SARS-CoV 2 (Covid 19) heterogeneous mortality rate across countries may be partly explained by life expectancy, calorie intake and prevalence of diabetes.

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Research Article

Keywords: Calorie intake, correlation, Covid-19 mortality, life expectancy, prevalence of diabetes, SARS-CoV 2

Posted Date: October 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-86498/v2

Version of Record: A version of this preprint was published at Human Ecology on October 1st, 2020. See the published version at https://doi.org/10.1007/s10745-020-00191-z.

Abstract

SARS-CoV 2 continues to disproportionately kill people across the world. To understand the reasons for such heterogeneity, we isolated dietary and environmental factors that can either prime or suppress human immunity. We grouped phytochemical and micronutrient rich food (fruits, vegetable and spices) as immunity primers while smoking, alcohol consumption, pollution, high calorie intake and diabetes as immunity suppressing factors and determined correlations with Covid-19 death per million populations (C19DM) using multiple linear regressions or where necessary, best fit trend lines. We also determined correlations between life expectancy alone or in combination with other factors and C19DM. Based on the data, we found no evidence that immunity primers explain C19DM heterogeneity across countries. This observation did not change even after including immunity suppressing factors in the models. Of all the factors under study, life expectancy (years), calorie intake (Kcal/person/day) and prevalence of diabetes (%) had significant association with C19DM ($R^2 = 0.301$, $p < 0.000$). Therefore, these three factors should be further explored when trying to understand Covid-19 disproportionate mortality across countries.

Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV 2) causes coronavirus disease (Covid-19) that continues to kill people disproportionately across the world. More deaths are reported in developed countries than developing countries. This might be due to rigorous reporting in developed countries. Many developing countries are currently under-reporting Covid-19 cases due to poor health surveillance systems characteristic of those countries as well as lack of testing kits. As of 6th May 2020, US had reported over 1.2 million cases while most countries in Africa and the Middle East reported fewer cases (https://www.worldometers.info/coronavirus/). At the same time US had conducted almost 7.7 million tests (over 23000 tests per million population) while Russia and Germany had done 4.4 million (over 30500 tests per million) and 2.5 million (over 30,000 tests per million) respectively. Relative to the number of tests conducted, San Marino had the highest deaths per million population (1200) while Belgium, Spain, Italy, and France had 700, 550, 480, 400 deaths per million population, respectively. These figures highlight significant heterogeneity in terms of fatality of Covid-19 across the globe.

A number of hypotheses have been developed to explain this heterogeneity in Covid-19 mortality. One is that countries where Bacillus Calmette–Guérin (BCG) vaccines had been used have lower infection and mortality rates than those countries where BCG had never been used[1] though the evidence is lacking[2]. The second hypothesis is that countries where malaria is common and where hydroxychloroquine had previously been used have lower infection and mortality rates from Covid-19. Moreover, other studies have reported reduction in severity of Covid-19 symptoms after taking hydroxychloroquine[3,4]. However, some studies have found no evidence that hydroxychloroquine is helpful in severe cases of Covid-19 infection[5,6] and may even be harmful[7]. Though these hypotheses have not been extensively tested, they may have merit, at least for now, in the absence of further epidemiological studies. It is notable that most countries suspected to be underreporting their cases due to poor health surveillance systems implemented universal BCG vaccines at some point in time while some have indeed used hydroxychloroquine to fight malarial infection. Therefore, it is tempting to believe that the available data supports the BCG and hydroxychloroquine hypotheses. Since Covid-19 is generally found to be severe in immune compromised individuals (>70 years of age) albeit with co-morbidities such as diabetes, hypertension, respiratory system disease, and cardiovascular disease[8,9], it is clearly necessary to consider factors that may affect human immunity.

Healthy immune systems play an important role in treatment and prevention of Covid-19[10]. Factors that contribute to better immune system functionality include healthy diet, physical exercise, ingestion of phytochemicals, protection of nasal and oropharyngeal mucosa, and cessation of smoking among others[10]. There is a wide variation across countries in terms of the relative effectiveness of these factors and by extension, there might be variations in how these factors may modulate human adaptive immunity in each country. Some phytochemicals found in diets rich in fruits, vegetables, and spices, are known to be antiviral[11,12,13,14]. The antiviral mechanism of these agents may be explained on the basis of their antioxidant activities, scavenging capacities, the inhibition of DNA, RNA synthesis, or the blocking of viral reproduction[12,15].

Covid-19 has high mortality rate in individuals >60 years old[16], categorically expected to have lower immunity. Chronic diseases are common in the elderly due to biological ageing and declining immunity, referred to as immunosenescence[17]. In most European countries where the Covid-19 mortality rate is currently higher, the proportion of elderly (>65 years) individuals and life expectancy are also high (https://www.worldometers.info/coronavirus/). There are a number of factors that may affect human immune response including diet, physical exercise, smoking, alcohol consumption, and environmental factors such as pollution (particulate matter 2.5 or PM 2.5). It is also reported that regular exposure to dirt optimizes immunity suggesting that people exposed to dirty conditions will develop stronger immunity to infections than those not likewise exposed[18]. Diets rich in fruit and vegetables provide adequate vitamin C, vitamin A, vitamin E, B-complex vitamins, and zinc that are immune modulators. Therefore, we developed and tested a hypothesis that countries that consume higher immunity boosting foods (fruits, vegetables, spices) and are exposed to fewer immunity suppressing factors (smoking, physical inactivity, alcohol, high caloric consumption, pollution) have lower Covid-19 deaths per million population (C19DM) than those countries consuming less immunity boosting food and are highly exposed to immunity suppressing factors. We predicted significant correlations between these factors individually or in combination and C19DM. We tested this hypothesis based on available Covid-19 data up to 6th May 2020 as provided by Worldometer (https://www.worldometers.info/coronavirus/).

Methodology

We followed country-specific daily data on Covid-19 on total cases, total deaths, total cases per 1 million population, death per 1 million population, and test per 1 million population for a total of 211 countries from the Covid-19 outbreak in Wuhan, China up to 6th May 2020, as reported on https://www.worldometers.info/coronavirus/. We identified dietary and environmental factors that may affect immunity. We searched for data on consumption of fruits, vegetables, and spices, smoking, alcohol consumption, pollution, calorie intake, life expectancy, physical inactivity, and prevalence of diabetes from various different websites; (https://www.who.int/; https://ourworldindata.org/food-supply; https://www.helgilibrary.com/; https://www.iqair.com/world-most-polluted-countries; https://www.health.ny.gov/environmental/indoors/air/pmq_a.htm; https://www.indexmundi.com/facts/indicators/SH.STA.DIAB.ZS/rankings; https://apps.who.int/gho/data/view.main.2463?lang=en). We grouped phytochemical rich food (fruits, vegetable, and spices) as immunity primers and smoking, alcohol consumption, pollution, high calorie intake, longer life expectancy, physical inactivity and prevalence of diabetes as immunity suppressers.

Data analysis

We conducted ANOVA using SPSS (IBM SPSS Statistics 20) to generate correlation of determination coefficients (R^2) between different variables and C19DM for countries. We used multiple linear regression analysis to isolate factors with significant correlation coefficients ($p < 0.05$) with C19DM. Where necessary we used the best fit trend line (exponential, power, and logarithmic) to explain other relationships between factors C19DM.

Results And Discussion

There was significant linear relationship ($R^2 = 0.668, p < 0.000$) between total tests and total deaths reported for each country (Figure 3) suggesting that the more the Covid-19 tests are conducted in a country the higher the likelihood of more reported Covid-19 deaths. Since most developing countries were struggling to carry out massive screening tests for Covid-19 in the early stages of the pandemic these countries may have higher numbers of Covid-19 cases than have been reported to date. These data, therefore, suggest that if testing is intensified by those countries currently presumed to be under-reporting, the number of deaths reported as due to Covid-19 will likely rise.

There are disproportionate mortality rates from Covid-19 across the countries. Higher Covid-19 mortality rates are reported in countries with high life expectancy (>70 years) than those countries with lower (<70 years) life expectancy[16]. To test this we collected data on life expectancy (years) for all the countries (n = 207) and plotted against C19DM (Figure 1). We found a significant logarithmic relationship ($R^2 = 0.4662$, $p < 0.05$) between life expectancy and C19DM. The highest death rates occur for life expectancy between 75 and 85 years. We further divided countries into two groups; those with life expectancy below 75 years and those above 75 years. We found that the average death per million of population of countries with life expectancy below 75 years was 6.5 (n = 99), while for countries with life expectancy above 75 years (n = 111) C19DM was 90.4. Similarly, average total deaths in countries with life expectancy below 75 years was 102.5 (n = 99), while in countries above 75 years average total deaths was 2606.8 (n = 111) (Table 1). Unsurprisingly a large proportion of these countries are in Europe where health services are advanced. Therefore, these data suggest that the proportionally higher number of persons above 75 years may partly explain why those countries are reporting high C19DM. Due to immunosenescence, elderly persons tend to have poor immunity against infections[17]. In old age chronic diseases such as cancer, diabetes, hypertension, cardiovascular disease, and lung diseases are common decreasing resistance to Covid-19 infection and subsequently resulting in higher C19DM. This may partly explain why most African countries, whose populations are comparatively younger, have lower mortality rates than European countries.

There are a number of factors, both nutritional and environmental, that may lead to increased susceptibility to infection for persons over 70 years old. Good nutrition primes the immune system. Generally, diets high in fruits and vegetables are believed to be healthier due to significantly higher content of micronutrients (vitamin and minerals) and phytochemicals that are important for healthy immune systems. As noted above, fruits, vegetables, and spices are significant sources of phytochemicals some of which have antiviral properties[11,12,13,14]. We tested whether countries with high consumption rates of fruits, vegetables, and spices have lower C19DM. We also examined non-dietary factors that generally affect health and quality of life that could possibly explain, in part, the disproportionate death numbers among countries, such as pollution (PM 2.5), alcohol consumption (liters per capita), smoking (number of cigarettes per year), and physical inactivity. Separately or in combination, these factors are known to either increase the risk of respiratory problems (infection) or predispose individuals to obesity and diabetes and therefore have potential to increase the fatality rates of Covid-19 infections. Data to date show that total consumption of fruits and vegetables ($p = 0.393$), consumption of spices ($p = 0.771$), consumption of fruits ($p = 0.601$), alcohol intake ($p = 0.872$), smoking ($p = 0.606$), or physical inactivity ($p = 0.815$) do not have any significant effect on C19DM (Table 2), suggesting that these factors cannot explain disproportionate Covid-19 mortality across countries. However, prevalence of diabetes ($p = 0.028$), life expectancy ($p = 0.018$), and caloric intake ($p = 0.036$) had a significant effect on C19DM (Table 2). When we regressed for model significant factors only (prevalence of diabetes, life expectancy, and calorie intake), the significance of these factors to the model for prevalence of diabetes ($p = 0.004$), life expectancy ($p = 0.007$), or calorie intake ($p =0.029$) increased compared to the inclusion of other factors in the model (Table 3).

There was a significant logarithmic relationship ($R^2 = 0.4183$, $p<0.000$) between calorie intake (Kcal) per person per day and C19DM (Figure 2) suggesting higher calorie intake may be related to increased mortality rates of Covid-19. There was no clear relationship between alcohol consumption, physical inactivity, or smoking and C19DM (data not shown). There was an inverse power relationship between pollution and C19DM ($R^2 = 0.2585$, $p < 0.05$) (Figure 4). The higher Covid-19 death rate at lower pollution is due to lower PM 2.5 value in developed countries where mortality rate is high compared to developing countries. This may explain the inverse relationship between pollution (PM 2.5) and C19DM. Therefore it should not be interpreted as indicative that lower pollution is potentially associated with higher Covid-19 mortality. We therefore suggest use of a different parameter for air pollution and Covid-19 mortality.

Calorie intake is generally higher in developed countries where mortality rates from Covid-19 are also high. Calorie intake above 3000 Kcal per day is higher than the recommended daily requirement for most people and this may favor the development of obesity. Mortality rates generally increased above 3000 Kcal/person per day (Fig. 2) suggesting that high calorie intake may predispose people to Covid-19 infection either directly or indirectly. While high calorie intake is not a specific indicator for a particular health condition in this case, it is a risk factor for development of obesity and diabetes and may predispose people to various chronic diseases that may compromise the performance of their immune system against infections[19].

Persons with diabetes are 50% more likely to die from Covid-19 infection than non-diabetic persons of the same age[9]. However, diabetes in older age is also associated with cardiovascular disease, which could help to explain the greater likelihood of death from Covid-19 infection[9]. Diabetic persons have poor glycemic control that impairs many aspects of the immune response to viral infections and this effect is related to cytokine profiles and to changes in immune-responses including T-cell and macrophage activation[20]. Diabetes is also known to increase the severity of Covid-19 infections due to a mechanism involving angiotensin-converting-enzyme 2 (ACE2), a receptor for the coronavirus spike protein. Acute hyperglycemia has been shown to upregulate ACE2 expression on cells that might facilitate viral cell entry. However, chronic hyperglycemia is known to downregulate ACE2 expression making the cells vulnerable to the inflammatory and damaging effect of the virus,[9] suggesting that the SARS-Cov-2 may need sugar moiety to attach to a cell receptor. Prevalence of diabetes is high in the age group > 60 years and it is expected that Covid-19 mortality will be higher in countries with a larger proportion of elderly individuals. Among the factors we examine in this study, the data suggest that prevalence of diabetes, life expectancy, and calorie intake might have significant effect on C19DM and may partly explain the heterogeneity in Covid-19 mortality observed so far. However, this trend may likely change as developing countries, previously underreporting, are slowly increasing their Covid-19 screening capacity and therefore identifying increased numbers of Covid-19 infections thereby changing the current dynamics of the Covid-19 data.

Conclusion

Covid-19 has disproportionate mortality across countries that many studies have attributed to use of BCG and hydroxychloroquine, a vaccine for tuberculosis and a drug for treating malaria, respectively. Here we assess other factors that have strong correlations with Covid-19 disproportionate mortality and therefore should be further studied for a better understanding of Covid-19 mortality distribution. We determined that life expectancy, a proxy for higher proportion of elderly individuals, calorie intake, and prevalence of diabetes are positively associated with Covid-19 mortality across countries. Data to date show no evidence that consumption of foods that prime immunity or exposure to immunity suppressing factors reported here have any effect on Covid-19 mortality rates. However, the Covid-19 mortality distribution data may change as more countries, previously believed to be underreporting cases, have started identifying more cases through increasing their Covid-19 testing capacity. This means more Covid-19 deaths per million populations will likely be reported which may change current Covid-19 data dynamics. Future similar studies should be undertaken to detect any such changes.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

The authors declare that they have no conflict of interest.

Ethical approval

This study did not involve any human or animal subjects.

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Tables

Table 1. Effect of life expectancy (years) on average Covid-19 cases and deaths per one million population (C19DM) globally as of May 6, 2020

Life Expectancy (years)	Average C19DM	Average total cases/million population	Average Total death
>75*	90.4	1623	2606.8
<75**	6.5	159.8	102.5

Number of countries (n = 210); * n = 99; ** n = 111; C19DM; Covid-19 deaths per one million population

Table 2. Multiple regression analysis of Covid-19 death per million population (C19DM) with different factors

Model	Unstandardized Coefficients		t	Sig.
	B	Std. Error		
(Constant)	-589.813	153.570	-3.841	.000
Total fruits and vegetable consumption	-.231	.269	-.858	.393
Spices consumption (kg/year)	-2.579	8.832	-.292	.771
Prevalence of diabetes in 2019 (%)	-8.002	3.573	-2.240	.028
Alcohol intake (litres per capita)	.560	3.454	.162	.872
Smoking (number of cigarettes /year)	-.012	.023	-.518	.606
Life expectancy 2019 (year)	6.087	2.515	2.420	.018
Fruit consumption (kg/year)	.233	.444	.525	.601
Calorie intake (Kcal)	.091	.043	2.127	.036
Physical Inactivity[1] (%)	.286	1.222	.234	.815

Dependent Variable: death per one million population
[1] lack of physical activity. Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure (www.who)

Table 3. Multiple regression analysis of Covid-19 death per million populations with different factors).

Coefficients[a]				
Model	Unstandardized Coefficients		t	Sig.
	B	Std. Error		
(Constant)	-396.954	80.966	-4.903	.000
Prevalence of diabetes (%),	-5.953	2.055	-2.897	.004
Life expectancy in 2019 (year)	4.310	1.562	2.760	.007
Calorie intake (Kcal)	.057	.026	2.205	.029

a. Dependent Variable: death per one million population

Figures

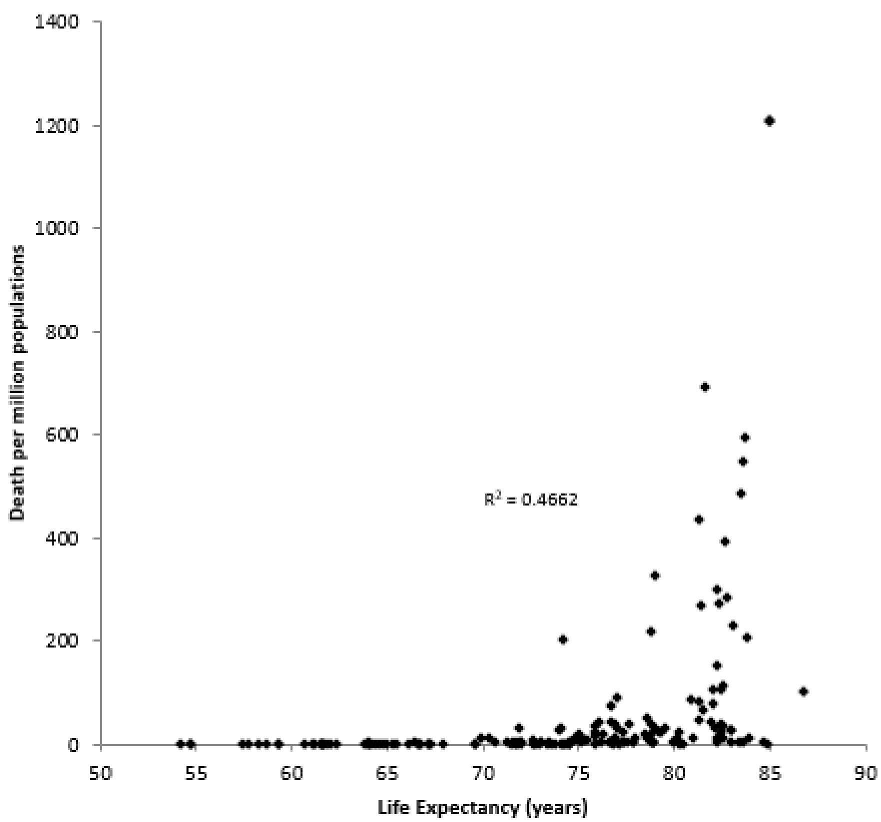

Figure 1

Life expectancy has strong logarithmic relationship with Covid-19 death per one million populations (C19DM) (n = 207). Each dot represents a country.

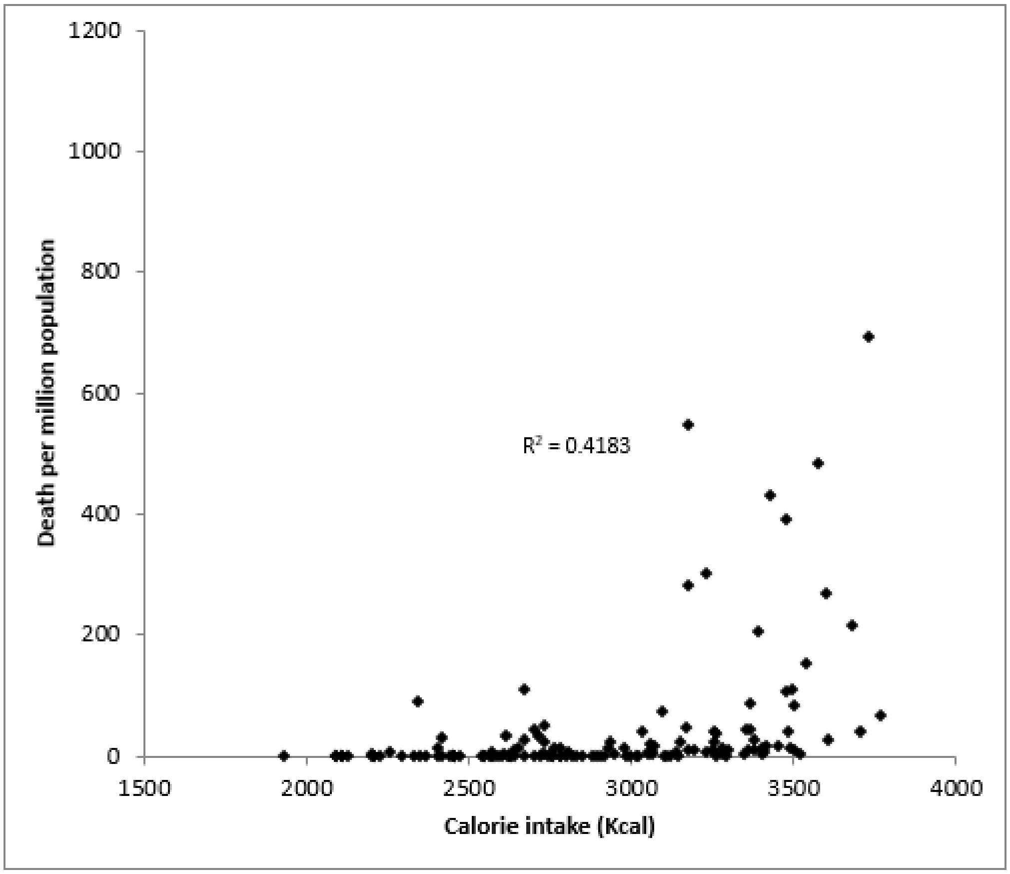

Figure 2

Calorie intake (Kcal/person/day) has logarithmic relationship with Covid-19 death per one million population (C19DM) (n = 162). Each dot represents a country.

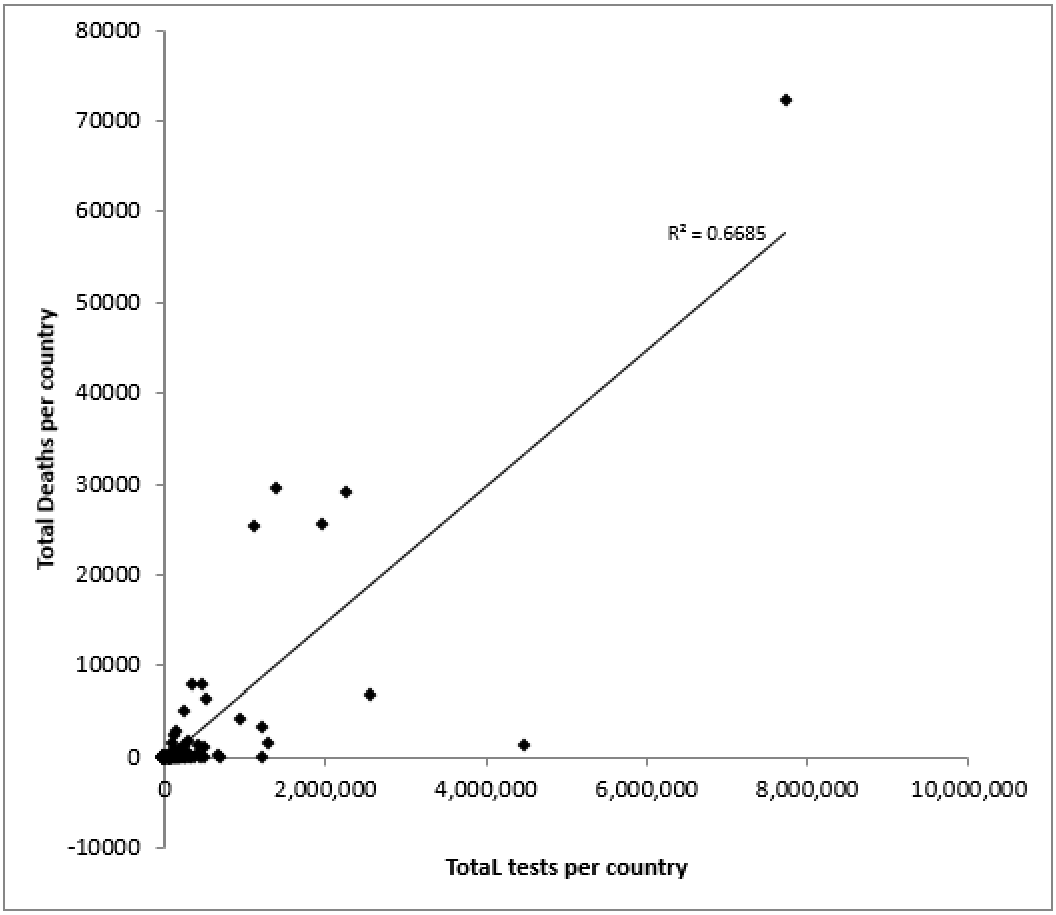

Figure 3

Total tests conducted against total death due to Covid-19 reported for each countries (n = 212). Each dot represents a country.

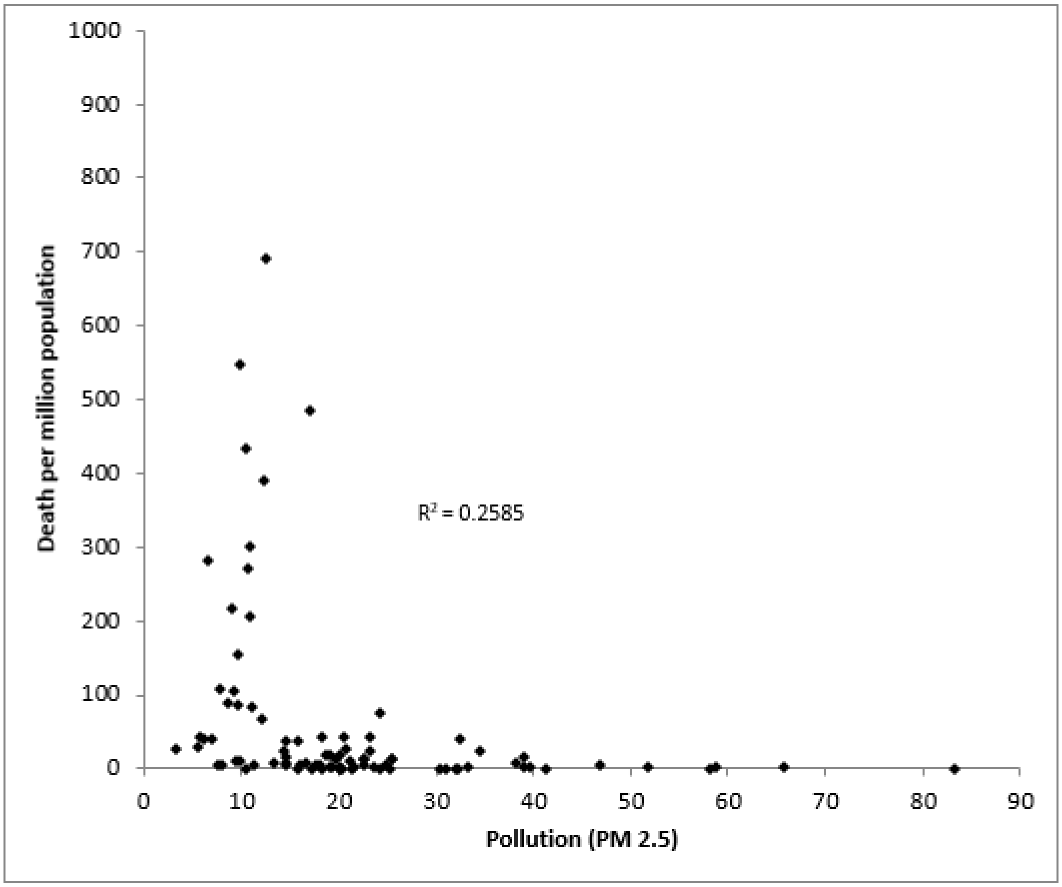

Figure 4

Pollution (PM 2.5) has an inverse power relationship with Covid-19 death per one million populations (C19DM) (n = 95). Each dot represents a country.