Ecological association between COVID-19 deaths and vitamin D deficiency among older adults: An international country-level systematic review and analysis

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Abstract

Background

The COVID-19 pandemic has been consistently associated with disproportionately high mortality among older adults, regardless of nation of origin. Previous research on pneumotropic viruses demonstrated an association between host vitamin D levels and viral disease state. Vitamin D deficiency (VDD) also disproportionately impact older adults. The objective of this study was to evaluate VDD and COVID-19 mortality worldwide during the first 50 days of the pandemic as experienced by each country.

Methods

Country-specific VDD prevalence among older adults was evaluated according to a systematic literature search of PubMed, CINAHL, EMBASE, and SCOPUS during April 2020. Data were obtained from the public Our World in Data database which reports COVID-19 mortality from European Centre for Disease Prevention and Control and country population characteristics, size and proportion of the population greater than 65 years, from the United Nations Department of Economic and Social Affairs. Country-specific cumulative mortality was modeled via negative binomial random coefficient growth curve models.

Results

Among 29 countries included in this analysis, VDD prevalence among older adults ranged from 6.9% in Canada to 69% in France. Cumulative COVID-19 deaths up to day 50 within each country, modeled via exponential growth curves, demonstrated an association with country-level VDD ($p = 0.0538$). However, the association was not robust when controlling for proportion of older adults in each country ($p = 0.2135$).

Conclusions

This ecological analysis is further evidence for VDD correction as a component of COVID-19 treatment, especially among older individuals. Inclusion of data cross-culturally (i.e., collected from countries worldwide) supports the theory that VDD is a universal mechanism contributing to COVID-19 mortality. Though definitive randomized controlled trials are still needed, the current study provides support for VDD screening and correction as the influenza season rapidly approaches in the Northern hemisphere.

Background

Sars-CoV-2 mortality differs widely by country. Factors contributing to this variation include differences in testing/reporting, access to healthcare resources, and the presence of and public adherence to policy interventions such as social distancing and mask-wearing. However, underlying biological mechanisms may also impact viral mortality. It is important to evaluate biological reasons for the difference in COVID-19 mortality, as failure to do so limits worldwide capacity to develop pharmacologic responses for treatment of infected symptomatic individuals. Furthermore, biological mechanisms affecting viral mortality are critical to providing insight as to why some infected individuals remain asymptomatic while others develop COVID-19. This latter phenomenon was recently observed in a population of individuals experiencing homelessness in Boston, Massachusetts: a stunning 88% of individuals testing positive for Sars-CoV-2 were asymptomatic.[1] This is double the otherwise-reported asymptomatic rate of 40–45%.[2]

One potential biological reason for differences in mortality is vitamin D status. Low vitamin D is known to increase risk of both upper and lower respiratory tract infections.[3] A recent (2019) systematic review and meta-analysis clarified that among individuals with vitamin D insufficiency (VDI) in particular, respiratory infection risk is negatively associated with vitamin D levels.[4] Thus, vitamin D status is likely relevant for the contemporary pneumotropic Sars-Cov-2 virus.

Vitamin D and the Immune System

Several molecular mechanisms for this relationship between VDI and viral infection have been proposed. Vitamin D normally suppresses Th1 cell proliferation and enhances a shift towards Th2 cellular responses; consequent reductions in interferon-gamma

and interleukin (IL)-2 follow.[5] Similarly, vitamin D modulates dendritic cell signaling to reduce IL-12 production (which limits development of a Th1 response) and promotes IL-10 (thus inducing a tolerogenic, non-inflammatory response).[6] Therefore, Th1 cells are increased in vitamin D insufficiency or deficiency (VDI/VDD). This overall shift towards a pro-inflammatory Th1-dominated state characterizes the immune status of symptomatic COVID-19 patients.[7] In addition, vitamin D interferes with enveloped viruses via a cathelicidin-mediated disruption of the viral envelope.[5] Cathelicidin is an endogenous anti-microbial peptide; it is upregulated in lung epithelial cells in the presence of vitamin D.[8] Cathelicidin-mediated disruption has also been demonstrated for other viral and bacterial pathogens.[5,8] Therefore again, low vitamin D status is associated with a reduction in capacity to respond to viral infection.

Supplementation of vitamin D during influenza virus infection has been shown to reduce excessive pro-inflammatory cytokine production, thus limiting inflammation-induced complications (e.g., pulmonary edema).[6] Some respiratory viruses, such as respiratory syncytial virus and rhinovirus, downregulate vitamin D receptor levels in human bronchial epithelial cells.[9] Exogenous supplementation improved *in vitro* antiviral activity through the aforementioned vitamin D-mediated cathelicidin pathway.

Vitamin D also suppresses CD26, a presumed adhesion molecule for Sars-Cov-2 virus host cell entry.[10] Given these links between vitamin D status and COVID-19, calls for vitamin D supplementation among vulnerable groups have been made: older adults, nursing home residents, individuals with diabetes mellitus or obesity, individuals with darker skin, health care workers, and individuals who smoke.[10]

Epidemiology of VDI and VDD

The Endocrine Society defines VDI and VDD as serum 25(OH)D levels below 75 nmol/L (30 ng/mL) or 50 nmol/L (20 ng/mL)[11]. VDI is one of the most common nutritional deficiencies worldwide.[12] Traditionally, VDI and VDD risk is highest among pregnant women, children, older individuals, institutionalized populations, and non-Western Immigrants.[13] A study of healthy French adults demonstrated 80.3% with vitamin D levels < 30 ng/mL and 34.6% with vitamin D levels below 20 ng/mL.[14] In this same study, VDI of < 20 ng/mL was associated with older age, living at a higher latitude, BMI > 24 kg/m^2, or having been sampled between the winter months of January and March.[14] Globally, winter months consistently demonstrate increased VDI.[13,15] The positive association between latitude and vitamin D status is stronger among Caucasians than non-Caucasians.[16] However, among a geographically-representative study of healthy Chinese adults, younger adults (18–39 years) had lower vitamin D levels than older adults (> 49 years), possibly due to increased time spent indoors by working, young adults.[17] No significant geographic differences were noted according to distance from the equator (and hence sunlight exposure), which the authors ascribed to the study's inclusion of coastal cities where fish consumption is high.[17] Finally, low vitamin D status can occur for a variety of factors even at low-latitude countries; a study of healthy adults in Syria found a positive association between VDI and female gender, and VDI and hijab-wearing; seasonality of VDI was noted in men, but not women for this study as well.[18]

Within the United States, the National Health and Nutrition Examination Survey has demonstrated increased risk for VDI among the following: African-American individuals, individuals with obesity, and individuals who self-rate as generally having poor health. Over one third of all US adults have VDD, and prevalence is also increasing among younger populations.[12] There is a significant ethnic difference in VDI, with higher prevalence noted among non-Hispanic blacks as compared to non-Hispanic whites.[13] This difference according to skin pigmentation is largely due to differences in dermal metabolism of relevant vitamin D precursors. Older adults often similarly demonstrate lower levels of vitamin D due to reduced dermal metabolism.[13] In addition, VDI also parallels US socioeconomic disparities; socioeconomic achievement, measured by completion of a college degree, is significantly negatively associated with VDI.[19]Among respondents with available vitamin D level data, 82% of African-Americans had VDI, followed by 69.2% of Hispanics.[20]

Study Purpose

The factors associated with low vitamin D status are similar to those risk factors associated with COVID-19.[21] Given the global importance of understanding the biological mechanisms underlying morbidity and mortality of Sars-CoV-2, the goal of this study is to evaluate the country-level relationship between COVID-19 mortality and VDD. Because vitamin D levels and clinical outcomes have been shown to be more pronounced among patients with lower vitamin D status,[4] VDD was specifically selected as the condition of analysis for this study.

Early investigations of this relationship have reported associations between population level vitamin D levels and COVID-19 impact in terms of population case rate, case mortality rate and population mortality rate[22–25]. However, these studies have relatively small sample sizes, focus on homogenous European populations, and are cross-sectional in nature, and thus do not provide insight to the impacts over time as the epidemic unfolded. Additionally, these studies did not justify the use of Pearson correlation or regression to assess the relationship, which assumes distribution of rates are normally distributed. To better understand the potential association between COVID-19 mortality and vitamin D deficiency in international populations, this study will assess determinants of COVID-19 deaths during the initial outbreak period in each country. We have focused on the number of deaths as it is clinically significant representation of disease severity and impact and it does not depend on testing strategies in each country.

Cumulative infectious disease death curves are typically visualized on a logarithmic-scale as early infectious disease growth is exponential. Over time, the exponential growth slows due to disease management and control (i.e. “flatten the curve”) and reduced population susceptibility (i.e. herd immunity, risk factors), resulting in an “S” shaped curve. Figure 1 shows the COVID-19 death curve for France from March 6 through July 20, 2020. An exponential growth model for the first 30 days indicated deaths were doubling approximately every 3 days, then the rate of increase began to slow. Many factors influence the shape and scale of the cumulative death curve for a country, including population size, the prevalence of risk factors like age and health status, and disease control measures.

COVID-19 has disproportionately impacted older individuals. In the US, it is estimated that 80% of the deaths are in people 65 years or older[26]. In addition to age-related changes in vitamin D metabolism, modifiable determinants of deficiency within older adult or elderly populations include medication polypharmacy, inadequate nutrition, and lifestyle changes lowering natural sun exposure.[27–30] Therefore, we have conducted an ecological country-level study of the relationship between the rate of vitamin D deficiency among older adults and cumulative COVID-19 deaths in countries during the initial outbreak period.

Methods

Data for this study was extracted from the “Our World in Data” data portal of the Oxford Martin Programme on Global Development at the University of Oxford on July 20, 2020[31]. In addition, published literature were searched systematically to determine population-level vitamin D status.

Mortality and Population Data

The Our World in Data public COVID-19 dataset contains number of cases and deaths reported by the European Centre for Disease Prevention and Control by country by day since the inception of the pandemic in December 2019. The dataset also contains current estimates of population size and proportion of the population 65 and older from by the United Nations, Department of Economic and Social Affairs, Population Division.

Vitamin D Data

Databases searched include PubMed, CINAHL, EMBASE and SCOPUS in April 2020. Search terms included “vitamin D,” and “insufficiency OR deficiency OR status.” Separate searches were performed by region by the addition of region name in the search (“Africa”, “Asia”, “Australia”, “Europe”, “North America”, “South America”). Studies published from January 2010 to April 2020 were included. This search yielded a total of 7,820 unique records. Records were then evaluated for relevance to the research question by two separate reviewers. The initial search also excluded case reports, reviews and meta-analyses, and case-control studies. Clinical trials were included only if the control group was population based. A total of 6,357 records were excluded based on these criteria.

After initial review, 7,820 unique records were evaluated for relevance to the research question. A total of 110 studies contained data pertaining to the research question of population-level data of VDD among older adults. These studies were ranked by country based on the study population, (1) country-wide population based, (2) regional population-based, (3) study specific. The most representative study with the most recent data of data collection was used for each country (See Table 1). Data were collected on the time and location of data collection, study population, laboratory methods, sample size and results. Studies were excluded if they did not collect data on elderly individuals of both sexes, or if they did not present information on vitamin D deficiency. We selected the Endocrine Society’s definition of vitamin D deficiency as less than 50 nmol/L (20 ng/ml).

Table 1
Literature on vitamin D deficiency among older adults

ID	Country	vitamin D Deficiency	Year of Data Collection	Season of Collection	*Age of Participants	Total N	Participant Sex Ratio (Female/Male)	Method of vitamin D Quantification
AUS	Australia[41]	36.0%	2009–2010	Spring	60–85	72	2.27	CLIA
BEL	Belgium[42]	65.7%	2008–2009	Whole Year	80+	367	1.76	CLIA
BRA	Brazil[43]	58.0%	2002–2007	Whole Year	72.8 ± 4.8	908	1.46	RIA
CAN	Canada[44]	6.9%	2012–2013	Whole Year	50–80	2,119	1.84	CLIA/LCMS
CHE	Switzerland[45]	34.4%	2009–2010	Whole Year	60+	1,470	1.15	–
CHN	China[46]	39.1%	2010–2013	Whole Year	60+	6,014	1.04	RIA
DEU	Germany[47]	49.4%	2009–2010	Whole Year	65+	1,385	0.75	CLIA/LCMS
ECU	Ecuador[48]	21.6%	2009	Summer	71.0 ± 8.3	2,374	1.21	HPLC
EGY	Egypt[49]	12.0%	–	–	60+	176	–	–
EST	Estonia[50]	55.0%	2001–2002	Whole Year	74 ± 6	900	1.99	LCMS
FIN	Finland[51]	65.1%	1998–2001	Whole Year	53–73	1,421	0.97	LCMS
FRA	France[50]	69.0%	2001–2002	Whole Year	73 ± 6	695	1.45	LCMS
GBR	United Kingdom[52]	55.3%	2012–2013	Whole Year	66.4 ± 8.8	6,004	1.21	CLIA
GRC	Greece[50]	59.0%	2001–2002	Whole Year	71 ± 4	578	1.15	LCMS
IND	India[53]	56.3%	2014–2015	Whole Year	60+	298	0.54	RIA
IRL	Ireland[54]	42.5%	2009–2011	Whole Year	50–80	5,356	1.14	LCMS
ITA	Italy[55]	64.2%	1998–2000	Whole Year	65+	867	1.30	RIA
JPN	Japan[56]	53.6%	2011–2013	Whole Year	40–74	9,084	1.26	CLIA
KOR	South Korea[57]	59.7%	2010–2014	Whole Year	65+	3,757	1.26	RIA
MEX	Mexico[58]	53.2%	2012	Whole Year	63.4 ± 9.5	1,772	1.42	CLIA
NLD	Netherlands[59]	26.4%	2008–2009	Whole Year	60–98	915	1.09	RIA
NOR	Norway[50]	27.0%	2001–2002	Whole Year	73 ± 6	636	1.17	LCMS
PRT	Portugal[60]	29.4%	2015–2016	Winter/Spring	> 65	1,500	1.39	CLIA
ROU	Romania[61]	28.3%	2012–2014	Whole Year	61–70	1,030	6.92	HPLC
RUS	Russia[62]	50.0%	–	–	65+	506	–	CLIA

RIA: Radioimmunoassay; CLIA: Chemiluminescent immunoassay; LCMS: Liquid chromatography tandem mass spectrometry; HPLC: High performance liquid chromatography

*Data are reported according to their presentation by each individual study. Age was reported by range, mean ± standard deviation, or range.

ID	Country	vitamin D Deficiency	Year of Data Collection	Season of Collection	*Age of Participants	Total N	Participant Sex Ratio (Female/Male)	Method of vitamin D Quantification
SGP	Singapore[63]	14.3%	1994–1998	Whole Year	45–74	504	1.29	CLIA
TWN	Taiwan[64]	28.7%	2008	Whole Year	55+	5,300	1.09	CLIA
USA	United States[65]	40.7%	2001–2002	Whole Year	50–85	1,826	0.98	RIA
ZAF	South Africa[66]	65.0%	2011–2013	Whole Year	73.1 ± 8.2	327	2.21	HPLC

RIA: Radioimmunoassay; CLIA: Chemiluminescent immunoassay; LCMS: Liquid chromatography tandem mass spectrometry; HPLC: High performance liquid chromatography

*Data are reported according to their presentation by each individual study. Age was reported by range, mean ± standard deviation, or range.

Statistical Analysis

The primary outcome was cumulative COVID-19 deaths, starting from the day of at least 5 total confirmed deaths in a country. Cumulative death curves exhibit early exponential growth followed by slower or variable growth rates until the outbreak is saturated, which would be evident by a stable, non-increasing trend segment. Cumulative deaths were modeled via random coefficient negative binomial growth curve models. Our hypothesis was that the country VDD prevalence among older adults was associated with COVID-19 deaths in a country during the early period of outbreak. The initial model included linear and quadratic effects of time, VDD prevalence, and two way interactions between VDD prevalence and time terms as fixed effects. The model intercept and time terms were included as random effects to account for variability among countries. Additional models included country population size and the proportion of the population that is 65 and older as covariates. All covariates were centered at the mean.

Results

Table 1 contains details of the international vitamin D literature review and corresponding vitamin D deficiency rates among older adults for the 29 countries in the study. Rates of vitamin D deficiency ranged from 6.9% in Canada to 69% in France. A lack of fit test to evaluate residual time trends in the initial VDD model indicated that cumulative deaths up to day 50 were fit well by the model with linear and quadratic time effects[32]. Thus, the study period was 50 days, beginning on the first day when the country reached 5 confirmed COVID-19 deaths (see Fig. 2).

Results from the random coefficient growth curve models are provided as Table 2. The initial test of our hypothesis (Model 1), indicated a marginally significant association between vitamin D deficiency and early exponential growth of COVID-19 deaths in a country ($p = 0.0538$). Adjusting for population size the relationship remained marginally statistically significant ($p = 0.0512$). However, the relationship between VDD in older adults and COVID-19 deaths was not statistically significant after controlling for the proportion of older adults in the population ($p = 0.2135$).

Table 2
Parameter estimates from negative binomial random coefficient growth curve models of COVID-19 deaths.

	Model 1			Model 2			Model 3		
	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value
Intercept	1.9466	0.1059	< .0001	1.9382	0.1013	< .0001	2.0429	0.1171	< .0001
Time	0.1993	0.0171	< .0001	0.1963	0.0171	< .0001	0.2095	0.0155	< .0001
Time*Time	-0.0020	0.0002	< .0001	-0.0020	0.0002	< .0001	-0.0022	0.0000	< .0001
VDD	-0.3021	0.5634	0.5962	-0.3423	0.5375	0.5298	-0.3404	0.6704	0.6162
Time*VDD	0.1806	0.0936	0.0538	0.1826	0.0936	0.0512	0.1122	0.0901	0.2135
Time*Time*VDD	-0.0019	0.0011	0.0811	-0.0019	0.0011	0.0771	-0.0010	0.0010	0.3354
Population				0.0297	0.0264	0.2712	-0.0090	0.0356	0.8036
Time*Population				0.0028	0.0047	0.5501	0.0065	0.0048	0.1763
Time*Time*Population				0.0000	0.0001	0.6319	-0.0001	0.0000	< .0001
Elderly							-1.1395	2.1938	0.6082
Time*Elderly							0.5717	0.2964	0.0540
Time*Time*Elderly							-0.0086	0.0033	0.0102
VDD = vitamin D Deficiency; Time was measured in days starting from the day of the 5th confirmed COVID-19 death in a country.									
Intercept and time terms are included in the model as random effects. All covariates were centered on the sample mean.									

Discussion

In an international country-level analysis of vitamin D deficiency in older individuals and COVID-19 deaths, we found a marginally significant association. The association remained when adjusting for the size of the population, but was not robust to adjusting for the age structure. This suggests the association between older adult population vitamin D levels and mortality is partially confounded by the proportion of population 65 years and older. At the population level, a greater relative proportion of older adults in a country may be associated with societal factors that affect vitamin D deficiency in this population such as differences related to housing/institutionalization, nutrition, physical activity, and/or healthcare services, which would indicate a mediating role of vitamin D deficiency. Alternatively, unobserved factors may account for the observed relationships between age structure, vitamin D deficiency and COVID-19 mortality.

Early cross-sectional ecological analyses have also reported evidence of an association between vitamin D deficiency and COVID-19 in Europe[22–25]. A marginal association between mean vitamin D levels and COVID-19 case and mortality rate (p = 0.05) was initially reported in a study of 20 European countries in April 2020[22]. Another study assessed the association between mean 25OHD in elderly residents to case mortality rate (CMR) in April 2020, in a limited sample of countries[24]. When restricting the sample to countries with similar testing strategies, this study reported a linear relationship between mean vitamin D levels and CMR (p = 0.014), and concluded that mean vitamin D was a better predictor for CMR than age-distribution, and comorbidities (diabetes and heart disease) although the sample size was extremely small (n = 6). Another ecological analysis of COVID-19 population mortality rates in June 2020 reported a strong linear correlation (p = 0.01) between mortality and severe vitamin D deficiency (25 nmol/L) in the general population of 10 European countries[25]. However, this association was not significant when using rates of vitamin D deficiency with a cutoff of 50 nmol/L. While our analysis does have a larger international sample of countries (n = 29) it does suffer from similar limitations of other ecological studies.

There is also evidence of a link between vitamin D deficiency and COVID-19 infection and severity from individual level analyses[33–35]. Single center studies in Switzerland and the US reported significantly lower serum vitamin D levels in individuals that tested positive for Sars-CoV-2[34,35]. A meta-analysis of 7 international studies concluded that serum vitamin D was significantly lower in COVID-19 patients with poor prognosis[33]. Ultimately, ecological and cross-sectional study designs are not fully able to control for possible confounding by factors associated with vitamin D, and a potential causal relationship would need to be confirmed in randomized clinical trials.

Clinical trials are underway world-wide to comprehensively assess the efficacy of vitamin D supplementation among individuals with COVID-19 and as a prophylactic measure among non-infected, high-risk individuals.[36] Results of these trials are highly anticipated. In the meantime, the relationship between vitamin D supplementation and VDI/VDD correction has been evaluated via randomized controlled clinical trials with other upper respiratory viral pathogen outcomes. A 2017 Cochrane review found that vitamin D supplementation was an effective prophylactic measure against viral respiratory infections with the greatest benefit experienced by individuals with initial low vitamin D levels.[37]

Vitamin D supplementation has also been studied in conjunction with influenza vaccine efficacy among people with VDI. Though vitamin D supplementation was associated with a tolerogenic immune response characterized by increased TGF-beta and a lower Th1:Th2 cell ratio, relative to the vaccine-only group, supplementation was not associated with differences in either antibody titers nor cathelicidin levels.[38] Thus, while vitamin D supplementation may indeed be one mechanism to ameliorate observed differences in COVID-19 disease severity, it is possible that VDI/VDD correction may not reduce viral mortality. In COVID-19, VDI has also been associated with a higher level of necessary care among hospitalized patients: prevalence of VDI was identified among 85% of ICU-admitted patients as compared to 57% of floor patients[39]. VDD has been associated with increased odds of testing positive for COVID-19 among patients at a University of Chicago hospital[34] .

In any case, the known relationship between VDD and influenza infection severity and the relative safety of vitamin D supplementation has resulted in calls for increased supplementation, identification, and correction of VDI/VDD as the winter season approaches in the Northern hemisphere and as coincident infections with Sars-Cov-2 and influenza viruses is expected[40].

Limitations

There are a number of limitations to of the present study. Firstly, while the marginal ecological association between the rate of vitamin D deficiency among older adults and COVID-19 deaths at the population level suggests vitamin D deficiency is an important COVID-19 risk factor, this study does not imply the relationship exists at the individual level. Secondly, we found this association was not robust to controlling for the age structure of a country. However, the analysis did not control for a number of other factors that may impact the relationship, such as seasonality, overall population health and lifestyle, or initial COVID-19 response time and strategy.

Other limitations are that there may be variation in COVID-19 death reporting methods and standards among countries and world regions leading to measurement error in the primary outcome. Similarly, measurement error may be present in the estimates of the prevalence of VDD among elderly due to variability in 25OHD assays across studies (Table 1). Because data on vitamin D deficiency among older adults was collected from literature, there is selection bias in favor countries who conducted nutritional research on elderly populations in recent years. Specifically, countries in the Middle East, Africa and South America were underrepresented. We compared countries that were included in the study to those that were not (n = 114), we found that those in the study had significantly greater population size ($p = 0.0005$), share of the population over the age of 65 ($p < .0001$) and total deaths at 50 days ($p < .0001$). Additionally, in an analysis of death curves controlling for population size and age-structure, we found that early exponential growth of deaths was significantly slower in countries not included in the analysis compared to those that were.

Conclusions

Physiologic and social factors are likely each highly predictive of COVID-19 infection and mortality. Longer-term interventions upon the social issues that contribute to differential disease burden are necessary and justified for improvement of health equity beyond the COVID-19 pandemic. In the meantime, data indicate that correction of low vitamin D levels may be an important preventative

intervention to address COVID-19 disparities. Furthermore, screening and treatment of VDI may constitute a future direction for additional prevention measures to reduce the burden of the COVID-19 pandemic among all populations.

Abbreviations

1. vitamin D deficiency (VDD)
2. vitamin D insufficiency (VDI)
3. Interleukin (IL)

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

All data sourced for this analysis were taken from publicly-available databases and/or published scientific literature. The dataset supporting the conclusions of this article are included within the article and its additional files.

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Not applicable

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Authors' Contributions:

FL conceived the study. KB and DD completed data collection. DD performed statistical analyses. All authors contributed to results interpretations and manuscript writing. All authors read and approved the final manuscript

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Figures

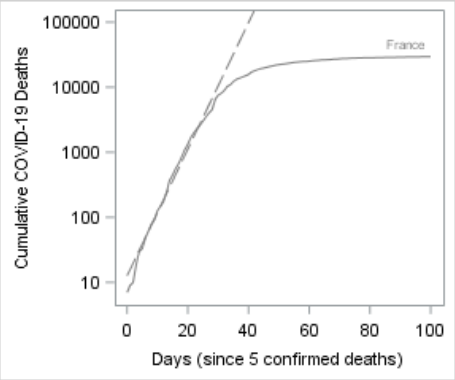

Figure 1

Cumulative deaths during the novel 2019 coronavirus outbreak in France Note: Modeling of the outbreak in France demonstrate early exponential growth.

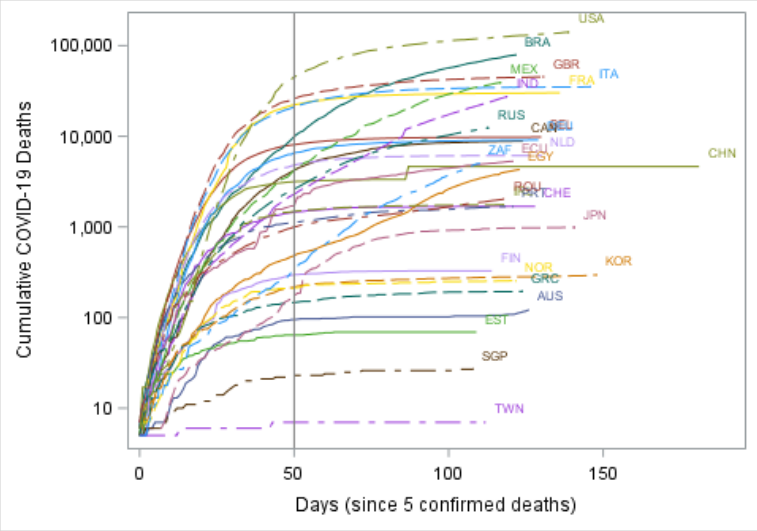

Figure 2

Cumulative deaths during 2019 coronavirus outbreak for the international sample of countries included in the analysis Note: n=29 countries included in this analysis.

Supplementary Files

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- PRISMA2009checklistVDD.doc
- SupplementaryInformation.docx