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Why has COVID-19 mortality been higher in certain countries than others? An ecological analysis of 204 countries

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Abstract

Background: It is unclear why certain countries have been more severely affected by COVID-19 than other countries.

Methods: In this ecological study we compared COVID-19 mortality and incidence/100,000 as well as 4 putative explanatory factors by WHO world region. Linear regression was then used to assess the country-level predictors of COVID-19 mortality/100,000 and incidence/100,000 in 204 countries with available data.

Results: COVID-19 incidence and mortality/capita were greater in Europe than other regions. This was despite a higher testing rate in Europe than other regions. Europe had an older population than all other regions and a higher prevalence of obesity than Africa, South East Asia and the Eastern Mediterranean.

Country level multiple linear regression revealed positive associations between mortality/capita and testing rate, percent of the population 65 years or older, and Europe compared to Western Pacific and South East Asia (all $P<0.005$). Results for the analyses with cases/100,000 as outcome variable were similar.

Conclusion: Our results suggest that older populations as well as other undefined regional and national factors, possibly related to efficacy of control efforts, are responsible for differences in national severity COVID-19 epidemics.

Background

Despite the SARS-CoV-2 virus first emerging and spreading in Asian countries, countries in Europe and elsewhere appear to have experienced more severe COVID-19 epidemics [1-4]. The reasons underpinning these differences in epidemic severity are unknown but of crucial importance in retarding the further spread of this virus [5, 6]. A common finding from studies around the world is that the majority of COVID-19 deaths occur in those above the age of 65 [7]. An older population structure may thus be an important risk factor [2]. Individual level cohort studies have also found strong associations between COVID-19 and obesity and a number of comorbidities such as diabetes and cardiovascular diseases [7, 8]. Because the prevalence of obesity varies dramatically between countries this could play an important role [9]. Differences in national responses are likely to play a large role but are difficult to quantify [5]. One parameter one can quantify is the number of COVID-19 tests performed per capita [7, 10]. Differences in viral virulence or transmissibility are thought to be unlikely to important due to the low rate of genotypic variation in SARS-CoV-2, worldwide [11]. Differences in host susceptibility may however play a role [12, 13]. One such possibility is the ACE-1 I/D polymorphism which has been shown to account for around 50% of the variation in ACE-1 expression between individuals [12]. The D-allele has been found to be a risk factor for some of the comorbidities linked to COVID-19 disease severity, such as hypertension, diabetes and cancer [12]. The D-allele has also been shown to be a risk factor for developing acute respiratory distress syndrome (ARDS) from all causes [12, 14]. One study has found an ecological association between COVID-19 mortality rates and the frequency of the D-allele within European countries [15]. Using an ecological study design, we evaluated which of these risk factors was associated with country-level COVID-19 mortality and incidence.

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Methods

Variables

Age of COVID-19 epidemic. The date the first case of COVID-19 was diagnosed in each country. This data was obtained from the ECDC data repository on 7 May 2020: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Cases/capita. The cumulative number of cases of COVID-19 infection per 100 000 inhabitants on 7 May 2020 per country. This data was obtained from the World of Meters data repository on 7 May 2020: https://www.worldometers.info/coronavirus/

Mortality/capita. The COVID-19 attributable mortality per 100 000 inhabitants. This data was obtained from the World of Meters data repository on 7 May 2020: https://www.worldometers.info/coronavirus/

Tests/capita. Cumulative number of nucleic acid amplification SARS CoV-2 tests conducted per country per 100 000 inhabitants up till 7 May 2020. This data was obtained from the World of Meters data repository: https://www.worldometers.info/coronavirus/

Percent elderly: The percent of the total population that is 65 years or older in 2018. Data extracted from the World Bank: https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS

Percent obese: The percent of the age standardized adult population with a body mass index of 30 or above in the year 2016. Data was taken from the World Health Organization: https://apps.who.int/gho/data/view.main.CTRY2450A?lang=en

ACE-1 ID/DD genotype prevalence. This was calculated as the prevalence of the ID plus DD genotypes per country. These figures were taken from a recent publication that provided national estimates for these based on a literature review [16].

WHO regions. Countries were categorized according to the 6 WHO world regions: Americas, Africa, Europe, Eastern Mediterranean, South East Asia and Western Pacific/East Asia: https://www.who.int/choice/demography/by_country/en/

Data analysis

Simple and multiple linear regression was used to assess the associations between each of the variables and deaths/capita or cases/capita. Log transformation was used for mortality/capita, cases/capita and tests/capita to create more normal distributions for inclusion in the linear regression analyses. All variables with a p-value of <0.01 in the univariate analysis were entered into the multiple regression analyses. The Wilcoxon rank-sum test was used to compare the values of the variables in different world regions. All regions were compared with Europe because mortality/capita and cases/capita were found to be highest here. The most recent data available as of 7 May 2020 was used for all the COVID-19 variables - tests/capita, cases/capita, mortality/capita and age of epidemic. A p-value of < 0.01 was considered statistically significant. The analyses were performed in STATA version 16 (Stata Corp, College Station, Tx).

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Results

As of 7 May 2020, 204 countries reported COVID-19 cases and 174 reported deaths. There was a large variation in the number of deaths per 100,000 inhabitants (mean 50, interquartile range [IQR] 20-310) and cases per 100,000 inhabitants (mean 1,985 IQR 450-11,185; Table 1).

COVID-19 incidence and mortality/capita were greater in Europe than other regions (Fig. 1, Table 1). This was despite a higher testing rate in Europe than other regions. Europe had an older population than all other regions and a higher prevalence of obesity than Africa, South East Asia and the Eastern Mediterranean (Fig 1.)

Country level simple linear regression revealed positive associations between mortality/capita and testing rate, percent elderly, percent obese and a negative association with the age of the epidemic (all P-values <=0.001; Table 1). On multiple linear regression these associations remained significant except the percent obese variable (Testing: coef. 0.28, 95% CI 0.09-0.47; Age of epidemic: coef. -0.04, 95% CI -0.06- -0.02; Percent elderly: 0.09, 95% CI 0.03-0.15). So too, mortality remained lower in Western Pacific and South East Asia than Europe.

Linear regression with cases/capita as outcome variable revealed similar results with the main exception that percent elderly was no longer a significant predictor in the multivariate analyses (Table 2).

Discussion

Both in terms of cases and attributable mortality, the COVID-19 epidemics have varied in their intensity between countries and regions. Individual level studies have found that being older and obese were strong risk factors for both severe symptomatic disease and mortality [7, 8]. Our ecological analysis found positive associations between these two variables and COVID-19 mortality. These findings suggest that a higher prevalence of elderly and possibly obesity may explain part of the differences in COVID-19 mortality. After controlling for these differences, however, the mortality/capita and cases/capita remains higher in Europe than other regions such as Western Pacific and South East Asia. This suggests that other factors play a role.

A number of explanations are possible. Firstly, we may not have adequately controlled for the ages of the national epidemics. Countries with more recent epidemics may have had more time and motivation to introduce more effective control programmes. This would not however explain the smaller epidemic size in Western Pacific countries, since these countries typically had earlier epidemics [4]. Secondly, our measures of age structure and obesity are relatively crude and may not have fully-captured the risk differences between populations [9]. Thirdly, differences in the speed, intensity and accurate targeting of testing, contact tracing and isolation likely played a role [3, 4, 17]. This fits with findings of narrative reviews that Western Pacific countries responses typically involved rapid, timeous, large scale screening, contact tracing and isolation early on in their epidemics that resulted in subsequent declines in incidence [3, 4, 17, 18]. Responses in European countries on the other hand tended to be slower, and less intense in terms of screening, contact tracing and isolation [1, 2, 4-6, 18, 19]. This was particularly evident in countries such as Sweden and the United Kingdom [20]. The United Kingdom briefly proposed pursuing a strategy of allowing the controlled spread of SARS-CoV-2 so as to develop 'herd-immunity' [20]. Fourthly, differences in host susceptibility may play a role. We found that Europe had a higher prevalence of the ID/DD-genotypes thought to confer increased risk for severe COVID-19 than Western Pacific. There was however no statistically significant association between ID/DD prevalence and mortality/capita or cases/capita in the country level analyses. We acknowledge that this conclusion must be tempered by the fact that we only assessed the effect of one susceptibility locus. Fifthly, differences in lock-down, quarantining, social-distancing or face mask usage may play a role. There were considerable differences in how these strategies were applied in countries [3-5, 17]. A number of authors have noted that the more widespread use of face masks in public in Western Pacific than European countries may have played a role in explaining differential spread [3, 21, 22].

Our analysis confirms the order of magnitude difference in COVID-19 incidence and mortality between Europe and the Western Pacific, South East Asia and Africa. Our results suggest that differences in the age structure and possibly the prevalence of obesity play a role in explaining the lower incidence in Africa and South East Asia. The fact that after controlling for these risk factors and the age of the national epidemics, the incidence and mortality remain significantly lower in South East Asia and Western Pacific than Europe suggest that other factors such as more effective control measures played a roll. This finding in turn suggests that where control strategies differ between Europe and Western Pacific, such as the use of face masks in public, the Western Pacific strategy should be favored.

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Authors' contributions

CK conceptualized the study, was responsible for the acquisition, analysis and interpretation of data and wrote the analysis up as a manuscript.

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Conflict of interest

The author declares that he/she has no competing interests.

Ethical approval

The analysis involved a secondary analysis of public access ecological level data. As a result, no ethics approval was necessary.

Informed consent

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Table 1. Simple and multiple linear regression analyses of the predictors of COVID-19 mortality per 100,000 inhabitants

		Univariate			Multivariate		
	N	Coef.	95% CI	P-Value	Coef.	95% CI	P-Value
Tests/100,000 (log)	153	0.713	0.574-0.852	<0.001	0.279	0.089-0.468	0.004
Age of Epidemic	166	-0.032	-0.050- -0.014	0.001	-0.038	-0.056- -0.021	<0.001
Percent 65 years or older	154	0.022	0.180-0.253	<0.001	0.090	0.029-0.151	0.004
Obesity (%)	146	0.113	0.078-0.149	<0.001	0.003	-0.039-0.045	0.885
Prevalence of ID/DD genotype	49	0.052	-0.002-0.105	0.059	NE		
WHO Region							
Europe	55	Ref					
WPacific	12	-2.515	-3.510- -1.519	<0.001	-2.624	-3.829- -1.419	<0.001
Africa	35	-3.801	-4.477- -3.126	<0.001	-0.700	-1.796-0.396	0.209
Americas	37	-1.253	-1.917- -0.589	<0.001	0.354	-0.442-1.151	0.380
EMedit	21	-2.356	-3.157- -1.554	<0.001	-0.519	-1.562-0.524	0.326
SEAsia	7	-3.744	-5.000- -2.491	<0.001	-2.127	-3.473- -0.782	0.002

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Table 2. Simple and multiple linear regression analyses of the predictors of COVID-19 incidence per 100,000 inhabitants

	Univariate				Multivariate		
	N	Coef.	95% CI	P-Value	Coef.	95% CI	P-Value
Tests/100,000 (log)	179	0.911	0.814-1.008	<0.001	0.695	0.523-0.867	<0.001
Age of Epidemic	194	-0.032	-0.048- -0.015	0.001	-0.019	-0.034- -0.005	0.01
Percent 65 years or older	173	0.212	0.171-0.252	<0.001	0.025	-0.032- 0.081	0.386
Obesity (%)	165	0.130	0.097-0.162	<0.001	0.008	-0.028- 0.043	0.678
Prevalence of ID/DD genotype	50	0.038	-0.004-0.080	0.079	NE		
WHO Region							
Europe	63	Ref			Ref		
WPacific	20	-2.703	-3.537- -1.870	<0.001	-1.681	-2.643- -0.718	0.001
Africa	46	-3.955	-4.585- -3.326	<0.001	-0.481	-1.463- 0.500	0.333
Americas	44	-1.635	-1.274- -0.998	<0.001	0.208	-0.517- 0.932	0.572
EMedit	22	-1.980	-2.784- -1.176	<0.001	-0.061	-1.032- 0.919	0.901
SEAsia	9	-3.546	-4.702- -2.388	<0.001	-1.118	-2.297-0.061	0.063

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Figure 1. Comparison of COVID-19 epidemics (mortality/capita and cases/capita), testing intensity (tests/capita), percent of the population 65 years of age or older, percent obese and prevalence of the ID/DD-genotypes of the ACE1 gene by WHO world region in all countries with available data as of 7 May 2020 (*** P<0.0001, **P<0.001, *P<0.01)

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