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Country-level determinants of COVID-19 case rates and death rates: An ecological study

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Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has had a variable worldwide impact, likely related to country-level characteristics. In this ecological study, we explored the association of COVID-19 case rates (per 100,000 people) and death rates (per 100,000 people) with country-level population health characteristics, economic and human development indicators, and habitat-related variables. To calculate country-level COVID-19 case and death rates, the number of cases and deaths were extracted from the Johns Hopkins Coronavirus Resource Center through September 30, 2021. Country-level population health characteristics, economic, human development, and habitat-related indicators were extracted from several publicly available online sources of international organizations. Results were tabulated according to world zones and country economies. Unadjusted and adjusted multiple imputation linear regression analyses were performed to examine the association between country-level variables (per 1-standard deviation [SD] increase) and COVID-19 case and death rates. To satisfy the linear regression model assumptions of normality of residuals, we used the square root transformation of both outcomes. A total of 187 countries and territories were analyzed, with a median (25th, 75th percentiles) aggregate COVID-19 case rate of 3,605 (463, 8,228) per 100,000, a COVID-19 death rate of 45.9 (8.9, 137.1) per 100,000, and a case-fatality rate of 1.6% (1.2%, 2.6%). On multivariable analyses, each country-level 1-SD higher percentage of adults with obesity (β coefficient 13.7; 95% confidence interval [CI] 13.7; 8.9, 18.4), percentage of smokers (5.8; 95% CI 1.2, 10.5), percentage of adults with high blood pressure (4.9; 95% CI 0.3, 9.6), and gross national income (GNI) per capita (9.5; 95% CI 4.6, 14.5) was independently associated with higher square root of COVID-19 case rate, while average household size (−1.7; 95% CI −12.3, −3.2) was independently associated with lower square root of COVID-19 case rate. Similarly, each 1-SD higher percentage of adults with obesity (1.76; 95% CI 0.99, 2.52), percentage of adults with high blood pressure (1.11; 95% CI 0.48, 1.74), percentage of adults with physical inactivity (1.01; 95% CI 0.10, 1.191), and travel & tourism competitiveness index (1.05; 95% CI 0.06, 2.04) was independently associated with higher square root of COVID-19 death rate, whereas GNI per capita (−0.92; 95% CI −1.81, −0.03), and average household size (−1.07; 95% CI −1.87, −0.27) was independently associated with lower square root of COVID-19 death rate. This ecological study informs the need to develop country-specific public health interventions

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to better target populations at high risk for COVID-19, and test interventions to prevent transmission of SARS-CoV-2, taking into consideration cross-country differences in population health characteristics, and economic, human development and habitat-related factors.

KEYWORDS
COVID-19, economics, environment and public health, geographic locations, population health, SARS-CoV-2

1 | INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has had an unprecedented impact on most countries around the world. Caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel coronavirus first identified in Wuhan, China, COVID-19 has spread across all continents, putting unprecedented pressure on health care systems and economies of many countries. In contrast to previously identified coronavirus strains that cause SARS, namely the SARS Coronavirus-1 (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the new strain revealed itself as far more infectious and able to spread quickly among individuals (Ye et al., 2020). However, not all countries have been equally affected by COVID-19, raising questions of potential internal and/or external factors inherent to each country that might positively or negatively affect both the spread of SARS-CoV-2 and the risk of lethality from the infection.

Several ecological studies have attempted to examine country-level characteristics to determine risk of COVID-19 and related mortality. Indeed, whereas travel and tourism, higher testing capacity, and higher per capita gross domestic product (a measure of a country's economic output) were factors associated with a higher incidence rate of COVID-19 (Pana et al., 2021), higher testing intensity was associated with a lower case fatality rate (Kenyon, 2020). Furthermore, advanced age (Dowd et al., 2020), obesity (Flint & Tahrani, 2020), hypertension (Zhou et al., 2020), diabetes mellitus (Zhou et al., 2020), smoking (Vardavas & Nikitara, 2020), pollution levels (Ogen, 2020) and health care resources (Ji et al., 2020) have all been linked to an increase in COVID-19-related mortality. The aim of our ecological study was to identify, at a global scale, potential country-level determinants of COVID-19 case rates and death rates, during the pandemic, with a focus on population health characteristics, and economic, human development and habitat-related indicators.

2 | METHODS

2.1 | Country-level COVID-19 case rates and death rates

To calculate country-level COVID-19 case rates and death rates, we first extracted the total number of COVID-19 cases and deaths reported by the Johns Hopkins Coronavirus Resource Center for the period of 31 December 2019 to 30 September 2021.[1] The population of countries and dependent territories for 2020 was obtained from the world-o-meter website[2] and was based on the latest United Nations Population Division estimates. COVID-19 case rates and death rates were then calculated and reported per 100,000 people.

2.2 | Geographic variables

Countries were grouped within continents and world zones in accordance with the geo-scheme devised by the United Nations Statistics Division,[3] and country-level COVID-19 case rates and death rates were averaged accordingly. In terms of latitude, countries were classified as located north or south of the equator. Population density was obtained from the United Nations Demographic and Social Statistics Division.[4]

2.3 | Country-level population health characteristics

Country-level population health characteristics were obtained from the 2019 World Bank Population Prospects,[5] the 2016 World Health Organization Report on Noncommunicable Diseases[6] and the 2020 World Population Review.[7] These characteristics included percentage of population 65 years and older, percentage of adults (ages 18 and older) with obesity, percentage of smokers (ages 15 and older), percentage of adults (ages 18 and older) with high blood pressure, percentage of adults (ages 20–79) with diabetes mellitus and percentage of adults (ages 18 and older) with physical inactivity.

2.4 | Country-level economic, human development and habitat-related indicators

Country-level economic, human development and habitat-related indicators were obtained from the 2020 world-o-meter Gross Domestic Product (GDP) Report,[8] the 2018 World Bank Urbanization Report,[9] the 2019 United Nations Human Development Report,[10] the 2019 World Economic Forum[11] and the 2019 United Nations Department of Economic Affairs Household Size and Composition Report.[12] The indicators included the percentage of national GDP (representing the value of all final goods and services produced within a nation in a given year) spent on national total health expenditure (representing the sum of general government and private health expenditures in a given year, calculated in national currency units in current prices); the travel & tourism competitiveness index, a measurement of the factors that make it attractive to develop business in the travel and tourism industry of individual countries, rather than a measure of a country attractiveness as a tourist destination (with a range of 1–7); urban population (as a percentage of total population); the human development index (HDI), a composite index measuring average achievement in 3 dimensions of human development, a long and healthy life, knowledge, and a decent standard of living (across 4 categories, including low [≤0.549], medium [0.550–0.699], high [0.700–0.799] and very high [≥0.800] HDI); gross national income (GNI) per capita, classified according to 4 ranges (low, lower-middle, upper-middle and high income) and reported in international dollars (intl.$), which is a hypothetical unit of currency that has the same purchasing power parity that the US dollar has in the United States at a given point in time; and average household size.

2.5 | Statistical analyses

Continuous variables are reported as mean (standard deviation [SD]) or median (25th, 75th percentiles) as appropriate. Binary variables are reported as counts (percentage). Descriptive results stratified according to world zones and country income were compared by the analysis of variance (ANOVA) test. Pairwise bivariate analyses were performed using the Pearson's correlation test, and the coefficient was displayed with 95% confidence interval (CI). Univariate and multivariable linear regression analyses were performed to examine the association of country-level population health characteristics, and economic, human development and habitat-related indicators, with our two outcomes of interest, country-level COVID-19 case rates and death rates. The set of candidate variables along with their rate of missing data and SD are shown in Supplemental Table S1. Assuming missing data in the candidate variables is missing at random, we used multiple imputation with chained equations to create 50 imputations using all candidate variables and the two outcomes of interest. To build the final multivariable model for each outcome, we performed backward elimination with *p* value to stay in the model set at 5%, by including only variables with a significant *p* value of less than .1 in the univariate multiple imputation analysis to enter in the multivariable model. We did not include the HDI predictor variable in the list of candidate variables because it is a summary composite variable and is highly correlated with other variables in the list (see Supplemental Table S1). Using these 50 backward elimination final models, we calculated the proportion of time a variable is retained in the final model out of the 50 possible backward elimination models. Only variables that were retained more than 25 times (50%) were included in the final model. Once an included variable was not significant in the final multivariable model, it was dropped, and the model was refitted one more time until all variables that are finally retained were significant with *p* value of less than .05. We refitted the same final multivariable model in the non-imputed original dataset to compare the results of the multiple imputation and complete case analysis. To make the effects of all predictors comparable, their effects are expressed per 1-SD increase (the SD value can be obtained from Supplemental Table S1). To satisfy the linear regression model assumptions of normality of residuals, we used the square root transformation of both outcomes. To interpret the effect of the covariate on the original outcome scale, a 1-SD change in the predictor is associated with a change in the outcome that is equal to ($2 \times \beta \times$ current value of outcome). We checked the linear regression model assumptions in each model fitted, in each of the 50 imputed datasets. We used the Q–Q plot of the residuals, the residuals versus fitted values and performed an omnibus test for global test assumptions, which includes skewness, kurtosis, link function and heteroscedasticity. We tested for presence of outliers for each model for each imputation with Bonferroni adjustment. We finally checked for high multicollinearity in the final multivariable model using the variance inflation factor (VIF). For each model, in each of the 50 imputed datasets, there was no indication of deviation from normality in the residuals, the constant variance assumption was met in all cases, there were no outliers significant at 5% using Bonferroni corrected *p* values and all VIF values were < 4. The results of the linear regression analyses are shown as change in square root of COVID-19 case rate and death rate (unadjusted and adjusted β coefficient) per 1-SD increase in the predictor variable, with 95% CI. Although multiple imputation was used for our main analyses, the results of complete case analyses are shown as supplemental material, as well as results of multiple imputation subgroup analyses based on the median HDI. All analyses were performed using SAS Enterprise Guide (Version 7.12, Cary, NC) and R language (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | COVID-19 case rates and death rates stratified by world zones

As of 30 September 2021, worldwide, there were 233,621,596 reported confirmed cases of COVID-19 across 187 countries and territories and 4,780,751 COVID-19-related deaths, with an aggregate median case rate of 3605 (25th, 75th percentiles 463, 8228) per 100,000 people; a median death rate of 45.9 (25th, 75th percentiles 8.9, 137.1) per 100,000 people; and a median case-fatality rate of 1.7% (25th, 75th percentiles 0.9%, 2.7%).

Table 1 displays COVID-19 case rates and death rates of countries grouped according to world zones. In brief, countries in Europe, the Americas and the Eastern Mediterranean tended to have the highest COVID-19 case rates ($p < .001$) and death rates ($p < .001$), compared to countries from the Western Pacific, Africa and South-East Asia. European countries, specifically, experienced the highest number of cases and deaths per 100,000 people; these countries had the highest mean percentage of people 65 years and older (17.0%), the highest mean percentage of smokers (28.1%) and the highest mean percentage of adults

TABLE 1 COVID-19 case and death rates and country-level characteristics stratified according to world zones

	Western Pacific $N = 15$ (8.0%)	Africa $N = 48$ (25.7%)	South-East Asia $N = 11$ (5.9%)	Americas $N = 35$ (18.7%)	Eastern Mediterranean $N = 24$ (12.8%)	Europe $N = 54$ (28.9%)	*p* Value
COVID-19 rate (per 100,000 people)							
Case rate	812 (323, 2327)	335 (164, 1009)	1540 (853, 2445)	4314 (3110, 7702)	3739 (348, 7753)	8429 (5889, 10,878)	<.0001
Death rate	9.1 (1.6, 34.9)	6.4 (2.2, 17.9)	32.5 (8.9, 42.7)	105.9 (49.7, 185.7)	23.1 (13.0, 80.9)	140.7 (84.7, 201.9)	<.0001
Population health characteristics							
Persons 65 years and older, %	9.9 (6.9)	3.6 (2.7)	7.5 (3.5)	9.4 (3.5)	4.3 (2.0)	17.0 (5.1)	<.0001
Adults with obesity, %	13.4 (10.5)	10.1 (4.7)	5.8 (2.2)	24.2 (4.0)	25.2 (10.1)	22.4 (3.2)	<.0001
Smokers, %	22.6 (5.3)	16.1 (7.2)	23.6 (10.4)	16.4 (8.0)	22.4 (8.3)	28.1 (6.7)	<.0001
Adults with high blood pressure, %	20.3 (3.3)	21.9 (3.7)	22.9 (1.9)	20.6 (3.8)	20.0 (3.6)	28.9 (5.6)	<.0001
Adults with diabetes mellitus, %	8.8 (4.5)	5.3 (3.9)	8.1 (2.2)	9.8 (2.6)	11.6 (4.7)	6.4 (1.9)	<.0001
Adults with physical inactivity, %	26.9 (11.7)	19.7 (8.6)	22.6 (7.4)	36.0 (7.2)	35.4 (12.5)	31.5 (9.2)	<.0001
Economic, human development and habitat-related indicators							
Percentage GDP spent on total health expenditure	5.4 (2.7)	5.6 (2.2)	4.3 (1.9)	7.0 (2.7)	5.6 (2.3)	7.8 (2.2)	<.0001
Travel & tourism competitiveness index	4.3 (0.7)	3.1 (0.4)	3.7 (0.7)	3.8 (0.6)	3.6 (0.5)	4.3 (0.6)	<.0001
Urban population percentage of total population	61.7 (26.0)	42.1 (18.1)	36.1 (11.9)	64.3 (20.9)	69.0 (22.1)	71.4 (16.1)	<.0001
Human development index	0.78 (0.13)	0.56 (0.12)	0.67 (0.07)	0.76 (0.08)	0.70 (0.13)	0.86 (0.07)	<.0001
GNI income per capita (intl.$)	16,842 (7038, 42,067)	2932 (1704, 5887)	8310 (6174, 12,863)	14,854 (9066, 22,610)	14,513 (5539, 41,331)	32,254(18,896, 46,344)	<.0001
Average household size	3.9 (1.1)	4.8 (1.2)	4.2 (0.7)	3.6 (0.7)	5.7 (1.6)	2.9 (0.9)	<.0001

Data shown as mean (standard deviation) or median (25th, 75th percentiles). GDP, gross domestic product; GNI, gross national income.

TABLE 2 COVID-19 case and death rates and country-level characteristics stratified according to country classification by income level

	Lower middle $N = 38$ (21.2%)	Upper middle $N = 45$ (25.1%)	Upper class $N = 96$ (53.6%)	*p* Value
COVID-19 rate (per 100,000 people)				
Case rate	303 (147, 482)	2528 (409, 5173)	7162 (3614, 10,237)	<.0001
Death rate	5.7 (1.5, 16.7)	34.9 (6.6, 102.9)	106.1 (43.1, 184.1)	<.0001
Population health characteristics				
Persons 65 years and older, %	3.2 (1.2)	6.0 (3.2)	13.2 (6.7)	<.0001
Adults with obesity, %	9.0 (4.3)	16.6 (8.8)	22.4 (7.2)	<.0001
Smokers, %	16.4 (7.3)	21.3 (8.8)	23.7 (8.6)	.0003
Adults with high blood pressure, %	21.7 (3.8)	21.8 (4.2)	24.6 (6.3)	.003
Adults with diabetes mellitus, %	4.7 (2.4)	8.9 (4.7)	8.4 (3.5)	<.0001
Adults with physical inactivity, %	16.9 (7.6)	23.7 (8.1)	34.3 (9.0)	<.0001
Economic, human development and habitat-related indicators				
Percentage GDP spent on total health expenditure	5.9 (2.4)	5.6 (2.0)	7.0 (2.6)	.0048
Travel & tourism competitiveness index	3.0 (0.3)	3.4 (0.4)	4.2 (0.6)	<.0001
Urban population percentage of total population	37.5 (15.2)	49.6 (17.4)	72.1 (18.5)	<.0001
Human development index	0.52 (0.08)	0.66 (0.09)	0.84 (0.08)	<.0001
GNI income per capita (intl.$)	2062 (1663, 2948)	7228 (5539, 9066)	28,610 (17,680, 45,632)	<.0001
Average household size	5.2 (1.2)	4.4 (0.9)	3.2 (1.1)	<.0001

Data shown as mean (standard deviation) or median (25th, 75th percentiles). Classification by income level available for only 179 (of the 187) countries and territories. GDP, gross domestic product; GNI, gross national income.

with high blood pressure (28.9%), likely reflecting a higher burden of co-morbidities. Eastern Mediterranean countries had the highest mean percentage of adults with obesity (25.2%), the highest mean average household size (5.7) and the highest mean percentage of adults with diabetes (11.6%), whereas countries from the Americas had the highest mean percentage of adults with physical inactivity (36.0%). By contrast, European countries had the highest mean percentage of GDP spent on total health expenditure (7.8%), the highest mean percentage of urban population (71.4%), the highest mean HDI (0.86) and the highest median GNI per capita (32,254 intl. $). African countries had the lowest mean travel & tourism competitiveness index (3.1).

On bivariate analyses, higher country latitude correlated with higher COVID-19 case rates ($r = 0.36$; 95% CI 0.23, 0.48) and higher COVID-19 death rates ($r = 0.23$; 95% CI 0.09, 0.36).

3.2 | COVID-19 case rates and death rates stratified by country income classification

Data from the World Bank classification of economies by income level was available for 179 countries. Table 2 displays the results stratified by country income classification, with a trend toward higher COVID-19 case rates ($p < .001$) and death rates ($p < .001$) in countries in the upper-middle to high-income category, compared to countries in the lower-middle income category. The 96 countries that qualified as high-income economies had a median GNI per capita of intl. $28,610 and had the highest mean percentage of urban population (72.1%); these countries also spent the highest mean percentage of GPD on total health expenditure (7.0%) and had the highest mean HDI (0.84) and highest mean travel & tourism competitiveness index (4.2). In terms of population health characteristics, high-income countries also had the highest mean percentage of people 65 years and older (13.2%), the highest mean percentage of adults with obesity (22.4%), the highest mean percentage of smokers (23.7%), the highest mean percentage of adults with high blood pressure (24.6%) and the highest mean of adults with physical inactivity (34.3%). Moreover, these countries had the lowest mean average household size of 3.2.

3.3 | Pairwise bivariate analyses correlating country-level characteristics with COVID-19 case rates and death rates

Results of the pairwise bivariate analyses are shown in Table 3. In terms of country-level population health characteristics, higher percentage of population ages 65 and older ($r = 0.53$; 95% CI 0.42, 0.63), higher percentage of adults with obesity ($r = 0.54$; 95% CI 0.42, 0.63), higher percentage of smokers ($r = 0.40$; 95% CI 0.26, 0.53), higher percent-

TABLE 3 Pearson's correlation coefficient (95% CI) of COVID-19 case rate and death rate with each variable

Variable	*N*	COVID-19 case rate per 100,000	COVID-19 death rate per 100,000
Persons 65 years and older, %	180	0.53 (0.42, 0.63)	0.52 (0.40, 0.62)
Adults with obesity, %	179	0.54 (0.42, 0.63)	0.46 (0.33, 0.56)
Smokers, %	146	0.40 (0.26, 0.53)	0.26 (0.10, 0.40)
Adults with high blood pressure, %	176	0.31 (0.17, 0.44)	0.35 (0.22, 0.47)
Adults with diabetes mellitus, %	182	0.12 (−0.03, 0.26)	0.02 (−0.12, 0.17)
Adults with physical inactivity, %	149	0.41 (0.26, 0.53)	0.41 (0.26, 0.53)
Percentage GDP spent on total health expenditure	165	−0.49 (−0.60, −0.37)	−0.44 (−0.55, −0.31)
Travel & tourism competitiveness index	179	0.36 (0.22, 0.48)	0.34 (0.20, 0.46)
Urban population percentage of total population	150	0.48 (0.34, 0.59)	0.37 (0.23, 0.50)
Human development index	181	0.48 (0.36, 0.58)	0.36 (0.22, 0.48)
GNI income per capita (intl.$)	180	0.64 (0.54, 0.72)	0.50 (0.38, 0.60)
Average household size	179	0.44 (0.32, 0.55)	0.19 (0.05, 0.33)
Country latitude	187	0.36 (0.23, 0.48)	0.23 (0.09, 0.36)

GDP, gross domestic product; GNI, gross national income; CI, confidence interval.

age of adults with high blood pressure (r = 0.31; 95% CI 0.17, 0.44) and higher percentage of adults with physical inactivity (r = 0.41; 95% CI 0.26, 0.53) correlated with *higher* COVID-19 *case* rates. In terms of country-level economic, human development and habitat-related indicators, higher percentage of GDP spent on total health expenditure (r = 0.36; 95% CI 0.22, 0.48), higher travel & tourism competitiveness index (r = 0.48; 95% CI 0.34, 0.59), higher percentage of urban population (r = 0.48; 95% CI 0.36, 0.58), higher HDI (r = 0.64; 95% CI 0.54, 0.72) and higher GNI per capita (r = 0.44; 95% CI 0.32, 0.53) correlated with *higher* COVID-19 *case* rates; and higher average household size (r = −0.49; 95% CI −0.60, −0.37) correlated with *lower* COVID-19 *case* rates.

Similarly, in terms of country-level population health characteristics, higher percentage of population ages 65 and older (r = 0.52; 95% CI 0.40, 0.62), higher percentage of adults with obesity (r = 0.46; 95% CI 0.33, 0.56), higher percentage of smokers (r = 0.26; 95% CI 0.10, 0.40), higher percentage of adults with high blood pressure (r = 0.35; 95% CI 0.22, 0.47) and higher percentage of adults with physical inactivity (r = 0.41; 95% CI 0.26, 0.53) correlated with *higher* COVID-19 *death* rates. There was no correlation of country-level percentage of adults with diabetes with either COVID-19 case or death rate. Similarly, in terms of country-level economic, human development and habitat-related indicators, higher percentage of GDP spent on total health expenditure (r = 0.34; 95% CI, 0.20, 0.46), higher travel & tourism competitiveness index (r = 0.37; 95% CI 0.23, 0.50), higher percentage of urban population (r = 0.36; 95% CI 0.22, 0.48), higher HDI (r = 0.50; 95% CI 0.38, 0.60) and higher GNI per capita (r = 0.19; 95% CI 0.05, 0.33) correlated with *higher* COVID-19 *death* rates; higher average household size (r = −0.55; 95% CI −0.55, −0.31) correlated with *lower* COVID-19 *death* rates.

3.4 | Unadjusted linear regression analyses examining the association of COVID-19 case rates and death rates with country-level characteristics

Tables 4 and 5 display the unadjusted multiple imputation-based results of the regression analyses. In terms of country-level population health characteristics, each 1-SD higher percentage of population 65 years and older, percentage of adults with obesity, percentage of smokers, percentage of adults with high blood pressure and percentage of adults with physical inactivity was associated with higher square root of COVID-19 case and death rate per 100,000. While each 1-SD higher percentage of adults with diabetes was associated with higher square root of COVID-19 case rate per 100,000, there was no association with square root of COVID-19 death rate per 100,000.

In terms of country-level economic, human development and habitat-related indicators, each 1-SD higher percentage of GDP spent on total health expenditure, travel & tourism competitiveness index, percentage of urban population, HDI and GNI per capita was associated with higher square root of COVID-19 case rate and death rate per 100,000. However, each 1-SD higher average household size was associated with lower square root of COVID-19 case rate and death rate per 100,000.

3.5 | Adjusted linear regression analyses examining the association of COVID-19 case rates and death rates with country-level characteristics

Tables 4 and 5 display the adjusted multiple imputation-based results of the regression analyses. In brief, on multivariable analyses, each

TABLE 4 Association of country-level population health characteristics, economic, human development and habitat-related indicators with $\sqrt{\text{Covid}-19 \text{ case rate per } 100,000}$ (multiple imputation-based results)

Variable	N	Unadjusted β (95% CI)	p Value	N	Adjusted β (95% CI)	p Value
Persons 65 years and older, %	187	20.6 (16.0, 25.1)	<.001			
Adults with obesity, %	187	20.1 (14.5, 25.7)	<.001	187	13.7 (8.9, 18.4)	<.001
Smokers, %	187	12.3 (6.5, 18.1)	<.001	187	5.8 (1.2, 10.5)	.014
Adults with high blood pressure, %	187	11.0 (5.7, 16.2)	<.001	187	4.9 (0.3, 9.6)	.038
Adults with diabetes mellitus, %	187	5.7 (0.3, 11.0)	.040			
Adults with physical inactivity, %	187	15.6 (10.1, 21.1)	<.001			
Percentage GDP spent on total health expenditure	187	12.7 (7.6, 17.9)	<.001			
Travel & tourism competitiveness index	187	20.2 (15.5, 24.9)	<.001			
Urban population percentage of total population	187	19.5 (14.8, 24.1)	<.001			
Human development index	187	25.9 (22.0, 29.8)	<.001			
GNI income per capita (intl.$)	187	18.3 (13.7, 23.0)	<.001	187	9.5 (4.6, 14.5)	<.001
Average household size	187	−18.5 (−23.2, −13.8)	<.001	187	−7.8 (−12.3, −3.2)	<.001

β is the change in the square root of COVID-19 case rate per 100,000 per 1 standard deviation (SD) higher in the predictor. To interpret the effect of the covariate on the original outcome scale, a 1-SD change in the predictor is associated with a change in the outcome that is equal to [2×β× current value of outcome]. GDP, gross domestic product; GNI, gross national income; CI, confidence interval.

TABLE 5 Association of country-level population health characteristics, economic, human development and habitat-related indicators with $\sqrt{\text{Covid}-19 \text{ death rate per } 100,000}$ (multiple imputation-based results)

Variable	N	Unadjusted β (95% CI)	p Value	N	Adjusted β (95% CI)	p Value
Persons 65 years and older, %	187	2.73 (2.09, 3.38)	<.001			
Adults with obesity, %	187	2.54 (1.81, 3.27)	<.001	187	1.76 (0.99, 2.52)	<.001
Smokers, %	187	1.38 (0.61, 2.15)	<.001			
Adults with high blood pressure, %	187	1.76 (1.05, 2.47)	<.001	187	1.11 (0.48, 1.74)	<.001
Adults with diabetes mellitus, %	187	0.40 (−0.34, 1.15)	.291			
Adults with physical inactivity, %	187	2.06 (1.29, 2.83)	<.001	187	1.01 (0.10, 1.91)	.029
Percentage GDP spent on total health expenditure	187	1.86 (1.17, 2.56)	<.001			
Travel & tourism competitiveness index	187	2.38 (1.70, 3.06)	<.001	187	1.05 (0.06, 2.04)	.037
Urban population percentage of total population	187	2.07 (1.39, 2.76)	<.001			
Human development index	187	2.89 (2.28, 3.50)	<.001			
GNI income per capita (intl.$)	187	1.41 (0.71, 2.11)	<.001	187	−0.92 (−1.81, −0.03)	.042
Average household size	187	−2.46 (−3.10, −1.83)	<.001	187	−1.07 (−1.87, −0.27)	.009

β is the change in the square root of COVID-19 death rate per 100,000 per 1 SD higher in the predictor. To interpret the effect of the covariate on the original outcome scale, a 1-SD change in the predictor is associated with a change in the outcome that is equal to [2×β× current value of outcome]. GDP, gross domestic product; GNI, gross national income; CI, confidence interval.

1-SD higher percentage of adults with obesity, percentage of smokers, percentage of adults with high blood pressure and GNI per capita remained independently associated with higher square root of COVID-19 case rate per 100,000, whereas each 1-SD higher average household size was independently associated with lower square root of COVID-19 case rate per 100,000.

Similarly, each 1-SD higher percentage of adults with obesity, percentage of adults with high blood pressure, percentage of adults with physical inactivity and travel & tourism competitiveness index was independently associated with higher square root of COVID-19 death rate per 100,000, whereas each 1-SD higher GNI per capita and average household size was independently associated with lower square root of COVID-19 death rate per 100,000.

Results of univariate and multivariable regression analyses using complete cases are shown in Supplemental Tables S2 and S3 and are generally consistent with the multiple imputation-based results.

Multiple imputation subgroup analyses among countries with an HDI above and below the median of 0.75 are displayed in Supplemental Tables S4–S7 and demonstrate similar trends, although most notable is the persistent strong independent association between country-level percentage of adults with obesity and higher square root of COVID-19 case rate and death rate per 100,000 irrespective of HDI status.

4 | DISCUSSION

The objective of our ecological study was to estimate the global burden of the COVID-19 pandemic with a focus on describing worldwide variations in SARS-CoV-2 infection rates and death rates in 2020–2021 according to geographic regions, country economies and country-level population health characteristics, and economic, human development and habitat-related indicators. COVID-19 case rates and death rates were computed across 187 countries and territories and grouped according to the six world zones and the four country income categories. As of 30 September, 2021, worldwide, a median of 3605 per 100,000 people worldwide experienced COVID-19 and 45.9 per 100,000 people died from COVID-19, with an aggregate median case-fatality rate of 1.6%. Higher COVID-19 case rates and death rates were observed in countries located in Europe, the Americas and the Eastern Mediterranean compared to other world regions. European countries, notably, experienced the highest number of cases and deaths per 100,000 people and tended to have the highest mean percentage of adults with high blood pressure, smokers and seniors, likely reflecting a higher burden of co-morbidities. Eastern Mediterranean countries had the highest mean percentage of adults with obesity and diabetes mellitus and the highest mean average household size, whereas countries from the Americas had the highest mean percentage of adults with physical inactivity. European countries had the highest mean GNI per capita, the highest mean percentage of GDP spent on total health expenditure, the highest mean percentage of urban population and the highest mean HDI. There were disproportionately more SARS-CoV-2 cases and deaths per 100,000 people in countries in the upper-middle to high-income category. These observations trended with higher mean population urbanization, higher mean percentage of GDP spent on total health expenditure, higher mean HDI and higher mean travel & tourism competitiveness index, which is an indirect measure of touristic-related activity.

In our multivariable analyses, country-level indicators that were independently associated with higher COVID-19 case rates included higher percentage of adults with obesity and high blood pressure, higher percentage of smokers and higher GNI per capita, likely reflecting higher comorbidities and increased access to COVID-19 testing in more developed countries. The independent association of lower average household size with higher COVID-19 case rates may be confounded by a lower square footage of living space per person, resulting in a higher risk of indoor transmission of SARS-CoV-2.

Country-level indicators that were independently associated with higher COVID-19 death rates included higher percentage of adults with obesity, high blood pressure and with physical inactivity, likely reflecting a higher burden of comorbidities. The independent association of a higher travel & tourism competitiveness index with a higher COVID-19 death rate might reflect cross-country differences in travel intensity, which might have further strained overwhelmed healthcare systems in the early period of the pandemic. By contrast, country-level indicators that were independently associated with lower COVID-19 death rates included higher GNI per capita and higher average household size, the former likely reflecting better access to health care services and the latter possibly reflecting better household support. Advanced age (Dowd et al., 2020), obesity (Flint & Tahrani, 2020), hypertension (Zhou et al., 2020), diabetes mellitus (Zhou et al., 2020), smoking (Vardavas & Nikitara, 2020), higher air pollution levels (Ogen, 2020) and lack of health care resources (Ji et al., 2020) have been linked to COVID-19-related mortality, consistent with several of our findings linking higher country-level percentage rates of obesity, high blood pressure and physical inactivity with higher COVID-19 death rates.

Our observations linking higher COVID-19 case rates to higher prevalence rates of obesity is concerning given the worldwide obesity epidemic. Studies have linked high body mass index (BMI > 35 kg/m^2) to a higher risk of severe COVID-19 and hospitalization (Lighter et al., 2020). Excess ectopic fat deposition might reduce protective cardiorespiratory reserve and promote immune dysregulation through an enhanced cytokine release syndrome (Sattar et al., 2020). Indeed, adipocytes produce interleukin-6, which increases disproportionately in patients with obesity and sepsis, including COVID-19 (Leisman et al., 2020) (Sindhu et al., 2015) (Khaodhiar et al., 2004). A large meta-analysis of 61 studies recently demonstrated that patients with obesity (defined by a BMI > 30 kg/m^2) were at an increased risk for severe disease and death from COVID-19 (Ho et al., 2020). The presence of obesity is likely confounded by the presence of comorbid conditions.

There is clear evidence that climatic factors can influence the spread of SARS-CoV-2. While the exact relationship between seasonal change and the spread of COVID-19 in different parts of the world is unclear, the common coronaviruses are highly seasonal, and there have been concerns about the seasonal spread of SARS-CoV-2 especially in the northern hemisphere. In our study, we observed a positive correlation between country latitude and SARS-CoV-2 infection rates and death rates, consistent with this hypothesis. A study from Australia also suggested that COVID-19 spreads faster in periods of lower humidity during winter, suggesting that dry weather promotes disease transmission (Ward et al., 2020b). In another study, an overall decrease in relative humidity of 1% was associated with an increase in COVID-19 cases by 7–8% (Ward et al., 2020a). These observations support the hypothesis that SARS-CoV-2 is more likely to remain in suspension in less humid air, thereby facilitating airborne transmission of the virus.

Ecological studies have been used to answer a number of questions in health services research (Saunders & Abel, 2014) (Tu & Ko, 2008). In a rapidly evolving worldwide pandemic such as COVID-19, and with the wealth of aggregated data that are available through international organizations such as the World Health Organization, the United Nations, the World Bank and the World Economic Forum, the use of ecological study designs can be informative and valuable in a rapidly evolving situation such as an emerging public health emergency, as they can help rapidly answer questions to implement public health measures. The main strength of our ecological study is that it is hypothesis generating regarding the observed associations between country-level aggregated data and COVID-19 case rates and death rates. Several of the identified ecological associations between the exposure and outcome variables are biologically plausible and consistent with what is already known at the individual-subject level, such as obesity, smoking, high blood pressure, travel and tourism index, GNI per capita and household size. By grouping country-level population health characteristics, economic, human development and habitat-related variables, performing multiple imputation multivariable analyses and using square root transformation of COVID-19 case and death rate change to satisfy the linear regression model assumptions of normality of residuals, our analytical approach helped minimize the potential for over-interpretation of our results and the generation of spurious findings. However, our observations must be balanced by the fact that we cannot draw definitive conclusions about individual-subject-level associations based on our findings derived from aggregated data.

Limitations of our study include the use of country-level characteristics, which were not contemporaneous to the pandemic time-period, the presence of unmeasured confounders, and most importantly, ecological inference fallacy, which linked country-level COVID-19 case rates and death rates to these aggregate indicators. Moreover, variation in COVID-19 testing rates between countries might have underestimated the true identification of COVID-19 cases and related deaths.

In conclusion, this ecological study provides insight into important associations between country-level indicators and rates of infection and death from SARS-CoV-2. Higher COVID-19 infection rates were observed in countries with higher prevalence rates of adults with obesity and high blood pressure, higher percentage rates of smokers, higher GNI per capita and lower average household size. Higher COVID-19 death rates were observed in countries with higher prevalence rates of adults with obesity, high blood pressure and physical inactivity, higher travel & tourism competitiveness index, higher GNI per capita and lower average household size. Further studies are needed to develop global health interventions that are country specific to better target populations at high risk for COVID-19, and test environmental interventions to prevent indoor transmission of SARS-CoV-2, taking into consideration human development and habitat-related variables that are unique to each country.

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ETHICS STATEMENT

This ecological study was not considered human subjects research and did not require approval by the Institutional Review Board (No. NHSR003).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no relevant financial interests pertaining to this study.

AUTHOR CONTRIBUTIONS

Research idea and study design: B.L.J. and L.T.J.; data acquisition: L.T.J., and C.E.M.; data analysis and interpretation: C.E.M, H.T., M.B. and B.L.J.; statistical analysis: H.T.; supervision or mentorship: B.L.J. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. B.L.J. takes responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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