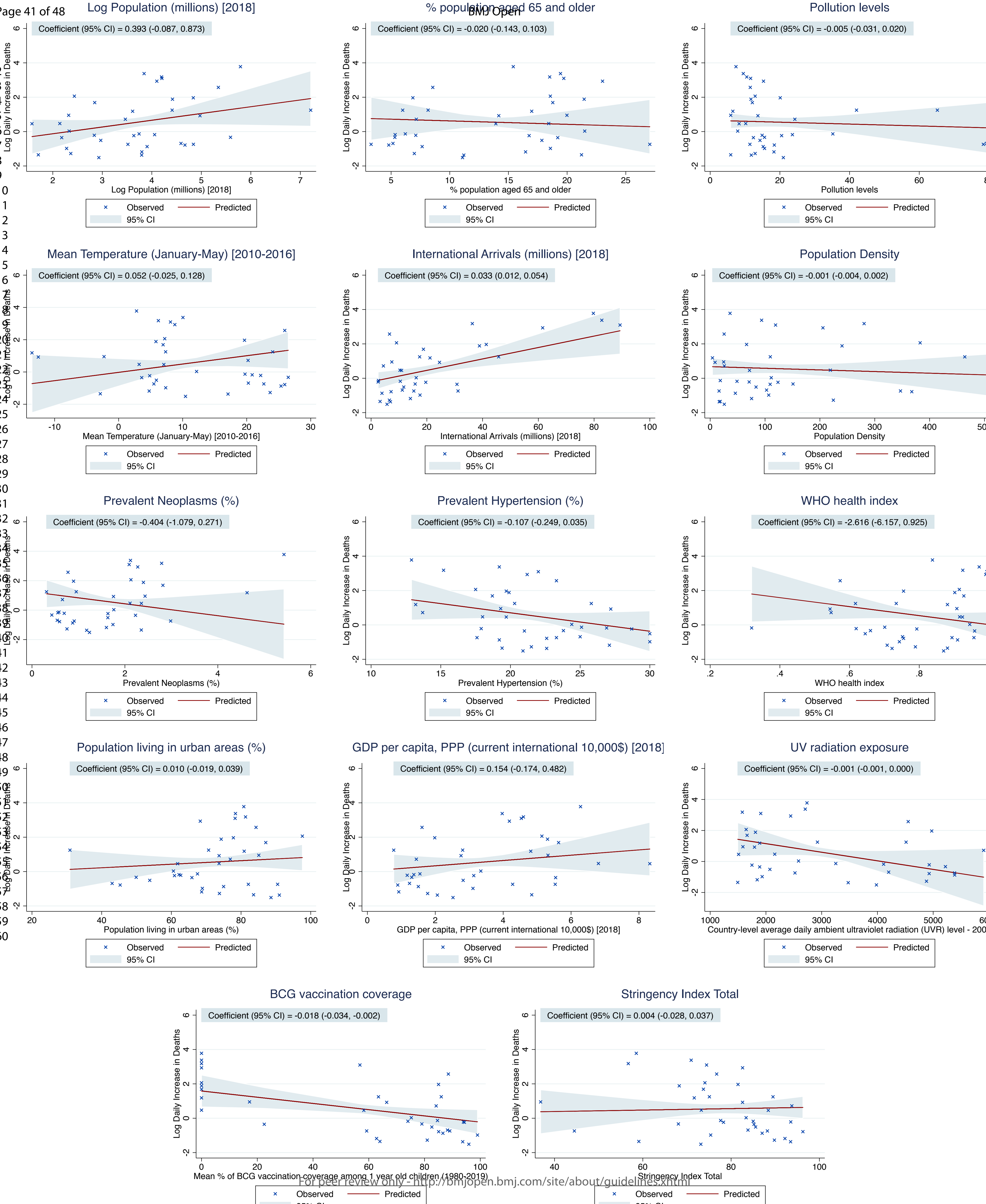
Figure 2. Predicted (based on the results of the multivariable linear regression) and observed country-level mortality rate (mean daily increase in deaths until the peak in mortality) as a function of the recorded country-level number of international arrivals in 2018 (millions). The solid red line represents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


Deaths
0
500
1000
1500
2000
0
20
40
60
80
Days

International Arrivals (millions) [2018]




Log Population (millions) [2018]
Coefficient (95% CI) = 0.393 (-0.087, 0.873)
Log Daily Increase in Deaths
Log Population (millions) [2018]
% population aged 65 and older
Coefficient (95% CI) = -0.020 (-0.143, 0.103)
% population aged 65 and older
Pollution levels
Coefficient (95% CI) = -0.005 (-0.031, 0.020)
Pollution levels
Mean Temperature (January-May) [2010-2016]
Coefficient (95% CI) = 0.052 (-0.025, 0.128)
Mean Temperature (January-May) [2010-2016]
International Arrivals (millions) [2018]
Coefficient (95% CI) = 0.033 (0.012, 0.054)
International Arrivals (millions) [2018]
Population Density
Coefficient (95% CI) = -0.001 (-0.004, 0.002)
Population Density
Prevalent Neoplasms (%)
Coefficient (95% CI) = -0.404 (-1.079, 0.271)
Prevalent Neoplasms (%)
Prevalent Hypertension (%)
Coefficient (95% CI) = -0.107 (-0.249, 0.035)
Prevalent Hypertension (%)
WHO health index
Coefficient (95% CI) = -2.616 (-6.157, 0.925)
WHO health index
Population living in urban areas (%)
Coefficient (95% CI) = 0.010 (-0.019, 0.039)
Population living in urban areas (%)
GDP per capita, PPP (current international 10,000$) [2018]
Coefficient (95% CI) = 0.154 (-0.174, 0.482)
GDP per capita, PPP (current international 10,000$) [2018]
UV radiation exposure
Coefficient (95% CI) = -0.001 (-0.001, 0.000)
Country-level average daily ambient ultraviolet radiation (UVR) level - 2004
BCG vaccination coverage
Coefficient (95% CI) = -0.018 (-0.034, -0.002)
Mean % of BCG vaccination coverage among 1 year old children (1980-2019)
Stringency Index Total
Coefficient (95% CI) = 0.004 (-0.028, 0.037)
Stringency Index Total
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 Republi	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

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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

*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.