Obese communities among the best predictors of COVID-19-related deaths

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Introduction **Coronavirus disease 2019 (COVID-19) is the largest outbreak to strike the world since the Spanish flu in 1918. Visual examination of the world map shows a wide variation of death tolls between countries. The main goal of our series is to determine the best predictors of such discrepancy.**

Methods **This is a retrospective study in which the rate of COVID-19 deaths was correlated with each of the following independent variables: total tests per 1 million population, gross domestic product (GDP), average temperatures per country, ultraviolet index, median age, average BMI per country, food supply, Bacille Calmette-Guerin compulsory status, and passenger traffic.**

Results **BMI per country proved to be the second best predictor of death rate with an *R* value of 0.43, and GDP being the best predictor with *R*=0.65.**

Conclusion **This article shows a tight correlation between average BMI, food supply per country, and COVID-19-related deaths. Such predisposing factors might operate by upregulating the inflammation pathway in heavily struck countries, leading to easier triggering of the infamous cytokine storm syndrome. Obesity also increases cardiovascular and respiratory morbidities, which are coupled to increased ICU demand and deaths among infected cases. *Cardiovasc Endocrinol Metab* 9: 102–107**

Cardiovascular Endocrinology & Metabolism 2020, **9**:102–107

Video abstract: ***http://links.lww.com/CAEN/A25.***

Keywords: coronavirus disease 2019 deaths, obesity, upregulated inflammation

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Received 9 May 2020 **Accepted** 28 May 2020

Introduction

Coronavirus disease 2019 (COVID-19) started as a small outbreak in the city of Wuhan, China. The first case can be tracked to 17 November 2019. On 22 March, COVID-19 was confirmed as a pandemic by the WHO. Two smaller outbreaks caused by the coronavirus (CoV) occurred earlier during this century, namely severe acute respiratory syndrome (SARS-1) [1,2] and Middle East respiratory syndrome.

Examination of the death rates across the globe clearly shows unclear discrepancies between the northern and southern hemispheres [3]. Temperatures have been postulated as a key player in such discrepancy, as well as humidity which Ma *et al.* [4] proved to decrease deaths from COVID-19, this might be via attenuation of viral virulence. This report goes in agreement with Martínez-Sobrido *et al.*, who proved that temperatures not only influence the viral capacity to spread but also affect viral pathogenesis. Higher temperatures are capable of inducing inactivating mutations to some key viral pathogenic proteins. Another factor that might be implicated in the higher number of deaths in the northern hemisphere is the higher passenger traffic to countries pertaining to this area. This would lead to an increased number of cases and subsequently COVID-19-related deaths [4,5].

However, as much as those theories could offer an explanation, they seem unsatisfactory if a closer look is given to each country's status. Italy, one of the most ravaged

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.cardiovascularendocrinology.com.

2574-0954 DOI: 10.1097/XCE.0000000000000218

countries by the disease, definitely has warmer environmental temperatures in comparison to Russia or Scandinavian countries, which clearly continue to demonstrate to date, a lesser number of deaths than in Italy. This has raised the need for an alternative hypothesis.

COVID-19 deaths have been mainly linked to hyperinflammation. The so-called 'cytokine storm' syndrome is a state of hypersecretion of cytokines induced by SARS-CoV-2. This hypercytokinemia has been also described in the previous SARS-1 outbreak. There are even reports that link the baseline levels of cytokines in patients' sera to the occurrence of complications [6,7]. This knowledge can help us look into the factors that can trigger higher levels of cytokines from one population to another or those. Aging has been proposed as an important state of augmented inflammatory tendency [8].

Another important cause of hyperinflammation susceptibility is the type of food intake. Vegetarian diet has been linked to lower cytokine levels, while fast foods, high-fat content, trans-fat, and carbohydrate-rich foods have been associated with an upregulated state of inflammation [9].

Muscogiuri *et al*. have discussed in his review of literature the available mechanisms by which obesity can result in more COVID-19-related complications. Low-grade vascular inflammation, impairment of T cell memory are the two immunologic sequelae of obesity that are regarded as key inducers of obesity-related COVID-19 complications. Moreover, vitamin D deficiency and metabolic-associated liver disease are known sequelae of obesity and are also important causes of immune dysregulation. Obesity is also associated with a hypercoagulable state, and in view of the increasing evidence linking death in patients with COVID-19 to vascular thrombotic events; this might give an additional explanation to the increased risk of death in obese patients infected with COVID-19. Finally, yet importantly, an important risk factor related to obesity is the significant increase in respiratory, cardiovascular, and endocrinal comorbidities [10].

Certain vaccines such as Bacille Calmette-Guerin (BCG) vaccine have a role in taming the immune response of affected individuals with a resulting decrease in inflammatory tendency [11]. Ozdemir *et al*. compared the rates of deaths in European countries implementing BCG vaccination and those who abandoned the vaccine. Death rates were significantly lower in European countries implementing BCG vaccination [12]. Despite these promising findings, Miyasaka *et al*. suggested that that BCG exerts heterogenous variable effects on the immune system depending on its strain. He suggested that the Japanese strain of the vaccine is significantly superior than others in stimulation of the primary immune response when compared to the African and Danish strains [13]. Kumar *et al*. underlined the absence of confounder analysis in all studies relating BCG to a decreased number of COVID-19 deaths [14].

We hypothesize that countries with a higher BMI, average, and higher average caloric supply reflecting fast-food practices, could be linked to increased rates of COVID-19 deaths along with other causes of augmented inflammation such as aged populations, lower rates of BCG vaccination. Therefore, the main outcome parameter of this study is to prove or disprove a possible relationship between COVID-19 deaths and the aforementioned risk factors.

Methods and statistical analysis

This retrospective study included the retrieval of the following data from their respective sources:

(1) The total number of deaths per 1 million population of each country (TD/1M).
(2) The number of tested subjects per 1 million population of each country (TT/1M). The previous items were retrieved from the updated WHO report of 5 April [15].
(3) (a) The average temperatures per country from November 2019 to April 2020 (Temp). (b) The average ultraviolet index per country. Temperatures and ultraviolet indices were retrieved from the data of the national centers for environmental information [16].
(4) The average gross domestic product (GDP) per country reflecting their economic status (GDP). GDP were retrieved from the world bank report [16].
(5) The passengers' traffic per country from air world transport statistics [17].
(6) BCG status from the BCG World Atlas [18].
(7) The average BMI per country and food supply per country from the WHO fact sheet on noncommunicable diseases [19].
(8) The median age per country [20].

Univariate and multivariate regression analyses were performed to determine the best predictor of the number of COVID-19 deaths per 1 million population per country and expressed in the form of scatter plots. This was followed by receiver operating characteristic analysis presented as interactive dot diagrams to determine the cutoff temperatures predicting a positive outcome concerning COVID-19 deaths as defined by a death rate <1 per 1 million population of the affected country.

Results

Table 1 is a multivariate analysis showing the best predictors of COVID-19 deaths. Among all suggested predictors, GDP was found to be the best predictor with $R = 0.65$, and $P < 0.001$. BMI was the second-best predictor with an R coefficient of 0.43; while food supply was the best third predictor with an R coefficient of 0.42. Among the three best predictors; only GDP and BMI achieved statistical significance by multivariate regression.

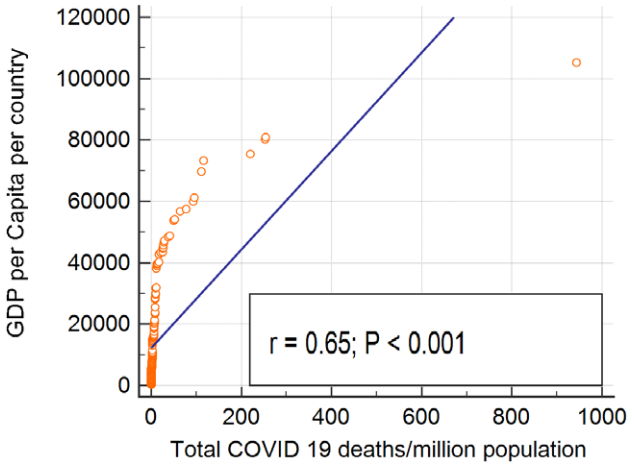
Figures 1 and 2 is a scatter plot showing the respective relationship between TD/1M as the dependent variable on one side, and each of the two best predictors of

Table 1 Epidemiologic predictors of coronavirus disease 2019-related deaths

	r	*P* in univariate regression	*P* in multivariate regression
GDP	0.65	<0.001	<0.001
Passenger traffic rate	0.36	<0.001	NS
TT/1M	0.27	<0.001	NS
Temperature	−0.39	<0.001	NS
Ultraviolet index	−0.25	<0.001	NS
BMI	0.43	<0.001	0.044
Food supply	0.42	<0.001	NS
BCG compulsory status	−0.4	<0.001	NS
Median age	0.25	<0.001	NS

A $P<0.05$ was considered statistically significant.
BCG, Bacille Calmette-Guerin; NS, nonsignificant; *P*, Pearson coefficient of statistical significance; TT/1M, the number of tested subjects per 1 million population of each country; *r*, correlation coefficient.

Fig. 1



Scatter plot showing the relationship between GDP and COVID-19 deaths indexed to 1 million population per country. COVID-19, coronavirus disease 2019; GDP, gross domestic product; *n*, number of countries included in the study; *P*, Pearson coefficient for statistical significance; *r*, correlation coefficient.

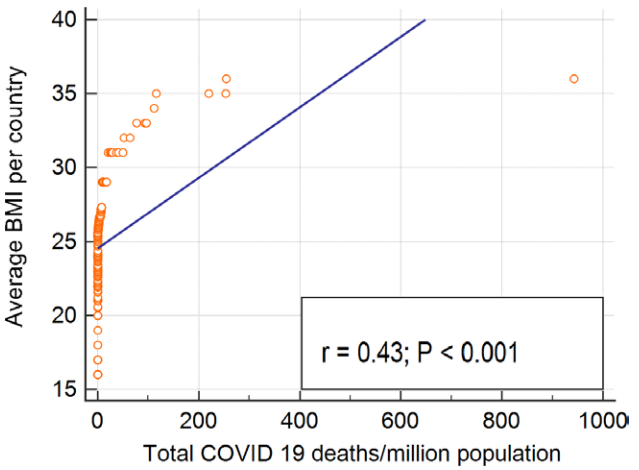
COVID-19 deaths, respectively, GDP and BMI per country.

Figure 3 is an interactive dot diagram showing the cut-off temperature defining a good outcome of death (1) as defined by deaths of <1 per 1 million population per country. A temperature higher than 22.98°C was predictive of a positive outcome with 100% sensitivity and specificity.

Discussion

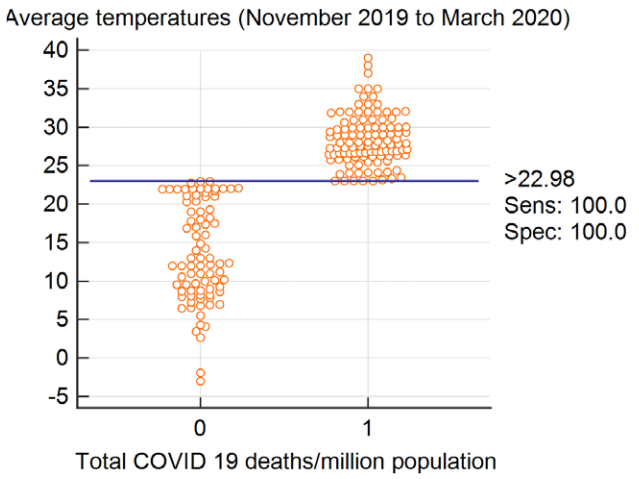
Temperatures are not the only factor that differentiates countries above and below the equator, but for reasons related to history and colonialism, countries above the equator were more fortunate to develop robust economies and better GDPs. In our study, GDP was found to be the best predictor of COVID-19-related deaths. The

Fig. 2



Scatter plot showing the relationship between BMI per country and COVID-19 deaths indexed to 1 million population per country. COVID-19, coronavirus disease 2019; *n*, number of countries included in the study; *P*, Pearson coefficient for statistical significance; *r*, correlation coefficient.

Fig. 3



Interactive dot diagram showing the cutoff temperature predicting positive outcome of mortality (1) as defined by mortality <1 per 1 million population of the affected country.

higher-income countries displayed higher COVID-19 deaths, in a surprising paradox. One might have thought that higher income is associated with better healthcare availability and greater resources that may be allotted to protection.

There are several factors found within countries with higher GDP that might explain this surprising paradox. One of them is eating habits, which are tremendously affected by income.

In our study, BMI and food supply were found to significant predictors of COVID-19 deaths People in low-income countries derive nutritional energy mainly from carbohydrates; the contribution of fats is small, but protein is the same as that for high-income countries, and that of meat and dairy are negligible. In high-income countries, nutritional energy is mainly derived from carbohydrates and fat, with a substantial contribution of meat and dairy. Economic growth is almost always coupled with changes in food habits [3]. A complex range of social and economic factors that tip the energy balance is not well-understood, despite a vast body of research. Another factor is BMI, which distinguishes healthy weight from overweight (BMI at or above 25 kg/m^2), and obese (BMI at or above 30 kg/m^2), where an increased risk of chronic disease and death is seen in populations where BMI is higher. Experts increasingly point to technological innovations as a key mechanism driving the energy imbalance. Technological innovations refer to improvements that have lowered the costs associated with food consumption, and a sedentary lifestyle. However, whether obesity is more attributable to dietary excess or physical inactivity, both factors are mainly prevalent in countries with high GDPs. In our study, higher COVID-19 deaths were linked to populations with higher BMI. This link was the second strongest link after GDP as a predictor of COVID-19 deaths. Obesity might operate through several mechanisms.

First of all, it increases comorbidities which might be an important predisposing factor for mortality from COVID-19. A recent report by Richardson *et al*. demonstrated that the commonest comorbidities associated with COVID-19 deaths are actually related to metabolic syndrome, namely obesity, diabetes, and hypertension with subsequent increased cardiovascular risk. Obesity is also considered a major trigger of a restrictive lung pattern. Yang *et al*. report goes in agreement with our findings and those of Richardson *et al*. Cardiovascular comorbidities were found as a major risk factor of COVID-19-related deaths and increased need for supplemental oxygen as well as ICU admission [21].

Moreover, obese communities reflect certain food trends, which are associated with a higher tendency for inflammation. Diets that promote inflammation are high in refined starches, sugar, saturated and trans-fats, decreased omega-3 fatty acids, natural antioxidants, fiber from fruits, vegetables, and whole grains.

Poor eating habits, commoner in higher BMI communities, are associated with an upregulated cytokine profile. Upregulated cytokines and enhanced inflammation include overexpression of (interleukin) IL-6, tumor necrotic factor, and other key cytokines that have been involved in COVID-19-related deaths. These factors might explain why COVID-19 deaths are higher in obese communities. The weaker correlation with average food supply might signify that the possible upregulated inflammation in countries with higher BMI, is not only related to the amount of food consumed but rather the types of food and distribution of food supply [9,22–24]. The latter facts might explain why obesity was the second best predictor of COVID-19-related deaths.

Muscogiuri *et al*., released important recommendations about nutritional intake amid the pandemic. They stressed the importance of avoiding excess carbohydrates that might induce low-grade inflammation and obesity. Antioxidants and fiber-rich diets have been suggested to improve T cell function. Vitamin D supplementation, especially in the sun-deprived lockdown state, was suggested as mandatory. Vitamin D deficiency is linked to increased vulnerability to respiratory infections [25].

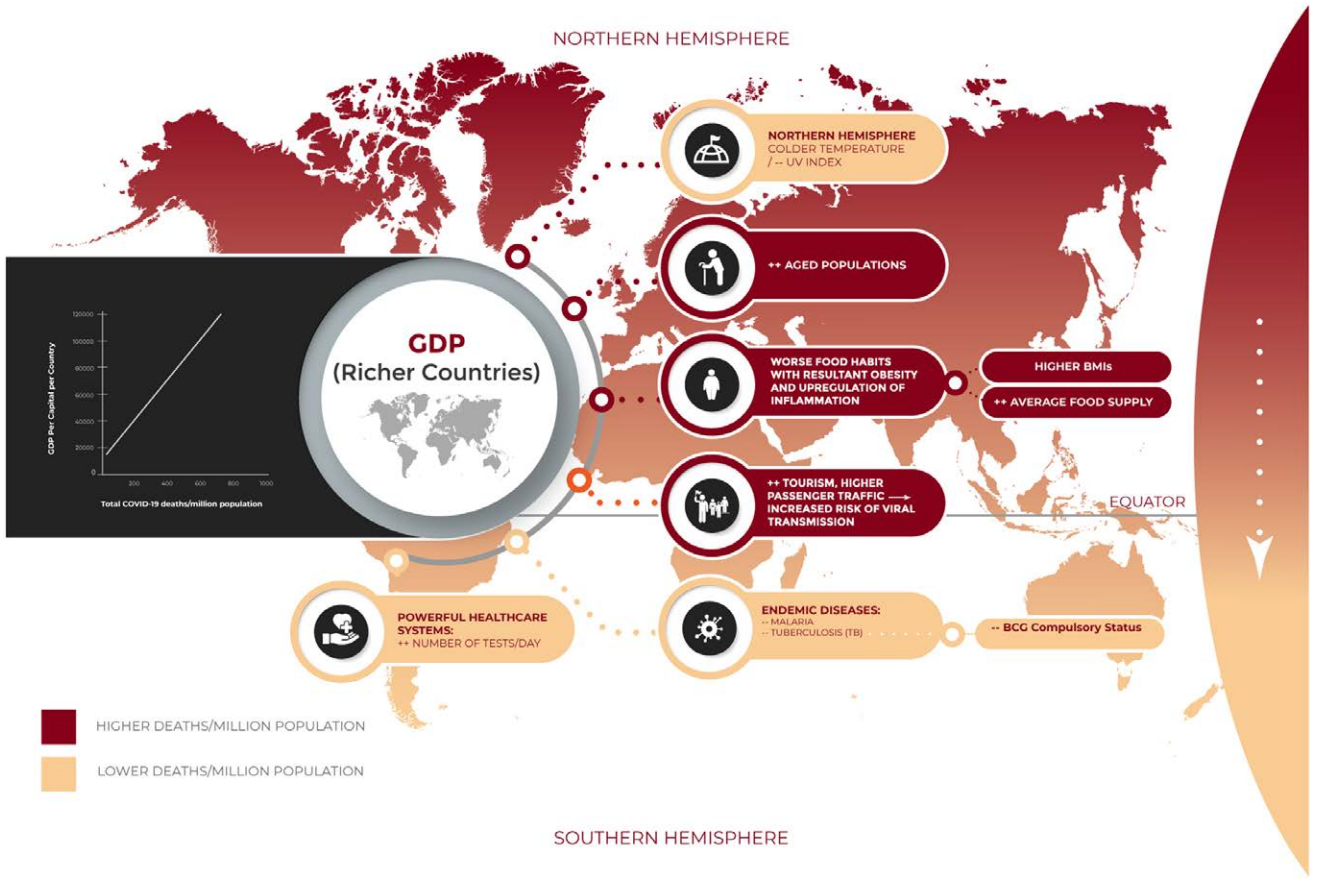
Besides the two best predictors of deaths, namely GDP and BMI, it is worth mentioning other potential relationships elucidated in our study. In our series, there was a negative relationship between temperatures and TD/1M, signifying that mortality and viral virulence might be tamed by higher temperatures. This goes in agreement with the recent report published by Ma *et al*., stating that higher temperatures and humidity were able to reduce death caused by COVID-19 [4].

A possible explanation of the relationship between GDP and COVID-19 deaths is the higher ability to screen infected cases. Developed countries have a better ability to test more suspected cases, and to trace the source of infection, as a result of more efficient healthcare systems. In our study, there were better statistical correlations between GDP and TT/1M on one hand and TD/1M than that observed between TD/1M and temperature. This might raise a significant concern of unintended nonreporting in countries at or below the equator, which might explain the reduced number of cases and deaths [26].

GDP might also act through other factors than under-reporting. An important game-changer in countries with low GDP is the tourism and rate of international flights. This virus has invaded almost every country via human transmission across borders. More vulnerable economies are known to have a reduced number of tourists per year, and the overall limited number of flights boarding their airports yearly compared to developed countries [17]. The lack of tourism and lower passenger in some countries might have saved them from an early surge of cases and therefore decreased the number of COVID-19-related deaths. This explains the positive statistically significant relationship depicted between TD/1M and passenger traffic.

Finally, yet importantly, higher-income countries have abandoned BCG vaccination since 1972, this might explain the inverse relationship between COVID-19 deaths and countries with BCG compulsory status, which was associated with a lower number of deaths. BCG

Fig. 4



Summary of epidemiologic predictors of COVID-19-related deaths. BCG, Bacille Calmette-Guerin; COVID-19, coronavirus disease 2019; GDP, gross domestic product.

vaccination seems to upregulate key regulatory cytokines such as IL-10, which plays a crucial role in preventing the elevation of certain cytokines, namely, IL-6, the main cytokine implicated in 'cytokine storm' syndrome of COVID-19 [27–30].

Conclusion

In summary, our preliminary data suggest that countries with higher GDP display significantly higher deaths than countries with lower incomes. GDP seems to act through several factors to increase the risk of COVID-19-related deaths. The most important of these factors is the eating habits and food supply of heavily struck countries. The latter might act via upregulating inflammation and increasing the risk of COVID-19-related hypercytokinemia. Despite the previously fixed belief that higher temperatures might be a game-changer in the COVID-19 epidemic, the discrepancy observed in cases was not best determined by meteorological factors but rather by metabolic factors such as BMI and food supply. Also, countries below the equator tend to have weaker economies with more vulnerable healthcare systems. Dynamics of the economy might also operate through factors such as tourism and flight rates, which might have delayed or contained the spread of cases in the southern hemisphere.

Figure 4 summarizes the aforementioned discussed epidemiologic predictors.

Acknowledgements

I would like, as a first author, to thank all the families of the students who co-authored this work for wonderfully raising them. I would also like to thank Rana Gamal and Muhammad Ibrahim for the editing of the video abstract. We would also like to thank the Pixagon Agency headed by Dr Nadine El Husseiny for providing us with her artwork in Figure 4. Finally, yet importantly, we thank Prof. Fathy Khodair, former Dean of Faculty of Medicine, Cairo University, for pointing out the equatorial differences in COVID-19 severity and distribution of cases.

Conflicts of interest

There are no conflicts of interest.

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